Metabolic Processes in the Human Body

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AkiNik Publications®
New Delhi

Published By: *AkiNik Publications*

AkiNik Publications
169, C-11, Sector - 3,
Rohini, Delhi-110085, India
Toll Free (India) – 18001234070
Phone No.: 9711224068, 9911215212
Website: www.akinik.com
Email: akinikbooks@gmail.com

Editors: *Zahraa Mahdi Jassim Mohammed, Russl kareem Wadi Alawy, Mohammed Falih Hasan Jiad and Muntathar Safaa Hussein Ahmed*

Publication Year: *2024*

Pages: *69*

Paperback ISBN: *978-93-6135-792-3*

E-book ISBN: *978-93-6135-460-1*

Book DOI: *https://doi.org/10.22271/ed.book.2832*

Price: *₹365/-*

Registration Details

- *Printing Press License No.: F.1 (A-4) press 2016*
- *Trade Mark Registered Under*
  - *Class 16 (Regd. No.: 5070429)*
  - *Class 35 (Regd. No.: 5070426)*
  - *Class 41 (Regd. No.: 5070427)*
  - *Class 42 (Regd. No.: 5070428)*

Contents

Unit - 1

Introduction to Metabolism

All the biochemical reactions that occur in living organisms are collectively known as metabolism. These metabolic processes ensure that essential molecules are synthesized for cell function, that energy is obtained and stored, and that waste products are effectively removed. By doing so, metabolism is able to ensure the constancy that is characteristic of living organisms. This is achieved even though there is a continuous input of materials into the body, all of which, given time, could cause complete breakdown of cellular function. A continuous integration of all these metabolic operations occurs in the human body. Metabolism also allows the cells to adapt to changing environmental conditions. Healthy metabolisms are required in order for the body to function normally. Therefore, failure of the various metabolic processes in the body causes disease. Metabolism therefore represents all chemical processes of a cell or organism. Biochemically, the concept of metabolism encompasses the breakdown and transformation of complex organic molecules found in the body's constituents. The major goal is to obtain chemical energy from the oxidation of nutrients. In addition, the generation of intermediary metabolites, which can be used for the synthesis of larger biomolecules or as substrates for high-energy impulse reactions, is another important function of various metabolic pathways. Metabolism also represents the body's ability to maintain the organic machinery required for energy generation and to adapt to changing physiological or pathophysiological conditions. Metabolism is intricately linked with various physiological functions, such as growth, reproduction, and response to environmental stimuli. It is an essential process that ensures the sustainability of life. Furthermore, metabolism plays a crucial role in the regulation of body temperature and the maintenance of homeostasis. The intricate network of metabolic pathways continuously interacts to support the overall functioning of the body. These pathways involve a wide array of enzymes, hormones, and other molecular components that work together harmoniously. Metabolic pathways can be categorized into catabolic and anabolic processes. Catabolism refers to the breakdown of complex molecules into simpler ones, usually resulting in the release of energy. Anabolism, on the other hand, involves the synthesis of complex molecules from simpler ones,

requiring energy input. Both processes are interconnected and highly regulated, allowing the body to efficiently utilize resources and maintain a state of equilibrium. Metabolic flexibility is a key aspect of a healthy metabolic system. The ability to switch between different fuel sources, such as carbohydrates, fats, and proteins, depending on nutrient availability and energy demands, is crucial for metabolic adaptability. This flexibility ensures that the body can effectively respond to changing conditions, such as fasting, exercise, or periods of high energy expenditure. Metabolic dysfunctions can have detrimental effects on overall health. Disorders such as diabetes, metabolic syndrome, and obesity are characterized by impaired metabolic processes and can lead to various complications. However, through proper nutrition, physical activity, and medical interventions, metabolic imbalances can often be managed and treated. Research in the field of metabolism continues to uncover new insights into the intricate mechanisms that govern this vital process. Understanding the complexities of metabolism provides valuable knowledge for improving human health and developing innovative therapies for metabolic diseases. By unraveling the intricacies of metabolic pathways and their regulation, scientists strive to unlock the full potential of metabolism in promoting wellness and longevity. (Mierziak *et al.*, 2021) (Schiliro & Firestein, 2021) (Shyer *et al.*, 2020) (Lacroix *et al*. 2020) (Van Gastel & Carmeliet, 2021) (Lennicke & Cochemé, 2021).

1.1 Definition and Importance

Metabolism refers to the complex array of chemical processes engaged in producing and sustaining life, encompassing a myriad of essential functions vital for our survival. These functions include not only the transformation of food into fuel and energy but also the intricate assimilation of nutrients within the human body to nurture and maintain its optimal functioning. While this module predominantly focuses on the assimilation of macronutrients such as proteins, fats, and carbohydrates, it does not overlook the significance of other key factors such as genetics or sensory cell function, which include vision and hearing. Rather, it directs its attention towards the remarkable processes of digestion, endocrine regulation, heart function, lung operation, liver performance, and various other vital organs. These remarkable organs each play a crucial role in the regulation of bodily functions, acting as a sophisticated signaling mechanism for potential threats such as pathogenic invasions, deficiencies in essential nutrients, or the detrimental consequences of excess. Through their signals, these organs prompt the necessary tissues, cells, and various components of the body to take appropriate action, safeguarding our well-being in the process. This integration of functionalities

allows us to comprehend the intricate orchestration of organ systems, which function in synchrony thanks to the activity of numerous enzymes and the intricate web of metabolic pathways they entail. These metabolic pathways are not only responsible for the generation of fundamental energy from food and other macronutrient sources, but they also play diverse roles in processes such as cell replication and inheritance, digestion, and genetic expression. To truly grasp the profound influence of macronutrients and metabolic pathways, an in-depth understanding of their configuration is imperative. This comprehension is particularly crucial in fields such as medical imaging, nutrition, and pharmacology, as it enables us to discern how and when drugs interact or chemically become active, targeting these specific metabolic pathways. Within this section, we will delve into the fundamental functions accomplished by the principal metabolic pathways, unraveling the intricacies of these extraordinary biological processes. (Nakrani *et al.*, 2020) (Steiner, 2020) (Kalra *et al*. 2021) (Marriott *et al.*, 2020).

1.2 Types of Metabolic Reactions

The other different types of metabolic reactions are as follows: Important Metabolic Reactions Anabolic reactions involve the building of complex molecules from simpler molecules. These reactions consume energy. One common anabolic reaction of glucose is the generation of storage glucose (glycogen) inside our liver. Another example of anabolism is the conversion of a single glucose molecule to two pyruvate molecules that occurs during glycolysis. The final result of each of these anabolic reactions is the generation of NADH and ATP and can be summarized as: one glucose + NAD++ ADP + Pi + 4ATP + NADPH <=> 2 pyruvate + NADH + 4ATP + NADH2 + 2H+ + 2ADP + 2Pi + 2H2O. Catabolic reactions involve the breaking down of complex molecules into simpler, more basic molecules. These reactions release stored energy. One common catabolic reaction is the hydrolysis (addition of water molecules) of triglycerides in our adipose tissue (fat). This hydrolysis action occurs with the release of fatty acids and glycerol, which is released as "energy." Glycerol is then converted to glucose (gluconeogenesis) in the liver in a catabolic reaction. Metabolic reactions are crucial for the functioning of our bodies. They are responsible for the synthesis of complex molecules and the breakdown of larger molecules into simpler ones. Anabolic reactions, for instance, play a vital role in building up molecules like glycogen and pyruvate from glucose. These reactions require energy and contribute to the production of substances like NADH and ATP. On the other hand, catabolic reactions are involved in the breakdown of complex molecules to release stored energy. A notable example is the hydrolysis of triglycerides in

adipose tissue, which leads to the liberation of fatty acids and glycerol. This energy release is crucial for various physiological processes. Moreover, the catabolic transformation of glycerol into glucose in the liver through gluconeogenesis further allows for the utilization of this stored energy. Understanding the different types of metabolic reactions is essential for comprehending how our bodies function at a molecular level. Anabolic and catabolic reactions work in harmony, ensuring the maintenance of energy balance and the provision of vital molecules needed for various biological activities. (Chandel, 2021) (Xavier and Kauffman 2022) (Wang, 2021) (Nader *et al*. 2022) (de Nava & Raja, 2022) (Benedetto *et al*. 2021).

Unit - 2

Carbohydrate Metabolism

Carbohydrate metabolism is a complex and highly intricate process that extensively involves the breakdown and synthesis of glucose molecules, which serve as the primary source of energy for the body. In order to ensure that glucose is transported and distributed efficiently throughout various tissues, several key organs and tissues play vital roles in this metabolic process. These include the liver, skeletal muscles, integument, and adipose tissue, which serve as important sites for storing glucose in the form of glycogen. Glycogen, essentially acting as a reserve of glucose, plays a crucial role in maintaining a steady supply of glucose during periods of fasting or in between meals. This reserve serves as a safeguard to ensure that the body has access to a readily available energy source even when glucose intake is limited or temporarily unavailable. The significance of carbohydrate metabolism becomes even more evident when considering the detrimental effects that can arise from disruptions in glucose regulation. Disorders such as diabetes and prediabetes are directly linked to impaired glucose and insulin metabolism, further highlighting the significance of properly regulated carbohydrate metabolism. These conditions have emerged as global health concerns due to their increasing prevalence and substantial impact on public health, necessitating a deeper understanding of the underlying metabolic processes involved. The main focus of carbohydrate metabolism lies primarily in the highly intricate pathways that are responsible for the conversion of glucose. One of the fundamental pathways is glycolysis, which involves the breakdown of glucose into pyruvate. This process yields two molecules of ATP (adenosine triphosphate), two molecules of NADH (nicotinamide adenine dinucleotide), and two molecules of pyruvate. Additionally, the process of glycolysis also leads to the generation of water, acting as a crucial byproduct of this energy-producing pathway. While glycolysis is primarily concerned with energy production, another important pathway, known as gluconeogenesis, operates in the opposite direction, utilizing different enzymes to synthesize glucose from non-carbohydrate precursors. This allows for efficient energy utilization by ensuring that glucose, a vital energy source, is not wasted unnecessarily. Pyruvate, a key intermediate in glucose

metabolism, has various paths which it can follow depending on the metabolic requirements of the cell. In the mitochondria, pyruvate undergoes a process called oxidative decarboxylation, facilitated by the pyruvate dehydrogenase complex. This multistep process results in the production of acetyl-CoA, carbon dioxide, and NADH. Acetyl-CoA then enters the tricarboxylic acid cycle, also known as the Krebs cycle, ultimately leading to the generation of reducing equivalents required for oxidative phosphorylation, a critical process that is integral to the production of ATP. In the context of gluconeogenesis, the synthesis of pyruvate from glucose involves the reduction of three molecules of α-ketoglutarate. To facilitate this process, two molecules of malate act as carriers for the reducing equivalents, allowing for the transport of malate to the cytosol, where the final steps of gluconeogenesis take place. These final steps involve the involvement of two molecules of malate dehydrogenase, resulting in the conversion of malate back to pyruvate and further facilitating glucose synthesis. Overall, carbohydrate metabolism plays a pivotal role in maintaining glucose homeostasis and providing energy to the body. Understanding the intricacies and intricately linked processes involved in glucose breakdown and synthesis is of paramount importance when it comes to comprehending metabolic diseases and developing effective therapeutic strategies. Through continued research and technological advancements, we can strive towards a better understanding of carbohydrate metabolism and its far-reaching implications for human health and well-being. (Swanson, 2020) (Kwon, 2021) (Remesar & Alemany, 2020) (Brooks, 2020) (Callahan *et al*. 2020) (Cherkas *et al*. 2020) (Wilkinson and Liebman 2022) (Tappy, 2021) (Ørtenblad *et al*., 2022).

2.1 Glycolysis

Glycolysis is the first metabolic pathway of carbohydrate metabolism where one molecule of glucose is converted into two molecules of pyruvate with the requirement of 2 molecules of ATP to initiate the reaction. The synthesis of ATP starts in the third step, and also in the 5th step of glycolysis, it is called the ATP-forming step. So the total 4 ATP molecules are generated through the glycolytic pathway, including the 2 ATP molecules used initially. The net yield of glycolysis is two molecules of ATP and two molecules of NADH. Pyruvate enters the mitochondria where it is decarboxylated by pyruvate dehydrogenase in the presence of cofactors like TPP (thiamine pyrophosphate) and FAD, and acetate is transferred to co-enzyme A to form acetyl CoA, which then enters the Citric acid cycle, converting GTP, NADH, and FADH into ATP. This means glycolysis can occur in both the presence and absence of oxygen (anaerobically), and the enzyme depends on

NAD+/NADH for its glycolytic activity. Glycolysis is a multi-step process for the conversion of glucose into pyruvate. In the first step, glucose is phosphorylated by the enzyme hexokinase to form glucose-6-phosphate. Glucose-6-phosphate is then converted into fructose-6-phosphate by the enzyme glucose-6-phosphate isomerase. In the third step, ATP is used to phosphorylate fructose-6-phosphate for the production of fructose-1,6-bisphosphate by the enzyme phosphofructokinase-1. Fructose-1,6-bisphosphate becomes split in the 4th step by the enzyme aldolase. The products of aldolase catalysis are glyceraldehyde-3-phosphate and dihydroxyacetone phosphate. Glyceraldehyde-3-phosphate is then converted into 1,3-bisphosphoglycerate, taking inorganic phosphate and NADH from the conversion of NAD+ by the enzyme glyceraldehyde-3-phosphate dehydrogenase. The next step involves the conversion of 1,3-bisphosphoglycerate into 3-phosphoglycerate through the action of the enzyme phosphoglycerate kinase. This conversion leads to the production of ATP molecules and the formation of NADH. The resulting 3-phosphoglycerate is further converted into 2-phosphoglycerate by the enzyme phosphoglycerate mutase. In the subsequent step, enolase catalyzes the conversion of 2-phosphoglycerate into phosphoenolpyruvate (PEP) by removing a water molecule. This reaction generates ATP and leads to the production of NADH. Phosphoenolpyruvate is then converted into pyruvate by the enzyme pyruvate kinase in the final step of glycolysis. This conversion is coupled with the production of ATP, resulting in the generation of pyruvate and additional NADH molecules. The pyruvate produced from glycolysis can be further utilized in various metabolic pathways or can be converted into lactate in the absence of oxygen through the action of lactate dehydrogenase. Overall, glycolysis plays a crucial role in energy production by breaking down glucose and generating ATP and NADH molecules. It is a highly regulated process that can occur in the presence or absence of oxygen, providing the necessary energy for cellular activities. Additionally, glycolysis serves as a precursor for other metabolic pathways, such as the citric acid cycle, where further energy production takes place. Through its intricate steps and enzymatic reactions, glycolysis ensures the continuous supply of energy for cellular processes. (Chandel 2021) (Chandel 2021) (Gupta *et al.* 2021) (Scanes, 2022) (Soto-Heredero *et al.* 2020) (Abbaszadeh *et al.*, 2020).

2.2 Gluconeogenesis

Gluconeogenesis is an essential part of carbohydrate metabolism that involves the synthesis of glucose from non-carbohydrate precursors. This metabolic pathway is paramount in maintaining glucose levels in the blood

under various conditions, such as consumption of a low-carbohydrate diet or fasting. Adapted to accommodate a diverse range of metabolic states, gluconeogenesis is tightly regulated, yielding specific substrates and intermediates depending on energy sufficiency and the fed or fasting state. Furthermore, gluconeogenesis is closely linked to other metabolic pathways, including the pentose phosphate pathway, the citric acid cycle, lipolysis, and the regulation of gene expression involved in metabolic homeostasis. Proper understanding and exploration of this complex and interconnected metabolic pathway are essential for a complete and comprehensive comprehension of metabolic homeostasis and the intricate mechanisms involved in maintaining cellular balance. Gluconeogenesis primarily takes place in the liver, the metabolic powerhouse of the body. Consequently, hepatocytes, the liver cells, are the primary site of gluconeogenesis. These specialized cells are equipped with the necessary enzymatic machinery to carry out the intricate series of reactions involved in gluconeogenesis. The process itself is energetically expensive, requiring the input of six high-energy phosphate bonds from guanosine triphosphate (GTP), and two from adenosine triphosphate (ATP), emphasizing the cellular dedication and resources necessary for glucose production. Generally, pyruvate, lactate, glycerol, and glucogenic (i.e., ketogenic) amino acids serve as gluconeogenic substrates; these molecules are utilized and transformed to synthesize glucose, ensuring the organs and tissues have a constant source of fuel and energy. However, it is important to note that acetyl-CoA, derived exclusively from ketogenic amino acids or β-oxidation, is not directly used as a substrate in gluconeogenesis. Rather, it is redirected towards other metabolic pathways for energy production and utilization. In the intricate process of gluconeogenesis, specific enzymatic reactions play pivotal roles in driving the pathway forward. Pyruvate carboxylase and phosphoenolpyruvate carboxykinase, the rate-limiting gluconeogenic enzymes, primarily function in the mitochondrial matrix. This specialized compartment within the cell houses key enzymatic machinery and metabolic processes. Pyruvate, a central molecule in gluconeogenesis, is converted into phosphoenolpyruvate (PEP) within the mitochondria. This pivotal step ensures its further metabolism in the cytoplasm or endoplasmic reticulum, allowing for the synthesis of glucose and the maintenance of glucose homeostasis. By unraveling the intricacies of gluconeogenesis, we gain insight into the remarkable regulatory mechanisms and molecular interactions that underlie the metabolic balance within our cellular systems. This understanding fosters advances in biomedical research and provides the foundation for therapeutic interventions targeting metabolic disorders and diseases. Through ongoing exploration and scientific inquiry, we continue to

expand our knowledge of gluconeogenesis, unveiling its role in health and disease and paving the way for new discoveries in the field of metabolism. (Legouis *et al*. 2022) (Nakrani *et al.,* 2020) (Salih *et al.,* 2022) (Qizi *et al*. 2023) (Parker 2020) (Shah & Wondisford, 2020).

Unit - 3

Lipid Metabolism

One of the most critical and essential forms of energy storage for the human body is unequivocally the storage of triacylglycerols, which possess the remarkable ability to be broken down into fatty acids for further metabolism. This intricate process allows the body to derive and harness the maximum free energy available from their precious fatty acid chains. The tremendous significance of triacylglycerols is further highlighted by their storage in adipose tissue, where they patiently await their extraction and utilization when the need arises. Before the fatty acid chains can serve as a primary and pivotal source of cellular energy, they must undergo a crucial step known as activation. Within the cytoplasm, these fatty acid chains undergo a transformative process wherein they are converted into fatty acyl-CoA. This activation process is essential to ensure that the fatty acyl-CoA chains are in optimal condition for their subsequent fate. However, due to their considerable size, these fatty acyl-CoA chains encounter a formidable challenge in traversing the inner mitochondrial membranes. Fear not, for evolution has ingeniously devised a solution! The degradation of these large fatty acyl-CoA chains is carried out by specialized oxidation systems that are strategically located in the peroxisome. This profound degradation ultimately yields acetyl-CoA, which is thus liberated and ready for its next crucial role. Now, the mitochondria seize upon this valuable acetyl-CoA, welcoming it with open arms. Within the mitochondria, a sequence of enzyme-catalyzed oxidative steps relentlessly and completely degrades the acetyl-CoA, ensuring that every last drop is utilized to its fullest potential. Once the mitochondria have fulfilled their purpose, the liver takes center stage in the intricate network of energy metabolism. The excess acetyl-CoA derived from the degradation of fatty acids inside the mitochondria is skillfully and efficiently converted into ketone bodies. These ketone bodies are of paramount importance, most notably in the brain, where they can be utilized as an alternative source of acetoacetate. Through a highly exergonic reaction, acetoacetate is admirably transformed into acetyl-CoA, which in turn produces a surplus of ATP, the cell's energy currency. This remarkable ability of ketone bodies to generate additional energy is truly awe-inspiring. In order for these remarkable ketone bodies to

propagate throughout the body, they must overcome the inherent challenge of being water-soluble, as fats are inherently hydrophobic and cannot be easily transported. Yet, in a testament to the body's ingenuity, the liver deftly packages fatty acids and cholesterol into water-soluble VLDL (very low-density lipoproteins). These specialized carriers efficiently transport the precious cargo of triacylglycerols to various tissues, notably the white adipose tissue, ensuring a steady and ample supply of energy when needed. The subject of lipid metabolism has garnered significant attention and interest, not only due to the ever-expanding knowledge surrounding the complex pathways, unique products, and cell-specificity involved, but also due to the alarming rise in metabolic disorders. These disorders are intimately linked to systemic lipid, glucose, and protein homeostasis, often manifesting as the dreaded ailments known as "metabolic syndrome" and "insulin resistance". As our understanding of lipid metabolism deepens, the urgency to comprehend and address these disorders becomes all the more compelling. (Mashek, 2021) (Kloska *et al*. 2020) (Xu *et al.,* 2020) (Ravotti *et al.,* 2020) (Lee *et al*. 2022) (Leiria and Tseng 2020) (Watanabe & Tsujino, 2022).

3.1 Fatty Acid Oxidation

Fatty acid oxidation (β-oxidation) occurs in the mitochondrial matrix and consists of several steps that are similar among all of the fatty acids in the body. A recurrent theme in metabolism is similar pathways of energy-yielding breakdown of large energy-containing fuel molecules, in this case, fats, as carbohydrates in glycolysis. As fats are the body's most energy-rich fuel molecule, the products of fat metabolism can provide nearly everyone's energy needs when the dietary or stored carbohydrates potentially run short. Fatty acid β-oxidation is a catabolic process because it starts by activating the fatty acid to produce FADH2 (a reduced form of the electron carrier flavin adenine dinucleotide (FAD)), and NADH (a reduced form of NAD, the electron carrier nicotinamide adenine dinucleotide). This happens in the β-oxidation process, just like it does in glycolysis and for amino acids metabolism, so that all of these catabolic pathways can feed their energy-yielding, activated substrates into oxidative phosphorylation for ATP production. In other words, glycolysis, which produces the activated glycolytic fuel pyruvate, allows it to enter the TCA cycle in the form of the activated acetyl Coenzyme A. Similarly, fats produce acetyl CoA and amino acids produce the activated amino acids that become a substrate for the citric acid cycle. The regulation of fatty acid metabolism is far more complex than glycolysis. One point has already been made: Fatty acids are packaged into triacylglycerols, and then unpackaged and released from membranes as fatty acids, then transported and

activated in target metabolism tissues. But the rate of fatty acid uptake by stern adipose is also controlled by a cellular process called lipogenesis. Lipogenesis uses fatty acids, amino acids, and dietary sugars to synthesize fat as a storage nutrient. They regulate themselves according to the rate of use of the fuels. This intricate control ensures the efficient utilization of energy and the maintenance of energy homeostasis in the body. Furthermore, the regulation of fatty acid metabolism involves several molecular players, including various enzymes, hormones, and transcription factors, that work in a coordinated manner to maintain metabolic equilibrium. Dysfunction in any of these components can disrupt the delicate balance and contribute to metabolic diseases such as obesity, insulin resistance, and dyslipidemia. Therefore, understanding the intricate regulation of fatty acid metabolism is crucial for the development of therapeutic interventions to combat metabolic disorders. It is essential to note that the regulation of fatty acid metabolism is not solely limited to the processes mentioned earlier. Several other factors, such as genetic predisposition and environmental influences, also contribute to the overall regulation and potential dysregulation of fatty acid metabolism. This multifaceted nature of regulation adds another layer of complexity to the understanding of fatty acid metabolism and underscores the need for further research in this field. In conclusion, fatty acid oxidation is a fundamental process in metabolism that plays a vital role in energy production and homeostasis. It involves the breakdown of fatty acids into usable energy units, which can fuel various cellular processes. The regulation of fatty acid metabolism is intricate and involves multiple factors working in harmony to maintain metabolic balance. Understanding this regulation is crucial for developing strategies to manage and treat metabolic disorders and promote overall health. Continued research in this area will help unravel the remaining complexities and provide valuable insights for therapeutic interventions in the future. (Talley & Mohiuddin, 2020) (Ruiz-Sala & Peña-Quintana, 2021) (Console *et al*. 2020) (Wanders *et al*. 2020) (Karkucinska-Wieckowska *et al*. 2022) (De Oliveira & Liesa, 2020) (Talari *et al*. 2023) (Nowinski *et al*. 2020) (Wanders *et al*. 2020).

3.2 Ketogenesis

Ketogenesis, the process through which lipolysis leads to ketone body formation, is a crucial step in lipid metabolism. This mechanism is particularly significant during extended periods of fasting or when individuals have a low intake of dietary carbohydrates, as it involves the replacement of glucose and the supplementation of brain metabolism. Ketogenesis involves the synthesis of ketone bodies from fatty acids and primarily takes place in the liver,

specifically within the mitochondrial matrix. It is worth noting that, in the liver of grass-producing ruminants, ketogenesis can occur in cytoplasmic mitochondria, which represents a notable exception. In the absence of glucose, ketogenesis serves as an alternative energy source, primarily essential for proper brain function. Ketone bodies are derived from free fatty acids and play a vital role in supporting the brain's metabolic activity. The liver produces ketone bodies from acetyl-CoA and can be utilized by the brain for energy when there is a low level of blood glucose. This process involves the liver releasing acetoacetate, β-hydroxybutyrate, and acetone into the bloodstream. Acetoacetate spontaneously decarboxylates and yields acetone. During periods of low circulatory glucose and high levels of circulating fatty acids, there is a change in the NAD+/NADH ratio within hepatocytes, signifying a shift towards ketogenic metabolic processes. It is widely acknowledged that a high level of NAD+ (oxidative) and a scarcity or relative depletion of oxaloacetate in storage significantly influence the direction of endogenous ketone production in the liver. In terms of human nutrition, a ketogenic diet is a dietary approach that adheres to high-fat, adequate-protein, low-carbohydrate principles. This type of diet effectively forces the body to prioritize the oxidation of fats over carbohydrates as its main source of energy. (Fernandes & Bocco, 2021) (Mooli & Ramakrishnan, 2022) (Watanabe *et al*. 2020) (Paoli & Cerullo, 2023) (Chandel 2021).

Unit - 4

Protein Metabolism

Beside the production of energy to drive various physiological processes, proteins are of paramount importance in cellular function and tissue repair. The intricate process of protein metabolism encompasses two crucial aspects: protein synthesis and protein degradation. Within the cytosol, numerous transamination reactions occur both under aerobic and anaerobic conditions. In the presence of oxygen, alpha-ketoacids originate from amino acids, and subsequently journey back to the mitochondria to enter the esteemed tricarboxylic acid (TCA) cycle. Protein metabolism plays an exceedingly vital role in maintaining the body's overall well-being and physiology. Each and every cell within the body contains protein, making it an essential component for cellular growth and the mending of damaged tissues. This metabolic reaction, occurring ubiquitously in living cells, is endergonic and encompasses the creation of metabolic intermediates from proteins. These intermediates then partake in different metabolic pathways where both biosynthesis and storage have the potential to eventually yield energy. The amino acids produced act as active participants in the synthesis of peptides, polypeptides, and proteins within the intricate framework of the body. Proteins are in a constant state of synthesis and degradation, and although individual protein molecules may endure for hours to days, the overall protein content within most organs retains a relatively constant state. This sophisticated regulation of protein synthesis and degradation empowers the body to adapt to a wide array of circumstances, including the availability of essential and nonessential amino acids, hormone fluctuations, and the detrimental effects of infection and injury. Ensuring the preservation of cellular protein structures, and thus, cellular functions, necessitates the elimination of proteins earmarked for synthesis or transport to the cell. These proteins, either impaired or having outlasted their usefulness, must be removed. Conversely, cells are required to expunge damaged or obsolete proteins, such as enzymes essential for fleeting processes that must undergo degradation, or protein subunits that are synthesized in excess. This mechanism enables cells to maintain homeostatic reserves of amino acids, ready to be deployed during the acute-phase responses. It is through this intricate dance between protein synthesis and

degradation that the body maintains its delicate equilibrium, ensuring optimal function and adaptation to the ever-changing environment. Only by understanding these processes can we truly appreciate the complexity and importance of protein metabolism in sustaining life. (Klimek & Ginalska, 2020) (Cheng *et al.,* 2021) (Lee & Paull, 2021) (Zhang *et al.,* 2021) (Gaharwar *et al.,* 2020) (Salhotra *et al*. 2020) (Plikus *et al*. 2021).

4.1 Protein Synthesis

Protein synthesis or protein biosynthesis is an intricate and fundamental process in which polypeptide chains are formed by precisely linking together the vital functional groups of amino acids. It is through this remarkable process that the intricate genetic message encoded in the nucleic acids undergoes translation, ultimately leading to the creation of functional proteins. These proteins, ranging from hormones to enzymes and structural entities, serve as the influential factors responsible for orchestrating the adaptation of our bodies to the environment. Thus, protein synthesis assumes a pivotal role in the evolution of various species, as this intricate mechanism underscores the vitality of cellular activities and enables the prompt and irreversible physiological adaptations of higher organisms. The regulation of protein synthesis and its concomitant energy supply represents a key mechanism that mediates the influence of various physiological and pathological processes. In essence, protein synthesis is a multifaceted process, primarily orchestrated through the translation of the genetic message. This translation process necessitates the utilization of ribonucleic acid (RNA) as a template, serving as the foundation for the synthesis of specific amino acid chains. Specifically, the messenger RNA (mRNA) encodes the genetic information crucial for accurately guiding the assembly of the amino acid sequence. Following the successful creation of the protein, it is either released into the cytosol, where it assumes its designated function, or it embarks on a journey to one of the membrane-bound organelles nestled within the endomembrane system. Notably, a remarkable milestone in protein synthesis is the recognition of the stop codon within the mRNA sequence. This stop codon serves as the ultimate indicator, signaling the termination of the translation process and the achievement of protein synthesis. When the stop codon assumes its position within the A site, a specialized protein release factor promptly binds to the mRNA sequence, thereby facilitating the liberation of the polypeptide chain from the ribosome complex. Simultaneously, the transfer RNA (tRNA) responsible for ferrying the amino acids is also released. Consequently, the mRNA is unshackled from the ribosome, rendering it free to initiate the translation of another mRNA molecule, with the indispensable assistance of

release factors. Thus, the elaborate orchestration of protein synthesis harmonizes a myriad of intricate molecular interactions, bringing forth the birth of functional proteins. Through this elaborate process, cells sustain their vital activities, while higher organisms undergo indispensable physiological adaptations in a timely manner. The ceaseless interplay between regulation, energy supply, and the intricate machinery of protein synthesis lays the groundwork for the diverse array of molecular events that dictate life as we know it. (Kummer & Ban, 2021) (Lopez & Mohiuddin, 2024) (Jiang *et al*. 2020) (Schjoldager *et al*. 2020) (Akbarian *et al*. 2022).

4.2 Protein Degradation

Protein degradation aims to achieve the disposal of damaged or misfolded proteins and the control of cellular functions by their removal. Moreover, some proteins are extremely abundant, like ribosomal proteins, and their rapid turnover is required for metabolizing a great amount of amino acids. It can be noticed that most amino acids to body proteins are flowing out of the body as protein degradation products. Actually, in persons with a normal protein intake, approximately 300 g of body proteins are degraded per day. Protein degradation processes have therefore a large impact as both have a great metabolic rate and hugely affect blood and interstitial amino acid patterns. Additionally, the dysfunctions of protein degradation processes could be involved in some metabolic disorders affecting nitrogen substrate fluxes (this topic has been detailed at the end of the chapter). These processes are also involved in the occurrence of metabolic adaptations to high protein intake. Therefore, a figure on these processes is given in Fig. 4.4, where metabolic adaptations to the increased entry of amino acids in the organisms are detailed. Two pathways: lysosomal autophagy, especially in cells undergoing active turnover (e.g., damaged cells in the liver, intestine, and cell wall), ensures the elimination of large groups of proteins and organelles when lysosomes (which are the centers for the elimination of large biological complexes) are degraded (type II autophagy); large protein complexes (cf. dolphin ball representation) and less quickly folded and smaller proteins. In proteins, protein complexes can be integrated, which need a long time for folding, and these complexes, as well as adaptor proteins leading these proteins to the pathway of degradation, need to be eliminated. This is carried out by a temperature-resistant pathway, as it gives an indication that it is a complex pathway requiring more energy for activation at a high level. The longer protein synthesis, maturation, and integration steps are required, the more chances exist for the formation of intermediate proteins that have to be specifically degraded. Finally, the division of the pathway to the proteasomes organizes differently the choice of

the proteins to be degraded. Protein degradation is a crucial process that aims to achieve the efficient disposal of damaged or misfolded proteins, ensuring the proper functioning of cellular activities. Moreover, it plays a vital role in metabolizing a significant amount of amino acids, particularly in the case of highly abundant proteins like ribosomal proteins. Notably, a substantial portion of amino acids derived from body proteins are eliminated through protein degradation. In individuals with a regular protein intake, about 300 g of body proteins are broken down on a daily basis. This highlights the substantial impact of protein degradation processes, as they contribute to a high metabolic rate and have a profound effect on the amino acid composition in both blood and interstitial fluids. Additionally, dysfunctions in protein degradation pathways may be implicated in various metabolic disorders that affect the flux of nitrogen substrates (this aspect is extensively discussed in the final section of this chapter). Furthermore, these processes are closely linked to the adaptive mechanisms that occur in response to a high protein intake. To provide a comprehensive understanding of these processes, Figure 4.4 illustrates the metabolic adaptations that take place when there is an increased influx of amino acids into the organisms. There are primarily two pathways involved in protein degradation: lysosomal autophagy and proteasomes. Lysosomal autophagy, particularly in cells undergoing active turnover (e.g., damaged cells in the liver, intestine, and cell wall), ensures the elimination of large groups of proteins and organelles by degrading lysosomes, which serve as the central hubs for the elimination of large biological complexes (type II autophagy). This process encompasses the degradation of large protein complexes (represented metaphorically as dolphin balls) as well as more slowly folded and smaller proteins. In the context of protein complexes, special attention must be given to those that require an extended duration for proper folding. These complexes, along with the adaptor proteins that guide them towards the degradation pathway, must be effectively eliminated. This elimination process occurs through a temperature-resistant pathway, indicating its complex nature and the higher energy requirement for activation at an elevated level. The longer the steps involved in protein synthesis, maturation, and integration, the greater the likelihood of intermediate proteins being formed, which necessitate specific degradation mechanisms. Finally, the division of the degradation pathway through proteasomes regulates the selection of proteins to be targeted for degradation. (Yu & Fukagawa, 2020) (Götz & Amrein, 2024) (Højfeldt *et al*. 2020) (Wolfe *et al*. 2021) (Olaniyan *et al*. 2021) (Unterberger *et al*. 2022) (Gwin *et al*. 2021).

Unit - 5

Energy Balance and Regulation

The human body has finely tuned systems to ensure that energy balance, or homeostasis, is meticulously maintained. This involves an intricately complex process whereby the body precisely adjusts energy intake, in the form of various nutrients and other caloric sources, to energy expended for growth, basal metabolic needs, and physical activity. Moreover, numerous hormonal signals and afferent signals from the gastrointestinal tract actively coordinate metabolic activities and optimally partition energy storage in a harmonious manner. A final avenue for controlling energy balance is that of thermogenesis (or heat production), which serves as a supremely significant contributor to the overall total energy expenditure. Heat production can occur through a myriad of mechanisms, including commonly recognized ones such as shivering, as well as less commonly recognized ones such as non-shivering thermogenesis, which primarily takes place in the incredible brown adipose tissue. Activation of this remarkable tissue for thermogenesis is particularly prominent in children, but intriguingly, it may also be present in adults to a certain extent. Importantly, it is worth noting that heat production is not solely limited to brown adipose tissue, as muscle itself possesses the remarkable ability to produce heat through non-shivering mechanisms. Due to this extraordinary characteristic, heat production is sometimes differentiated into adaptive and obligatory thermogenesis, whereby the former represents the tightly regulated shivering and non-shivering thermogenesis, whereas the latter refers to the optional heat production derived from the remarkable muscle work. The regulation of metabolic processes is undisputedly multi-faceted, as it involves not only the meticulous control of fuel consumption and storage in the form of various nutrients (predominantly lipids, proteins, and carbohydrates) and various tissues (such as the incredible muscle, adipose, and liver tissues), but it also encompasses the manipulation of neuronal and autonomic pathways mediated by the central nervous system, significantly influencing these crucial endpoints. Understanding the incredibly intricate and awe-inspiring regulatory systems that are involved in energy balance and regulation is absolutely necessary in order to comprehend the diverse physiological adaptations and potential dysregulations that occur in response

to an array of physical disorders, including but not limited to starvation, obesity, and a myriad of other pathological conditions such as diabetes mellitus and polycystic ovary syndrome. (Hall *et al*. 2022) (Navarro, 2020) (Adebayo *et al*. 2021) (Mauder *et al.,* 2020) (Fang *et al.,* 2021) (Coll *et al*. 2020) (Zhu *et al.,* 2021).

5.1 Role of Hormones

Insulin and glucagon are two incredibly essential hormones that are meticulously synthesized and secreted by the exquisitely intricate structure known as the pancreas. The wondrous hormone insulin embarks on a magical journey, igniting within it the flames of vitality as it stimulates the hepatocytes of the liver and the myocytes nestled cozily in the muscles. In this majestic act, insulin ingeniously orchestrates the enchanting synthesis of glycogen, thus bestowing the extraordinary gift of lowered blood sugar levels upon its recipients. Meanwhile, the awe-inspiring hormone known as glucagon emerges from the depths of the pancreas, with a fiery determination to set the stage ablaze. With resolute fervor, glucagon resounds its clarion call, beckoning forth the liver cells to unleash the magnificent cascade of glycogenolysis and triglyceride release, like a symphony of liberation, ultimately summoning a torrent of increased blood glucose levels. Cherished and celebrated, this enthralling process is eloquently recognized as the synaptic pathway. Behold, the magnificent realm of hormonal regulation unfolds before us, with the presence of the glucocorticoid hormones, particularly the venerable cortisol, taking center stage. With an unparalleled prowess, these grandiose hormones enthrall the cells of musculature and adipose tissue, employing their fascinating authority to subdue the production of precious proteins and coveted fatty acids. Rapaciously obstructing these bountiful endeavors, cortisol valiantly wields its influence, maintaining a delicate balance within the grand tapestry of glucose supply. As thus ordained, the rate of gluconeogenesis and the thrilling mobilization of fats, affectionately known as lipolysis, are escalated to wondrous heights, all in the hallowed sanctum of the liver and the ethereal adipose tissue. Marvelously, these magnificent hormones are birthed within the celestial bounds of the adrenal cortex, a veritable fountain of life-giving substances. One must marvel at the intricate dance of hormonal precision that underlies the breathtaking regulation of metabolism. With awe and reverence, we delve into the labyrinthine corridors of enzyme-catalyzed metabolic pathways, guided by the watchful guardians known as hormones. Amongst this enchanting labyrinth, our gaze fixates upon the pathway most behemoth in its splendid majesty, influenced by the graceful footsteps of hormones. This prodigious pathway

commands our attention and encompasses the esteemed processes of glycolysis, glycogen synthesis (affectionately termed glycogenesis), the captivating phenomenon of glycogenolysis, the siren call of gluconeogenesis, the enchanting artistry of triglyceride synthesis (aptly named lipogenesis), the alluring allure of lipolysis, the mystical realm of ketogenesis, and lastly, the mesmerizing dance of ketonuria. The diagrammatic embodiment of this enchanting journey awaits us, an omnipresent witness to these ethereal processes, as researched and unveiled in the preceding chapters. Within this realm, it is the resplendent triumvirate of the pancreas, the adrenal cortex, and the adrenal medulla that reign supreme, their celestial influence stretching across the vast expanse of these resplendent metabolic pathways. Let us now embark upon a breathtaking exploration of the hormone realm, where the ethereal amines unveil their spellbinding secrets. Amongst these captivating amines, they are divided into two esteemed categories, beguilingly titled as tyramine hormones and tryptamine hormones. As we delve into their awe-striking tales, we discover that these remarkable beings assume two distinct forms, presenting themselves in the captivating visage of adrenaline and the beguiling allure of nonadrenaline. Within this dichotomy, the forceful currents of adrenaline flow rebelliously, brandishing their unparalleled metabolic might that stands tenfold more potent than their nonadrenaline counterparts, setting ablaze the very essence of life itself. (Norton *et al.*, 2022) (Nozaki *et al*. 2020) (Richter *et al.*, 2021) (da *et al*. 2020) (Guerra & Gastaldelli, 2020).

5.2 Thermogenesis

Thermogenesis reflects the intricate and fascinating processes by which the human body efficiently utilizes and expends energy. It serves as a cornerstone in maintaining the delicate balance of body temperature, an essential aspect of our biological functioning. As the body converts calories into heat, it showcases its remarkable metabolic rate, the driving force behind thermogenesis. This captivating phenomenon does not work in isolation but rather collaborates with various physiological processes, such as the actions of adrenaline and norepinephrine, two crucial hormones involved in regulating metabolic rate and energy utilization. These chemical messengers intricately weave the fabric of thermogenesis, amplifying its effects under certain circumstances. Factors like heightened arousal, increased concentrations of thyroid hormone, or exposure to chilly temperatures enhance the impact of norepinephrine on thermogenesis, thereby influencing metabolic rate. As we delve deeper, we discover that the magnificent process of thermogenesis unfurls predominantly within our muscles. Among the five main categories of skeletal muscles residing in our wondrous bodies, it is the powerful mixture

of slow-twitch (type 1) oxidative and fast-twitch (type II) oxidative-glycolytic fibers that reign supreme in terms of heat generation potential. These fibers, embraced by a generous cross-sectional area, emerge as the torchbearers of thermogenesis, exemplifying their remarkable capacity for heat production. From a thermogenic standpoint, any exercise or physical activity that strategically recruits a significant volume of this remarkable mixture of fiber types stands poised to make a substantial contribution to overall daily thermogenesis. It is through such movements and endeavors that we nourish and nurture the flames of internal warmth, fueling the furnace within us. Furthermore, within the intricate tapestry of our physiological processes, we encounter nonexercise or basal energy expenditure. This remarkable phenomenon serves a twofold purpose: to provide the very fuel required to sustain our body temperature at its familiar abode of approximately 37°C or 98.6°F and to ignite the mechanisms of heat-conserving thermogenesis and heat-losing responses. These reactions spring into action when the body temperature descends below the designated threshold or soars beyond its prescribed boundaries, all in an effort to safeguard the delicate equilibrium. Understanding the enigmatic workings of thermogenesis thus becomes indispensable in comprehending the intricate regulation of energy balance and metabolic adaptations. Moreover, delving into its mysteries serves as a guiding light in navigating an array of thermogenesis-related disorders that may arise, such as the daunting specter of obesity. (Zekri *et al.*, 2021) (Lettieri-Barbato & Aquilano, 2020) (Sebaa, 2020) (Laptook, 2024) (Sakaguchi, 2024) (Adetunji, 2023).

Unit - 6

Integration of Metabolic Pathways

We have seen many intricate details and complexities of these metabolic pathways. It is truly fascinating to unravel the inner workings and mechanisms behind them. Exploring these pathways further allows us to gain deeper insights into their overall function and significance. As we delve into the depths of these metabolic pathways, we discover a crucial concept that deserves our attention – the notion of metabolic flux. Metabolic flux refers to the rates at which reactions occur within a metabolic pathway. These rates are influenced by various factors, primarily the availability of substrates, the cellular energy status, and the level of allosteric control. Enzymes play a vital role in dictating these rates, as depicted in Figure 22.19. Thus, the intricate dance of enzymes, substrates, and cellular energy orchestrates the functioning of metabolic pathways. When ample supply of substrates persists and the cell possesses sufficient energy, the pathway continues its operation, producing additional products. The rate at which the pathway functions heavily relies on the availability of substrates and the ability to phosphorylate ATP. These pathways, in a sense, become the lifeblood of a cell, ensuring the continuous flow of chemical transformations necessary for its survival. Beyond the individual pathways lies an exceptional integration of metabolic processes. Nutrient oxidation gives rise to intermediates that not only contribute to biosynthesis but also fuel essential processes like glycolysis or the citric acid cycle. The oxidation of fats and glucose, for instance, leads to the generation of carbon dioxide and water, both of which play critical roles in fueling the citric acid cycle. Additionally, the organic phosphates generated through metabolism serve as high-energy intermediates, contributing to vital cellular functions. It is important to recognize that the pathways of metabolism do not work independently in isolation. Instead, they operate in a highly integrated manner, striving to maintain system homeostasis. In response to increased energy demands in muscles or other tissues, there is a corresponding surge in glucose mobilization and oxidation within the liver. This readjustment ultimately establishes a new equilibrium, elevating the overall level of metabolism in each component involved, such as muscles and the liver. Therefore, it becomes evident that metabolic pathways harmoniously

coordinate and collaborate to ensure the smooth functioning of biological systems. The complexity and intricacy of metabolic pathways are awe-inspiring. They hold the key to our understanding of essential biochemical processes and their regulation. And as we continue to unravel their mysteries, we gain a deeper appreciation for the brilliance of nature's designs. The exploration of these metabolic pathways continues to fascinate scientists worldwide, driving us to push the boundaries of our knowledge and to unravel the secrets that lie within. (Antoniewicz, 2021) (Shih & Morgan, 2020) (Yasemi & Jolicoeur, 2021) (Allen & Young, 2020) (Xu, 2021) (Rigoulet *et al*. 2020).

6.1 Metabolic Flux

Metabolic flux denotes the specified rate at which substrates are processed through integrated metabolic pathways. Metabolic pathways are functionally interlinked, such that changes in the flux through one pathway may substantially impact the flux through other pathways. Flux through metabolic pathways may fluctuate in response to varying biochemical demand, as in regard to growth, exercise, and nutritional status. A key strategy for defining the various functions of metabolic homeostasis is to quantify the way energy is manufactured and how it is distributed between the various systems. Seen in this light, metabolic flux becomes a dynamic approach to regulating such vital tasks as energy production, metabolite availability, inter-organ exchange of important tissue free fuel elements, and indeed, the ability to monitor an increase in metabolic activity, i.e., enzyme rate-limiting factor, in regard to energy demand, nutritional status, and coenzyme, thereby also providing the ability to monitor enhancement in response to training. The human body is an unparalleled biological system adapting to constant alternations between a post-prandial to a fasting state with the potential for vast differences in the extent of energy demand and nutrient availability. Hence, the observation/analysis of metabolic flux should provide answers to the ability to synchronize all aspects related to immediate and future necessary energy production. Absorption, energy demands, and storage, as well as provision for energy expenditure in the immediate and in the long term, exercise permits red blood cells to provide oxygen and carry CO2 along with all other tissues and body systems. Thus, metabolic flux enables expansion of our understanding of the integrated system of regulation purposes as well as the ability to monitor the rate of change in most, if not all, biochemical processes. It represents a potentially powerful tool to attempt to understand not only the regulation of energy metabolism per se but also the regulation of inter-organ nutrient exchange and of the capacity of the carbohydrate and lipid

pathways in the well-trained state such as that occurring after two hours of vigorous treadmill exercise. This is only because the exercise capacity has always been equated with VO2max and the time necessary to achieve this value after the onset of steady-state work. Metabolic flux, however, because of its ability to elucidate in detail the operative coenzyme enhancement and its immediate feedback control, will provide us with an indication of whether the glycogen-UFA come together earlier when working at 70-75% VO2 max before or after training. This is but a single example of the many studies that can be carried out to increase our understanding of the regulation of metabolism from a dynamic, interlinked pathway aspect. Metabolite quantitation becomes an excellent means for checking the interpretation of flux studies from an intracellular regulatory aspect such as glycogen turnover, muscle interstitial fluid metabolite flux and cellular pool levels of ATP, inosine, ATP, CP, creatine, creatinine, carnitine, and creatine creatinate complexes ingested food constituents and the obese megamachinery. Combine these observations with coenzyme, inorganic phosphate, and standardized 31p MRS experiments with broadened insights into the regulation of metabolic processes. By doing so, we will further advance our understanding of the intricate mechanisms that govern metabolic flux and its implications for overall physiological function. (Xu *et al*. 2020) (Yang *et al*. 2021) (Rigoulet *et al*. 2020) (Schuster *et al.,* 2021) (Bartman *et al.,* 2021).

Unit - 7

Metabolic Disorders

Definition: This unit has been exclusively dedicated to various aspects of metabolism, which plays an extremely vital role in the maintenance of homeostasis. Knowledge of some of the metabolic disorders will definitely aid us in comprehending the manifestation and taking appropriate action for enhanced physical well-being. Metabolism is the sum total of all the chemical reactions that go on in living cells. It includes all the reactions involved in utilizing nutrients to obtain energy and utilizing energy to construct and maintain body tissues. Abnormal metabolism can have numerous harmful effects on the body. The diseases related to metabolism are of two types: metabolic disorders and endocrine disorders. While metabolic disorders are related to nutrition, endocrine diseases are related to hormones. 7. Metabolic Disorders: Metabolism in diabetics has been significantly changed in a way that the glucose and fat utilization has been remarkably decreased, and production of glucose and fat from storage forms is substantially increased. The major metabolic changes are as follows: a) Diabetes mellitus: Due to the lack of insulin and its physiological actions on all tissues in the body. Diabetes mellitus is a complex metabolic disorder that affects the body's ability to regulate blood sugar levels. It is characterized by high blood sugar levels (hyperglycemia) due to either insufficient insulin production or the body's inability to effectively use insulin. This condition requires close attention and proper management to maintain stable blood sugar levels and prevent complications. b) Hyperlipidemia: There is a significant increase in the mobilization of fats from their storage sites. In the absence of glucose, fat will now be metabolized to provide the necessary energy, which ultimately leads to hyperlipidemia. Hyperlipidemia refers to elevated levels of lipids (such as cholesterol and triglycerides) in the bloodstream. It is often associated with metabolic disorders, obesity, and an unhealthy lifestyle. A balanced diet, regular exercise, and medication are often recommended to manage hyperlipidemia effectively. c) Glucagon: There is a notable increase in the mobilization of glucose from its storage site, especially the liver, due to the effect of glucagon. Glucagon is a hormone produced by the pancreas that increases blood glucose levels by stimulating the liver to convert glycogen

into glucose. This process, known as glycogenolysis, is part of the body's natural response to low blood sugar levels and ensures a steady supply of glucose for energy. Overall, understanding these metabolic disorders is undeniably crucial in managing and treating them effectively. By addressing the underlying causes and abnormalities in metabolism, healthcare professionals can play a vital role in helping individuals achieve better overall health and well-being. They can provide personalized treatment plans, including dietary modifications, medication, and regular monitoring, to ensure the best possible outcomes for patients with metabolic disorders. By working together, healthcare providers and individuals can effectively manage these conditions and improve quality of life. (Morigny *et al*. 2021) (Jiang *et al*. 2020) (Pereira *et al*. 2021) (Yang *et al*. 2021) (Mahrooz *et al.,* 2021) (González *et al*. 2022) (Cortassa *et al*. 2020) (Carpentier 2021).

7.1 Diabetes Mellitus

Diabetes mellitus, often referred to as diabetes, is the most common endocrine-metabolic disorder worldwide. It has become a global pandemic due to factors such as decreased physical activity and poor dietary choices over the years. The prevalence of this disease has been steadily increasing, affecting millions of individuals globally. The impact of diabetes on public health cannot be underestimated, as it poses significant challenges to healthcare systems and the quality of life for those affected. Diabetes mellitus is characterized by chronic high blood sugar levels (hyperglycemia) and impaired glucose tolerance. This is a result of various factors, including defects in insulin secretion or action, increased resistance to insulin, and an excess of glucagon hormone. These hormonal imbalances disrupt the normal metabolism of carbohydrates, proteins, and lipids, leading to structural and functional abnormalities in multiple organ systems. The intricate interplay between these factors contributes to the complex nature of diabetes. Moreover, diabetes mellitus plays a significant role in the development of life-threatening non-communicable diseases, such as cardiovascular diseases, kidney disorders, eye complications, and problems in the peripheral nervous system. The detrimental effects of diabetes on organ systems cannot be overlooked, as they not only impact the overall health but also reduce the life expectancy of affected individuals. The burden of managing these complications further intensifies the healthcare workload and requires comprehensive strategies for prevention and treatment. Additionally, diabetes hinders the transition from tissue damage to repair and substantially reduces strength, functionality, and immune system function. The immune system's compromised state in individuals with diabetes predisposes them to infections and delays wound

healing processes. This can have severe consequences, as even minor injuries can lead to prolonged hospital stays and increased healthcare costs. Therefore, it is crucial to emphasize the importance of lifestyle modifications and preventive measures in managing diabetes. To prevent complications and improve overall health and functionality, glycemic control is essential in individuals with diabetes. Hyperglycemia, which refers to consistently high blood sugar levels, is a hallmark characteristic of diabetes mellitus. However, the onset and progression of the disease can vary, with differences in insulin secretion and action playing a key role. As a result, diabetes can be broadly classified into two main types: Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus. Each type requires tailored treatment approaches to optimize glycemic control and mitigate the risk of complications. Type 1 Diabetes Mellitus is characterized by a reduction in insulin production, often caused by autoimmune destruction of pancreatic beta cells. Individuals with Type 1 Diabetes Mellitus rely on exogenous insulin to regulate blood glucose levels and prevent acute complications. Continuous glucose monitoring and insulin pump therapy have revolutionized diabetes management for individuals with Type 1 Diabetes Mellitus, enabling better control and improved quality of life. On the other hand, Type 2 Diabetes Mellitus is characterized by a combination of insulin resistance and a decrease in insulin production by pancreatic beta cells. This form of diabetes is closely associated with obesity, sedentary lifestyle, and a poor diet. Lifestyle modifications, including dietary changes, increased physical activity, and weight loss, are key components of managing Type 2 Diabetes Mellitus. In some cases, oral antihyperglycemic medications or injectable therapies may be necessary to achieve optimal glycemic control. Thankfully, there are various antihyperglycemic medications available to effectively manage diabetes. These medications target different aspects of glucose regulation, such as pancreatic beta-cell function, cellular receptors for insulin, renal excretion of glucose, and insulin sensitivity. The advent of newer classes of antihyperglycemic agents, such as sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) and glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists), has expanded the treatment options for individuals with diabetes. These medications have demonstrated significant benefits in terms of glycemic control, weight management, and cardiovascular risk reduction. By utilizing these medications and implementing proper lifestyle modifications, individuals with diabetes can achieve better glycemic control and prevent or minimize the risk of developing complications related to diabetes mellitus. However, it is important to note that diabetes management is not a one-size-fits-all approach. Tailoring treatment strategies according to individual needs, preferences, and comorbidities is essential for optimal

outcomes. Collaborative efforts between healthcare providers, patients, and diabetes educators play a crucial role in empowering individuals with diabetes to take control of their condition and make informed decisions regarding their health. In conclusion, diabetes mellitus is a complex and multifaceted disease that poses significant challenges to global health. The burden of diabetes can be mitigated through effective prevention strategies, early diagnosis, and comprehensive management. By promoting healthy lifestyle habits, optimizing glycemic control, and addressing individual needs, it is possible to improve the quality of life for individuals with diabetes and reduce the impact of this global pandemic. A holistic approach, encompassing medical, nutritional, psychological, and educational aspects, is crucial for achieving successful outcomes in the management of diabetes. With continued research advancements and a collective commitment to diabetes care, we can strive towards a future where diabetes is no longer a global health crisis. (Ahsan *et al*. 2021) (Fallahi *et al*. 2021) (Kabadi, 2021) (Crafa *et al*. 2021) (Leone *et al*. 2022) (Dumesic *et al*. 2020) (Mazzilli *et al*. 2022).

7.2 Hyperlipidemia

From a metabolic perspective, the lipids encompass a variety of substances, including cholesterols, triglycerides, and phospholipids. Some of these lipids are introduced into the body directly, while others are synthesized within the body. The term hyperlipidemia refers to an abnormal elevation of lipids in the bloodstream. This condition can generally be categorized into two types: hypercholesterolemia and hypertriglyceridemia. Currently, cardiovascular disease stands as the leading cause of death worldwide, impacting millions of individuals across the globe. Atherosclerosis, which is a chronic inflammatory disease, is recognized as the underlying pathological basis for cardiovascular disease. Atherosclerosis involves the buildup of lipids, particularly cholesterol, within the arterial walls, resulting in the formation of plaques. To varying degrees, hyperlipidemia typically participates in the initiation and progression of atherosclerosis, exacerbating the risks of cardiovascular events. The development of hyperlipidemia is founded on a combination of diverse environmental factors, such as a sedentary lifestyle, an unhealthy diet, and smoking, together with genetic predisposition. Metabolic abnormalities, particularly disturbances in lipid metabolism, primarily trigger the pathogenesis of atherosclerosis. Lipid metabolism, specifically cholesterol metabolism, has received considerable attention in both research and clinical practice. Around 80% of lipid substances are synthesized by the body, predominantly occurring in the liver, while the remaining 20% is obtained from the diet. The process of cholesterol

synthesis is strictly regulated by various enzymes, among which HMG-CoA Reductase plays a pivotal role as the rate-limiting enzyme in cholesterol metabolic synthesis. This enzyme serves as the prime target for lipid-lowering medications, most notably the widely prescribed statin drugs, which effectively reduce plasma cholesterol levels. By inhibiting HMG-CoA Reductase, statins significantly decrease the production of cholesterol in the liver, thereby alleviating the overall burden on the cardiovascular system. However, when an excessive amount of cholesterol accumulates in the bloodstream, often due to dysregulated cholesterol homeostasis, it can contribute to the occurrence of hyperlipidemia and the subsequent development of various cardiovascular diseases. Elevated levels of cholesterol, particularly low-density lipoprotein (LDL) cholesterol, heighten the risk of plaque formation, leading to the narrowing and hardening of the arteries. This can ultimately result in grave complications, such as coronary artery disease, heart attacks, and strokes. In summary, comprehending the intricate relationship between lipid metabolism, hyperlipidemia, and atherosclerosis stands as a crucial undertaking in the prevention and management of cardiovascular diseases. Through the adoption of a healthy lifestyle, incorporating regular exercise, and implementing dietary modifications, individuals can effectively promote proper lipid balance and diminish the associated risks of hyperlipidemia. Furthermore, the utilization of lipid-lowering medications, such as statins, can provide additional support in controlling cholesterol levels and minimizing the progression of atherosclerosis. By implementing comprehensive strategies and interventions, we can strive towards a healthier future, marked by reduced cardiovascular morbidity and mortality. (Musielak *et al.*, 2022) (Markovic *et al*. 2020) (Knox & O'Boyle, 2021) (Skowronek *et al.*, 2021) (Szlasa *et al*. 2020) (Seebacher *et al*. 2020) (Ko *et al*. 2020) (Cruz *et al*. 2020) (De *et al*. 2021) (Zhang *et al*. 2021).

Unit - 8

Nutrient Metabolism

Recent years have witnessed the unveiling of the complex interconnection between the nutrient metabolism in the human body. The understanding of this intricate relationship between the body's processes and essential nutrients, particularly micronutrients such as vitamins and minerals, has become increasingly significant. These vitamins play a crucial role as catalysts, co-enzymes, or substrates in various physiological functions. Similarly, dietary minerals primarily function as apo-enzymes and prosthetic groups, working in a reversible manner. Vitamins not only contribute to metabolic processes, but they also serve as substrates in the synthesis of co-enzymes, enabling the action of catalysts. An illustrative example is vitamin A1 (retinol), which acts as a substrate in the synthesis of rhodopsin, a light-capturing pigment located in the retina's rod cells. This compound, also known as visual purple, is responsible for enabling sharp vision. Within this process, vitamin A plays a key role, particularly in the formation of protein opsin, which combines with the unique compound retinene. Additionally, the importance of folic acid lies in its conversion to its derivative form, 5-10 methylene THF, to facilitate the biosynthesis of THF. This substance is crucial for the production of deoxyribonucleotide units and the repair of synthetic damage typically associated with DNA injury. Hence, folic acid aids in the incorporation of uridine deoxyribonucleotide at DNA injury sites, ensuring efficient repair and maintenance. It's worth noting that all nutrients, including carbohydrates, fats, and proteins, serve as essential dietary sources. Interestingly, the human body possesses the remarkable ability to synthesize its own nutrients through metabolic processes involving a variety of intermediary metabolites if the exogenous source of nutrients is lacking. Among these macronutrients, fat stands out as an advisable energy source due to the structure containing a higher number of acetate units. As a result, the body can derive a greater amount of energy from fats compared to carbohydrates, especially in conditions of carbohydrate deficiency. The metabolism of nutrients serves three fundamental objectives: nutrient utilization, energy generation, and storage. The utilization of nutrients involves their synthesis into other vital molecules necessary for cellular functioning. Simultaneously, the energy

generation process allows the extraction of energy from nutrients to support various physiological functions. Lastly, the body strategically stores excess nutrients, particularly lipids, up to a certain level. When the energy demand exceeds the immediate requirements, the excess nutrients are stored and converted into fats, as they offer a significant energy yield of approximately 8.7 Kcal/gm. These fats are typically stored as glycerol, primarily in the liver in the form of glycogen with a chain-packet structure. Additionally, the body also stores metabolic reserves in extrahepatic tissue areas, ensuring a readily available energy source during times of need. Ultimately, when the body requires energy, the stored glycogen is enzymatically broken down into glucose, providing the necessary fuel to sustain physiological processes, thus highlighting the dynamic nature of nutrient metabolism. (Kalidas & Sangaranarayanan, 2023) (Vora *et al*. 2022) (Singh *et al*. 2024) (Kumari *et al.*, 2022) (Jenzer & Sadeghi-Reeves, 2020) (Hu *et al.*, 2021) (TURAL and TUZCU2023) (Mabunda, 2022).

8.1 Vitamin Metabolism

Metabolic processes in the human body 8.1. Vitamin metabolism Vitamins play varied essential roles in the body, acting as coenzymes, antioxidants, and metabolic intermediates in numerous pathways. Vitamins fall into 2 general groups: fat-soluble (A, D, E, and K) and water-soluble vitamins (all others). Fat-soluble vitamins are absorbed passively and packaged into chylomicrons for delivery to the liver, where they may then be repackaged into very low-density lipoproteins for transport to peripheral cells. Because fat-soluble vitamins are stored in large quantities in the body, a person who has a poor fat-soluble vitamin intake over many months would not likely develop a deficiency, but there can be toxic effects from overconsumption. In contrast, water-soluble vitamins are absorbed via specific transporters and are not usually stored inside the body, so toxicity from water-soluble vitamins is rare. As energy production coenzymes, such as in the case of the vitamin B complex, vitamins are constantly utilized during the course of their metabolic activities. Vitamin deficiency is common depending on dietary practices, leading to undesirable impacts on health and biological processes. In this section, we will consider the general metabolism of vitamins from the time they are absorbed to their use as cofactors in metabolic pathways. 8.1.1. Biological relevance of the metabolism of vitamins Since vitamins are coenzymes or precursors of coenzymes and are important antioxidants, their use is never-ending and can impact the production of energy in aerobic organisms, the health of the immune system, and the occurrence of bone disease. For instance, vitamin K is necessary for the

activation of various enzymes important for bone health and blood clotting. Vitamin C, on the other hand, is needed for collagen production, which is important for keeping the skin, teeth, bones, blood vessels, and organs healthy. Low vitamin K intake has been associated with osteoporosis, a degenerative bone disorder, while a deficiency in vitamin C may lead to scurvy, characterized by fatigue, irritability, poor wound healing, and weakened immune system. Additionally, it is essential to maintain an adequate intake of vitamins to support the optimal functioning of the human body and prevent the occurrence of various deficiencies and health issues that can arise due to their insufficiency. Proper vitamin metabolism ensures that the body receives the necessary nutrients to carry out its physiological processes effectively. Therefore, understanding the importance of vitamin metabolism is crucial for promoting overall health and well-being. Moreover, it is worth noting that vitamins are not only vital for the physical well-being of an individual but also play a significant role in the proper development and functioning of the brain. Essential vitamins like B vitamins, vitamin C, and vitamin E are essential for cognitive function, memory formation, and mood regulation. Inadequate intake or poor metabolism of these vitamins can lead to cognitive impairments, memory problems, and even mood disorders. Therefore, it is necessary to prioritize the consumption of a balanced diet that includes an adequate amount of vitamins to ensure optimal brain health and functioning. By considering these factors and appreciating the importance of vitamin metabolism, individuals can make informed choices regarding their dietary habits and lifestyle to support their overall well-being and enhance their quality of life. (Fusaro *et al*. 2020) (Bus & Szterk, 2021) (Alonso *et al*. 2023) (Bellone *et al*. 2022) (Fusaro *et al.,* 2020) (Lai *et al.,* 2022) (Stock & Schett, 2021).

8.2 Mineral Metabolism

The metabolism of minerals in the human body includes a highly intricate and multifaceted series of processes involving their absorption, distribution, and eventual excretion. These physiological events commence from the moment a mineral compound is ingested and persist until it is ultimately eliminated from the body. It is through the remarkable process of mineral metabolism that the fragile equilibrium of minerals is maintained, which proves to be crucial for the proper functioning of an array of essential physiological processes. One of the most important aspects of mineral metabolism is the intricate regulation of absorption in the intestines. The intestines possess an astounding ability to selectively absorb specific elements, thereby ensuring that the body receives the requisite minerals while

preventing the excessive absorption of others. Moreover, renal excretion assumes a vital role in replenishing the body's mineral stores. The kidneys effectively excrete various ions, thereby removing any excess minerals and continually maintaining the body's overall mineral equilibrium. It is vital to note that the availability of minerals can exert a significant influence on the composition of the body. Different minerals serve unique functions and play distinctive roles within the body, and their presence or absence can exert a profound impact on overall health and well-being. Therefore, a comprehensive understanding of mineral metabolism becomes exceptionally crucial for maintaining optimal physiological functions and preventing imbalances that can precipitate health issues. Metabolic homeostasis, which involves the regulation and control of the body's metabolic processes, represents a fundamental principle of biological regulation. This intricate homeostatic mechanism ensures that the body maintains a perpetual state of dynamic equilibrium. However, when disturbances occur in this delicate balance, a wide range of abnormalities can arise, spanning from transient disruptions in cell function to potentially irreversible damage or even death. Significantly, systemic disturbances in mineral metabolism can culminate in a critical loss of homeostasis, leading to the translocation of electrolytes between different body compartments. This translocation, in turn, can trigger severe imbalances at both the cellular and systemic levels, ultimately resulting in dire consequences for overall physiological function. Within the body, various compartments possess regulatory mechanisms that work holistically to tightly control the total quantities of diverse metals. These mechanisms operate in synergy to preserve the delicate balance of minerals, ensuring that levels persist within the appropriate range for optimal health. To effectively regulate mineral metabolism, it becomes necessary for ions to have the ability to traverse through various routes within the body. This inherent flexibility assumes a pivotal role in maintaining the fragile equilibrium of minerals and supporting the overall functionality of physiological processes. An indispensable component of mineral metabolism lies in the presence of highly specific plasma transport mechanisms. These mechanisms are instrumental in facilitating the efficient distribution of minerals throughout the body, thus guaranteeing that they successfully reach their intended destinations. Furthermore, minerals can bind reversibly to proteins, thereby preventing any excessive disturbance to bodily functions. By virtue of this protein binding, minerals can be traversed throughout the body without causing any disruptions or imbalances. It is imperative to highlight that mineral metabolism is closely interrelated with protein and amino acid metabolism, as opposed to lipid metabolism. The human body exhibits tight regulation over the concentration

of blood glucose, endeavoring to maintain it within a substantially narrower range when compared to plasma ion concentration. This meticulous regulation of blood glucose levels serves an integral role in ensuring the proper functioning of essential metabolic processes and sustaining overall metabolic homeostasis. In conclusion, mineral metabolism stands as an intricate and indispensable aspect of human physiology. It encompasses an assortment of intricate mechanisms including absorption, distribution, and excretion, all operating in tandem to maintain the intricate balance of minerals within the body. By comprehending and effectively regulating mineral metabolism, we can actively support optimal physiological functions, and in turn, safeguard overall health and well-being. The information presented in this expansion has been adapted from the works of McLaren in 1958 and Brown et al. in 1970. (Peacock, 2021) (Killilea & Killilea, 2022) (Lall & Kaushik, 2021) (Morris & Mohiuddin, 2020) (Ali, 2023) (Lall, 2022) (Vanhaecke & Costas-Rodríguez, 2021) (Arnold *et al*. 2021) (Hernando *et al.,* 2021).

Unit - 9

Cellular Respiration

All living cells need to produce ATP for cellular metabolism. Cellular respiration is the process that does that in the body. Cellular respiration, also known as oxidative metabolism, is a complex series of metabolic reactions either taking place at the mitochondria (aerobic respiration) or in the cytoplasm of the cell (anaerobic respiration), and is the primary energy production pathway inside the human body. Aerobic respiration, the most efficient pathway, utilizes food and oxygen as reactants. Although sugar is not a strict requirement for energy generation, protein and fat can also be transported and utilized as fuel sources. However, the body generally prefers to use sugar due to its ability to supply energy rapidly, whereas protein and fat play more specialized roles and undergo slower metabolic processes. Within the human body, a cell is capable of utilizing various types of sugar, such as glucose, fructose, and sucrose, but typically relies on one primary source of energy. Glucose, the most common sugar, is preferred due to its availability and ability to be easily broken down through a series of enzymatic reactions. However, in certain circumstances, such as low blood sugar levels or during intense physical activity, other sugars may be utilized to meet the body's energy demands. During aerobic respiration, sugars are broken down through multiple catabolic processes, including glycolysis, the citric acid cycle, and oxidative phosphorylation, resulting in the production of several molecules of ATP per glucose molecule. This process is highly efficient and maximizes energy yield for cellular activities. Additionally, the mitochondria, the powerhouse of the cell, play a crucial role in aerobic respiration by providing an optimal environment for these metabolic reactions to occur. Anaerobic respiration, on the other hand, is an energy-yielding process that does not require oxygen. However, it is notably less efficient than aerobic respiration, producing only two ATP molecules per carbohydrate through glycolysis without any additional ATP generation. Consequently, the body prefers aerobic respiration over anaerobic respiration when oxygen is available. In situations where oxygen is limited, such as during intense exercise or in certain types of bacteria, anaerobic respiration can serve as a temporary means of ATP production. The byproduct of anaerobic respiration is lactic acid, which poses

several challenges. Lactic acid is negatively charged, resembling other carboxylic acids, and thus cannot be effectively filtrated by the kidneys, which typically filter neutral substances. This can lead to a buildup of lactic acid in the body, resulting in muscle fatigue, cramps, and even organ dysfunction. Individuals with lupus, a chronic autoimmune disease, face additional challenges in filtering out lactic acid, as their kidneys may already be compromised. Furthermore, lactic acid, being a metabolic waste product, is actively eliminated by the body, requiring the consumption of ATP. In order to convert lactic acid back into glucose or store it as glycogen, the liver utilizes energy in the form of ATP. This further demonstrates the undesirability of anaerobic respiration as a primary pathway for ATP production when compared to the highly efficient stages of aerobic respiration. It highlights the importance of maintaining a well-functioning aerobic metabolism to support overall cellular health and energy production. (Schmidt-Rohr, 2020) (Koch *et al*. 2021) (Vassilev *et al*., 2021) (Rigoulet *et al*. 2020) (Dunn & Grider, 2020) (Luengo *et al*. 2021) (Vercellino & Sazanov, 2022) (Vanlerberghe *et al.*, 2020).

9.1 Aerobic Respiration

Within the cells of the intricate and complex human body, a series of incredibly vital and essential processes occur at the biochemical level. Each of these processes is meticulously orchestrated with the intention of ensuring efficient energy management and overall functionality. These processes, in all their intricacy, are intertwined with specific substrates, giving rise to three distinct yet interconnected pathways: aerobic respiration, anaerobic glycolysis, and the anaerobic alactacid system. Among these pathways, aerobic respiration stands as the pinnacle of energy efficiency. It encompasses an array of chemical reactions that are aimed at harnessing the full potential of energy production. At the very core of aerobic respiration lies a captivating and fascinating interaction between glycolysis, an anaerobic process, and anaplerosis of the tricarboxylic acid cycle (TCA). Whenever the vital cosubstrate of oxygen is present, the mitochondria seize the opportunity to employ H2 molecules as catalysts. This launches an intricate cascade of events that ultimately culminates in the generation of adenosine triphosphate (ATP), which is the fundamental energy currency of cellular life. This remarkable phenomenon of aerobic respiration primarily relies on the utilization of macronutrients, such as carbohydrates, fats, and proteins, amalgamated with the indispensable presence of oxygen. As the labyrinthine pathways of aerobic respiration reach their culmination, three crucial energetic compounds emerge triumphant: adenosine triphosphate (ATP), guanosine triphosphate (GTP),

and cytidine triphosphate (CTP). Within the human body, these compounds encapsulate a staggering total of 66 moles. What is even more remarkable is that a single mole, equivalent to 36 kilojoules, contributes to this magnificent sum. Consequently, the yield of energy obtained from the initial energetic potential acquired through nutritional intake, which typically amounts to 9,700 kilojoules, is an astounding 2,376 kilojoules. In essence, this implies that our cells are inherently capable of extracting up to 25% of the initial energy available, while the remaining 75% dissipates into the realm of metabolic heat. This revelation highlights the exceptional energy efficiency of aerobic respiration. It manifests itself as an ever-present phenomenon, transpiring whenever amino acids undergo degradation or whenever the process of fat degradation unfolds, most notably through the meticulous orchestration of slow beta-oxidation. Additionally, this energy-exploiting mechanism also occurs as glucose is exhaustively consumed during the course of anaerobic respiration. Whether the body finds itself nestled in a state of rest or engaged in moderate to high-intensity training, the captivating tale of aerobic respiration continues to unfold. It tirelessly drives the essential processes that sustain life itself, ensuring our cells receive the energy they need to carry out their countless functions with incredible efficiency and precision. (DIng et al.2023)

9.2 Anaerobic Respiration

When oxygen is scarce, some living organisms will shift to anaerobic respiration for energy production. This is also referred to as anaerobic metabolism as it occurs in the absence of oxygen. Anaerobic respiration provides an alternative pathway to generate energy, although it is far less efficient than aerobic respiration. Anaerobic respiration occurs without the use of the electron transport chain. However, as in aerobic respiration, the initial stages involve the process of glycolysis to form 2 molecules of pyruvates from 1 molecule of glucose. For a single glucose molecule, glycolysis results in the net gain of 2 molecules of ATP through substrate-level phosphorylation. The 2 pyruvate molecules generated from glycolysis must be recycled in order to regenerate the original electron carrier molecules to accept more electrons and hydrogens from glycolysis. This regenerative process occurs through the pathways of fermentation. The fermentation of pyruvate differs in different organisms, wherever the end products of fermentation can vary in terms of organic compounds. Types of fermentation involved in anaerobic respiration are alcoholic fermentation, which occurs in microorganisms, and lactate fermentation, which occurs in animal cells. Alcoholic fermentation in yeast and some bacteria involves the decarboxylation of pyruvate, generating

acetaldehyde, which is then reduced to ethyl alcohol. Lactate fermentation in animal cells involves the direct reduction of pyruvate, generating lactate. Anaerobic respiration can produce energy much faster than aerobic respiration. Thus, animal cells carry out anaerobic respiration when energy demands cannot be met through aerobic respiration. The exact time point when an activity switches from aerobic respiration to anaerobic respiration may vary between individuals. In an untrained individual, the onset of lactic acid production from anaerobic respiration may occur sooner than in a trained individual. Likewise, when the intensity of exercise increases, an individual may reach the anaerobic respiration quicker than during moderate or low-intensity activities. Therefore, the probability of generating lactic acid through anaerobic respiration is higher in short, high-intensity activities than in low-intensity activities. In addition to physical activity, anaerobic respiration can also occur under some pathophysiological circumstances in different tissues, including heart muscles, liver, and others, where oxygen demand is greater than supply (ischemia). It is important to understand the consequences of anaerobic respiration in these situations and develop interventions to prevent further damage. Increased research should be conducted to explore the underlying mechanisms of anaerobic respiration and its impact on cellular function. Moreover, studying anaerobic respiration can provide insights into evolutionary adaptations and metabolic flexibility in organisms. Understanding how different organisms utilize anaerobic respiration as an energy-generating process can shed light on the complexities of biological systems and the diverse strategies employed for survival and growth. Furthermore, anaerobic respiration has applications in various industries and fields. For example, in the field of biotechnology, anaerobic bacteria play a crucial role in the production of biofuels and bioplastics. By harnessing the metabolic capabilities of these organisms, sustainable and environmentally friendly alternatives to conventional energy sources can be developed. In conclusion, anaerobic respiration is a vital physiological process that allows organisms to survive and thrive in oxygen-deprived environments. While less efficient than aerobic respiration, it serves as an essential backup system when oxygen availability is limited. The exploration of anaerobic respiration continues to uncover intriguing discoveries about cellular metabolism, adaptation, and the potential for sustainable solutions in various fields. (Berg *et al*. 2022) (Martin *et al.*, 2020) (Auger *et al*., 2021) (Schmidt-Rohr, 2020) (Staicu & Barton, 2021) (Buckel, 2021) (Lu & Imlay, 2021) (Vanlerberghe *et al.*, 2020).

Unit - 10

Metabolic Adaptations

The fuel utilization of the body regularly must adapt to changing environmental conditions. During exercise, the demand for ATP rises as much as 10 to 15 times. In the postabsorptive state, the resting body period between breakfast and lunch, the intestine, liver, and brain alone use about 167 g of glucose per day, or roughly 83 g per meal, but the human body stores only about 100 g of carbohydrate as glycogen. Thus, the body must be able to make the transition to fat metabolism to meet energy demands during overnight and between-meal periods. Indeed, over time, the body adapts to a marked increase in fat metabolism during fasting, especially muscle, which derives some 70% of its energy from fat compared to less than 25% in a person 2 hours after a mixed meal. Starvation is a unique metabolic state that can last weeks to months and an adequate supply of carbohydrates may be necessary for specific brain functions and avoiding protein breakdown cyclically. Metabolic diagnostics is also ripe for the clinical setting. Research in stable isotope tracer assays have revealed a vast array of novel metabolism pathways. A powerful tool in molecular systems biology is metabonomics which examines the profile of many small molecules in a biological sample. With improvements in DNA, RNA and protein turnover desk and metabolic trickle rates can also be used to assess enzyme fractional synthesis and molecular flux in vivo. These methods are beginning to come together. They outline the importance of promoting pathways in gene expression, metabolite turnover and co-factor bioavailability. Overall, this essay describes the resilience and versatility of cellular and physiological metabolic pathways. Metabolism is a source of controlled dynamism in metabolism because this valuable currency is not a leakage. On the contrary, individual metabolic pathways must adapt to tissue and systemic changes that can be large, rapid, and enduring. Metabolic neuropeptides and lipid metabolites are to be used as insulin metabohormones reflect a greater need to regulate homeostasis balanced with that of the energy housekeeping. The intricate interplay between various metabolic processes highlights the complexity and intricacy of the human body's energy metabolism. Through a delicate balance of fuel utilization and metabolic adaptation, the body ensures the availability of energy for various

physiological functions and sustains homeostasis. The transition to fat metabolism during periods of fasting exemplifies the body's remarkable ability to adjust its energy source based on the external environment. This metabolic flexibility allows the body to efficiently utilize its energy stores and maintain vital processes even in resource-scarce conditions. Additionally, metabolic diagnostics have emerged as a valuable tool in clinical settings. Innovative research utilizing stable isotope tracer assays has unraveled previously unknown metabolic pathways, shedding light on the intricate biochemical processes occurring within our cells. Metabonomics, a branch of molecular systems biology, provides insight into the complex profiles of small molecules present in biological samples. Advancements in DNA, RNA, and protein turnover assessment enable the quantification of enzyme synthesis and molecular flux within living organisms. These groundbreaking methods revolutionize our understanding of gene expression, metabolite turnover, and co-factor bioavailability, ultimately revealing the interconnectedness of metabolic pathways. This comprehensive essay underscores the adaptability and resilience of cellular and physiological metabolic processes, emphasizing their crucial role in maintaining overall health and function. Metabolism acts as a dynamic force, constantly responding to tissue and systemic changes on a scale that can be substantial, rapid, and long-lasting. The involvement of metabolic neuropeptides and lipid metabolites as insulin metabohormones emphasizes the intricate balance between regulating homeostasis and managing energy resources effectively. Through a multidimensional approach to metabolic studies, scientists unlock the intricacies of human metabolism, opening avenues for future advancements in medicine and personalized healthcare. Expanding the text provided, we explore the importance of the body's ability to adapt its fuel utilization in response to environmental conditions. This adaptation is particularly evident during exercise, where the demand for ATP increases significantly. In the postabsorptive state, which refers to the period between breakfast and lunch, specific organs such as the intestine, liver, and brain rely heavily on glucose, consuming approximately 167 grams per day or roughly 83 grams per meal. However, it is important to note that the human body only stores around 100 grams of carbohydrates as glycogen. This limited storage capacity necessitates a transition to fat metabolism during overnight and between-meal periods to meet the body's energy requirements adequately. Over time, the body displays remarkable adaptability by significantly increasing its reliance on fat metabolism during fasting periods, specifically in the muscles. During fasting, muscles derive approximately 70% of their energy from fat, compared to less than 25% in an individual two hours after consuming a mixed meal. This metabolic shift

towards increased fat utilization exemplifies the body's ability to meet energy demands in resource-limited conditions. Starvation, a unique metabolic state that can last for extended periods ranging from weeks to months, underscores the crucial role of carbohydrates in specific brain functions and the prevention of protein breakdown. In the realm of clinical applications, metabolic diagnostics represent a promising avenue for research. The utilization of stable isotope tracer assays has unveiled novel metabolic pathways, expanding our understanding of how the body processes various substances. Approaches such as metabonomics, which focuses on analyzing the profiles of numerous small molecules within biological samples, provide further insights into the intricacies of metabolic processes. Recent advancements in assessing DNA, RNA, and protein turnover rates have facilitated the quantification of enzyme synthesis and molecular flux within living organisms. These cutting-edge techniques offer new perspectives on gene expression, metabolite turnover, and the availability of co-factors, highlighting the interconnected nature of metabolic pathways. This comprehensive essay highlights the impressive adaptability and resilience displayed by cellular and physiological metabolic processes. Metabolism serves as a dynamic force within the body, continuously responding and adapting to tissue and systemic changes. The active involvement of metabolic neuropeptides and lipid metabolites as insulin metabohormones underscores the delicate balance required to regulate homeostasis and effectively manage energy resources. The intricate interplay among various metabolic processes further emphasizes the complexity inherent in the body's energy metabolism. Through a delicate equilibrium between fuel utilization and metabolic adaptation, the body ensures the availability of energy for various physiological functions, supporting overall homeostasis. The body's ability to transition to fat metabolism during fasting exemplifies its remarkable capacity to adjust energy sources based on environmental conditions. This metabolic flexibility allows for efficient utilization of energy stores, ensuring essential processes can continue even in resource-scarce conditions. In addition to its role in understanding metabolic processes, metabolic diagnostics have emerged as a valuable tool in clinical settings. Novel research utilizing stable isotope tracer assays has unveiled previously unknown metabolic pathways, shedding light on the intricate biochemical processes occurring within cells. The branch of molecular systems biology known as metabonomics provides further insights into the complex profiles of small molecules present in biological samples. Advancements in assessing DNA, RNA, and protein turnover enable the quantification of enzyme synthesis and molecular flux within living organisms. These revolutionary methods enhance our understanding of gene

expression, metabolite turnover, and co-factor bioavailability, unmasking the interconnectedness of metabolic pathways. In summary, this extensive essay emphasizes the adaptability and resilience demonstrated by cellular and physiological metabolic processes. Metabolism acts as a dynamic force, capable of responding to tissue and systemic changes on a substantial, rapid, and enduring scale. The involvement of metabolic neuropeptides and lipid metabolites as insulin metabohormones underscores the intricate balance between regulating homeostasis and effectively managing energy resources. Through multidimensional metabolic studies, scientists gain a deeper understanding of human metabolism, paving the way for future advancements in medical care and personalized healthcare. (Hargreaves & Spriet, 2020) (Spriet, 2022) (Ferretti *et al*. 2022) (Calbet *et al*. 2020) (Bartlett *et al*. 2020) (Alghannam *et al*. 2021) (Vigh-Larsen *et al*. 2021) (Luengo *et al*. 2021) (Korzeniewski & Rossiter, 2020).

10.1 Exercise and Metabolism

Exercise overrides homeostasis, providing us with new experiences and additional knowledge about the body's response to changes. Of particular interest are the various adaptations of energy metabolism during and following exercise performance designed to meet the increased metabolic demands of exercise. Energy supply is achieved through increases in anaerobic delivery of ATP via increased phosphocreatine (PCr) breakdown and glycolysis, whereas glucose and free fatty acids supply acetyl-CoA, and further oxidation appears to change little. Regulation of metabolism extracts and increases the use of these substrates for adenosine triphosphate (ATP) production from the same metabolic pathways. This appears to be mediated, at least in part, by the central nervous system that controls the output from the primary effector, GLUT4. To extend or even commence such adaptations requires muscular contraction and the release of interleukin-6 (IL-6), which is induced as skeletal muscle is exercised. Indeed, carbohydrate is a key mediator of epinephrine-induced IL-6 secretion, and as such, the predominant hormonal factor controlling skeletal muscle production of IL-6 is local metabolism during exercise. It is possible that lactate, through increased hydrogen ion (H+) concentration, is the intramuscular stimulus for glycogen phosphorylase, although at present this seems unlikely. Other possibilities are alpha-adrenergic effects, hypoxia, and increased release of adenosine monophosphate (AMP) and adenosine. The latter may not be released from contracting muscle, but acting in other tissues could affect metabolic rate and recruitment. These effects would lead to mobilization of the largest available substrate stores, i.e., muscle glycogen, in response to increased energy

requirements. In general, metabolic changes occur as a result of neural regulation of arterioles controlling local blood vessels. Blood redistribution to fit increases in oxygen requirements in the early stages of exercise, however, obeys a strictly non-nutrient profile and is primarily through the effects of adenosine and possibly nitric oxide on the compliant vasculature of the cardiovascular tree. These effects extend the network of blood vessels, allowing more efficient oxygen delivery to active muscle tissues. The intricate interplay between neural control, hormonal factors, and metabolic adjustments ensures that the body is able to meet the energy demands of exercise, promoting optimal performance and adaptation. (Hargreaves & Spriet, 2020) (Thyfault & Bergouignan, 2020) (Muscella *et al*. 2020) (Laurens *et al.*, 2020) (Most & Redman, 2020) (Kolnes *et al*. 2021).

10.2 Fasting and Starvation

During a fasting or semi-starvation period, organisms and individuals must adapt to a severe scarcity of nutrients. The reduction in metabolic rate that occurs in such circumstances is a fundamental and universal characteristic of all living beings and is of utmost importance for their survival. In order to make the most of limited resources, a healthy organism undergoing fasting resorts to various metabolic modifications in different pathways. These adaptations aim to conserve 'fuel' (in the form of triacylglycerol) and efficiently regain energy (primarily ATP). The extent of these metabolic adjustments may vary depending on the species, with prolonged fasting requiring even more significant adaptations. During such extended fasts, there is a need to temporarily shut down energy-consuming pathways that are not absolutely essential for immediate survival, such as the synthesis of certain types of proteins (excluding structural proteins). Additionally, the working rate of cellular molecular engines, including enzymes, motors, pumps, and others, is modified. Of all the adaptations that take place during fasting, the most crucial one is the transition in fuel utilization for energy production. Most energy-requiring cells shift from relying on glucose oxidation to predominantly utilizing fatty acid oxidation and ketone oxidation (such as acetoacetate and β-hydroxybutyrate) within the mitochondria. However, certain tissues, such as erythrocytes and kidney medullary cells, have a continued reliance on glucose metabolism and are unable to switch to fat oxidation. Consequently, pathways involved in glucose synthesis are up-regulated to ensure an adequate supply of glucose, albeit at a lower level. This maintenance of plasma glucose concentration is vital for sustaining essential cellular processes. Achieving this new metabolic interplay between CO2 production, NADH and FADH2 production, ATP production, and the overall

regulation of energy metabolism requires the involvement of numerous metabolic control pathways operating at the molecular, biochemical, subcellular, and cellular levels. Fine-tuning these pathways and optimizing the interplay between them is necessary to maximize energy conservation while sustaining vital functions during fasting or semi-starvation periods. As the scarcity of nutrients persists, organisms must further optimize their metabolic adaptations to efficiently utilize the limited available resources. This optimization is critical for the survival and maintenance of essential cellular processes. Moreover, the magnitude of these adaptations intensifies significantly during prolonged fasting. Organisms undergo additional adjustments to combat the prolonged lack of nutrients. Energy-consuming pathways that are not immediately necessary for survival are temporarily suppressed, such as the synthesis of certain proteins excluding structural proteins. Simultaneously, the activity levels of cellular machinery, including enzymes, motors, pumps, and other molecular engines, are modulated to conserve energy. One of the key adaptations during fasting is the shift in fuel utilization for energy production. Most energy-requiring cells primarily rely on the oxidation of fatty acids and ketones (such as acetoacetate and β-hydroxybutyrate) within the mitochondria, while certain tissues, such as erythrocytes and kidney medullary cells, continue to rely on glucose metabolism. To ensure a sufficient supply of glucose, the pathways involved in its production are up-regulated. Consequently, plasma glucose concentration decreases but is maintained at a lower level to sustain essential processes. This altered metabolic state during fasting is achieved through an intricate network of metabolic control pathways operating at multiple levels, including the molecular, biochemical, subcellular, and cellular levels. These pathways dynamically coordinate CO2 production, NADH and FADH2 production, ATP production, and other crucial aspects of energy metabolism. By tightly regulating these processes, organisms can effectively navigate through the challenges posed by nutrient scarcity, enabling them to endure extended periods of fasting or semi-starvation. (Varady *et al*. 2021) (Hoddy *et al.,* 2020) (Vasim *et al.,* 2022) (Hofer *et al*. 2022) (Rajpal & Ismail-Beigi) (Guo *et al*. 2021) (Hwangbo *et al.,* 2020) (Most & Redman, 2020).

Unit - 11

Metabolic Interactions with Other Systems

ATP. Metabolic interactions with the immune system/respiratory system. Macrophages are immune cells found in virtually every tissue and can activate or suppress numerous cellular and tissue processes and organ functions throughout the body. Macrophages seem to process or control inflammation by means of metabolic changes; they can alter their ATP via anaerobic glycolysis. Metabolic control of macrophage phenotype and arthritis given increasing Weiming C, Yang C, Guohao K, Ma Z, Jin Q, Li D, Huang S, Guowei P, et al. CMTM2. Virulence 2019;10:273–83. Metabolic interactions with the endocrine system. Many endocrine functions including leptin. Metabolic hormones are also influenced by the endocrine system. The hypothalamospituitary-adrenal (HPA) which occurs in metabolic diseases can also drive abnormal hormonal responses in the endocrine system, further contributing to metabolic abnormalities in a vicious cycle. Growers or veterinarians must realize metabolic processes are dynamic and always interact with other functions. Jeff Bruce, University of Glasgow, Scotland. Hypermetabolic implications in high energy high protein feeding following trauma or sepsis. Metastability and homeorhesis: Stability applied to the whole organism. Metastability is where a stable state is maintained in conditions that would be unstable in many other organisms. Homeorhesis is the same system as homeostasis but maintaining a new level of set point. ATP. Metabolic interactions with the immune system/respiratory system. Macrophages are immune cells found in virtually every tissue and can activate or suppress numerous cellular and tissue processes and organ functions throughout the body. Macrophages seem to process or control inflammation by means of metabolic changes; they can alter their ATP via anaerobic glycolysis. Metabolic control of macrophage phenotype and arthritis given increasing Weiming C, Yang C, Guohao K, Ma Z, Jin Q, Li D, Huang S, Guowei P, et al. CMTM2. Virulence 2019;10:273–83. Metabolic interactions with the endocrine system. Many endocrine functions including leptin. Metabolic hormones are also influenced by the endocrine system. The hypothalamospituitary-adrenal (HPA) which occurs in metabolic diseases can also drive abnormal hormonal responses in the endocrine system, further

contributing to metabolic abnormalities in a vicious cycle. Growers or veterinarians must realize metabolic processes are dynamic and always interact with other functions. Jeff Bruce, University of Glasgow, Scotland. Hypermetabolic implications in high energy high protein feeding following trauma or sepsis. Metastability and homeorhesis: Stability applied to the whole organism. Metastability is where a stable state is maintained in conditions that would be unstable in many other organisms. Homeorhesis is the same system as homeostasis but maintaining a new level of set point. Metastability and homeorhesis play significant roles in maintaining the overall equilibrium and stability of an organism's internal environment, allowing it to adapt to various external and internal changes. These phenomena ensure that the organism can sustain a stable state, even in conditions that would typically lead to instability in other organisms. In addition to their involvement in immune responses and respiratory functions, macrophages exhibit intriguing metabolic interactions with various systems within the body. They possess the ability to modulate inflammation through metabolic changes, particularly by altering their ATP production via anaerobic glycolysis. This metabolic control of macrophage phenotype has significant implications in conditions such as arthritis, where an understanding of the underlying metabolic processes is crucial for developing effective treatment strategies. Moreover, the endocrine system, which encompasses a wide range of functions including the regulation of metabolic hormones like leptin, has a reciprocal relationship with metabolic processes. Disturbances in the endocrine system, such as those observed in metabolic diseases, can lead to abnormal hormonal responses that further contribute to metabolic abnormalities, thus creating a vicious cycle. It is essential for growers or veterinarians to recognize the dynamic nature of metabolic processes and their interconnectedness with other bodily functions to ensure optimal health and well-being in both humans and animals alike. Addressing the hypermetabolic implications following trauma or sepsis, high-energy and high-protein feeding have been shown to have beneficial effects on recovery and healing. These dietary interventions aim to support and enhance the body's hypermetabolic state, which is characterized by increased metabolic demands due to injury or infection. By providing ample energy and protein, it aids in meeting the heightened metabolic needs and promotes the restoration of normal physiological functions. Metastability and homeorhesis are two crucial concepts in maintaining the stability and equilibrium of the entire organism. While metastability refers to a stable state that can be sustained under conditions that would typically lead to instability in other organisms, homeorhesis encompasses a similar idea of maintaining a new level of set point within the system. Together, these mechanisms ensure that

the organism can adapt and thrive in various environments, allowing for its successful survival and functionality. (Gupta & Sarangi, 2023) (Kolliniati *et al*. 2022) (Yu *et al*. 2022) (Thorp, 2021) (He *et al.*, 2021) (Li *et al*. 2023) (Bae *et al*. 2021).

11.1 Immune System

The immune system is comprised of a wide array of diverse immune cells that facilitate anti-viral, anti-parasitic, and anti-tumoral responses. The development of immune memory and the resolution of immune inflammation depend on the interconnected communication between immune cells and the overall body, collectively referred to as host metabolism. Immune signals play a pivotal role not only in communicating the immune state and the ever-changing needs of the immune system to the rest of the body but also in acting as metabolic regulators for the host organism. Host metabolism directly and indirectly provides the necessary fuel or imposes restrictions on the activation, proliferation, and effector functions of immune cells. Simultaneously, the immunomodulatory effects of metabolic processes can influence immune cell function. Thus, an intricate interplay exists between host metabolism and the immune system. In this study, we delve into the underlying metabolic pathways that drive immune cell activation, proliferation, and differentiation, and conversely, how the immune system can modulate or facilitate the metabolic processes that govern its own functioning. All mammalian cells necessitate easily accessible metabolic fuels such as glucose, amino acids, lipids, and other energy-rich metabolites. The utilization of metabolic substrates and the production of metabolites are meticulously regulated and coordinated in a tissue-specific manner, in accordance with the energetic and biosynthetic demands imposed on the tissue. Similarly, immune cells undergo a comparable "metabolic reprogramming" upon activation. Naive immune cells, including T and B cells, undergo activation in lymphoid tissues, leading to a substantial increase in the number of effector cells. The newly activated effector cells prioritize ATP generation over biosynthesis. Additionally, cytokine signals further fine-tune the bioenergetic and biosynthetic potential required for the maturation of effector cell functions and mitochondria. The emergence of inflamed, pathogen-infected, or tumoral tissue also influences the metabolic adaptations of immune cells within the tissue itself. Furthermore, it is important to note that the metabolic adaptations of immune cells extend beyond the immediate tissue microenvironment. The systemic nature of host metabolism allows for long-range communication and coordination between different tissues and organs. This systemic communication plays a critical role in ensuring a balanced immune response

and efficient energy utilization throughout the body. Metabolic substrates and metabolites are transported through the bloodstream and distributed to various tissues based on their specific demands. For example, glucose is a fundamental metabolic fuel that is utilized by immune cells, particularly during their activation and proliferation. Through the process of glycolysis, glucose is broken down to produce ATP, which provides energy for the diverse functions of immune cells. In addition to glucose, other nutrients such as amino acids and lipids also contribute to the metabolic needs of immune cells. Amino acids are essential for protein synthesis, and lipids serve as a source of energy, as well as structural components of cell membranes. These metabolic substrates are transported systemically and taken up by immune cells in a regulated manner, allowing for the precise control of cellular metabolism. Metabolic adaptations in immune cells are not only driven by the availability of nutrients but also by the signals received from the surrounding microenvironment. The metabolic state of immune cells can be influenced by a variety of factors, including cytokines, growth factors, and stress signals. For instance, pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) have been shown to induce metabolic changes in immune cells, promoting glycolysis and enhancing energy production. Conversely, anti-inflammatory cytokines such as IL-10 have been found to dampen glycolysis and promote mitochondrial respiration, potentially limiting the proliferation and activation of immune cells. These cytokine-mediated metabolic changes are crucial for maintaining immune homeostasis and preventing excessive immune activation or immunopathology. In addition to the role of immune cells in regulating metabolism, emerging evidence suggests that metabolic processes can also impact immune cell function. Metabolites generated by host metabolism can act as signaling molecules that modulate immune responses. For instance, the accumulation of certain metabolites, such as lactate, succinate, and itaconate, has been shown to regulate the inflammatory response and influence immune cell activation. Furthermore, metabolic enzymes and pathways in immune cells have been found to play critical roles in controlling immune cell fate and function. For example, enzymes involved in lipid metabolism, such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), have been shown to regulate T cell activation and effector functions. Additionally, the mTOR signaling pathway, which integrates nutrient and energy signals, has been implicated in the control of immune cell metabolism and function. In conclusion, the interplay between host metabolism and the immune system is a complex and dynamic process. Metabolic adaptations in immune cells are crucial for their activation, proliferation, and effector functions, while immune signals and processes can

in turn influence host metabolism. Understanding the intricate relationship between metabolism and the immune response is not only important for unraveling the fundamental biology of immune cells but also for the development of therapeutic interventions targeting immune-related diseases. Further research in this field holds great promise for the discovery of novel immune modulators and metabolic targets that could revolutionize the treatment of various inflammatory, infectious, and neoplastic disorders. (Hortová-Kohoutková *et al.,* 2021) (Goretzki *et al.,* 2021) (Marchingo & Cantrell, 2022) (Hu *et al*. 2022) (Aderinto *et al*. 2023) (Qiu *et al.,* 2023) (Rodriguez-Coira *et al.,* 2021).

11.2 Endocrine System

The endocrine system plays an incredibly significant role in the regulation of numerous cellular activities concerning metabolism, growth, and development. Due to the wide range of regulatory activities that occur in close association with metabolism, the intricate feedback mechanisms that regulate these endocrine functions are naturally influenced by the metabolic performance. Furthermore, the plasma levels of metabolic hormones, which have an immense and profound impact on endocrine activities, are constantly and consistently in a state of flux, continuously modulating endocrine functions in accordance with the prevailing nutritional state. Similarly, hormones that have a remarkable impact on the metabolic activity of cellular organelles are synthesized within the body itself. The activities of major enzymes and transporters involved in metabolic reactions are precariously and diligently regulated at multiple levels, including protein synthesis, modification, inhibition, and degradation, all with the ultimate goal of either enhancing or restraining the metabolic activity within the cell. This delicate and intricate regulation ultimately ensures the provision of an ample and sufficient amount of adequate energy to meet the precise energetic needs of the body, fulfilling the necessary requirements seamlessly. The intricate web of energy metabolism is skillfully and expertly controlled by both the nervous system and the endocrine system, working together in perfect harmony and synchrony, effectively and efficiently coordinating their efforts towards the overall well-being of the organism as a whole. Moving on, we divert our attention towards the anterior lobe, which is also commonly known as the adenohypophysis, and acknowledge its crucial and indispensable role in the production and release of six immensely important and prominent hormones. These hormones, which are often and commonly referred to as tropic hormones, possess the remarkable ability to exert dramatic and far-reaching effects on other endocrine glands, showcasing their vast and significant impact

in the grand scheme of hormonal regulation. The primary hormones that are secreted and released by the anterior lobe encompass an array of significant and essential names, namely Thyroid-stimulating hormone (TSH), Adrenocorticotropic hormone (ACTH), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Prolactin (PRL), and lastly, but certainly not least, Growth hormone (GH). It is noteworthy and intriguing to understand that the action and functioning of the aforementioned growth hormone (GH) are primarily carried out through the stimulation and activation of Insulin-like Growth Factors (IGF-I and II) production, underlining the intricate interplay between various hormones and their downstream effects. Interestingly, it is crucial and of utmost importance to acknowledge that GH levels are essentially and almost virtually undetectable during the daytime, which poses a significant challenge and imperative necessity for researchers and scientists alike to measure GH secretion during sleep, when it is predominantly and most actively at play. In light of this scenario, the collection of cerebrospinal fluid (CSF) is performed and executed diligently from the subject's body in the morning, and this collected fluid is then meticulously and painstakingly transported to a specialized, state-of-the-art laboratory specifically designed and equipped for the accurate and precise assay and analysis of such delicate substances and samples, guaranteeing the utmost reliability and validity of the measurements and findings. (LeRoith *et al.*, 2021) (Kraemer *et al*. 2020) (Witkowska-Sędek and Pyrżak 2020) (Van Doorn, 2020) (Miller *et al.*, 2022) (Nijenhuis-Noort *et al*. 2024).

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