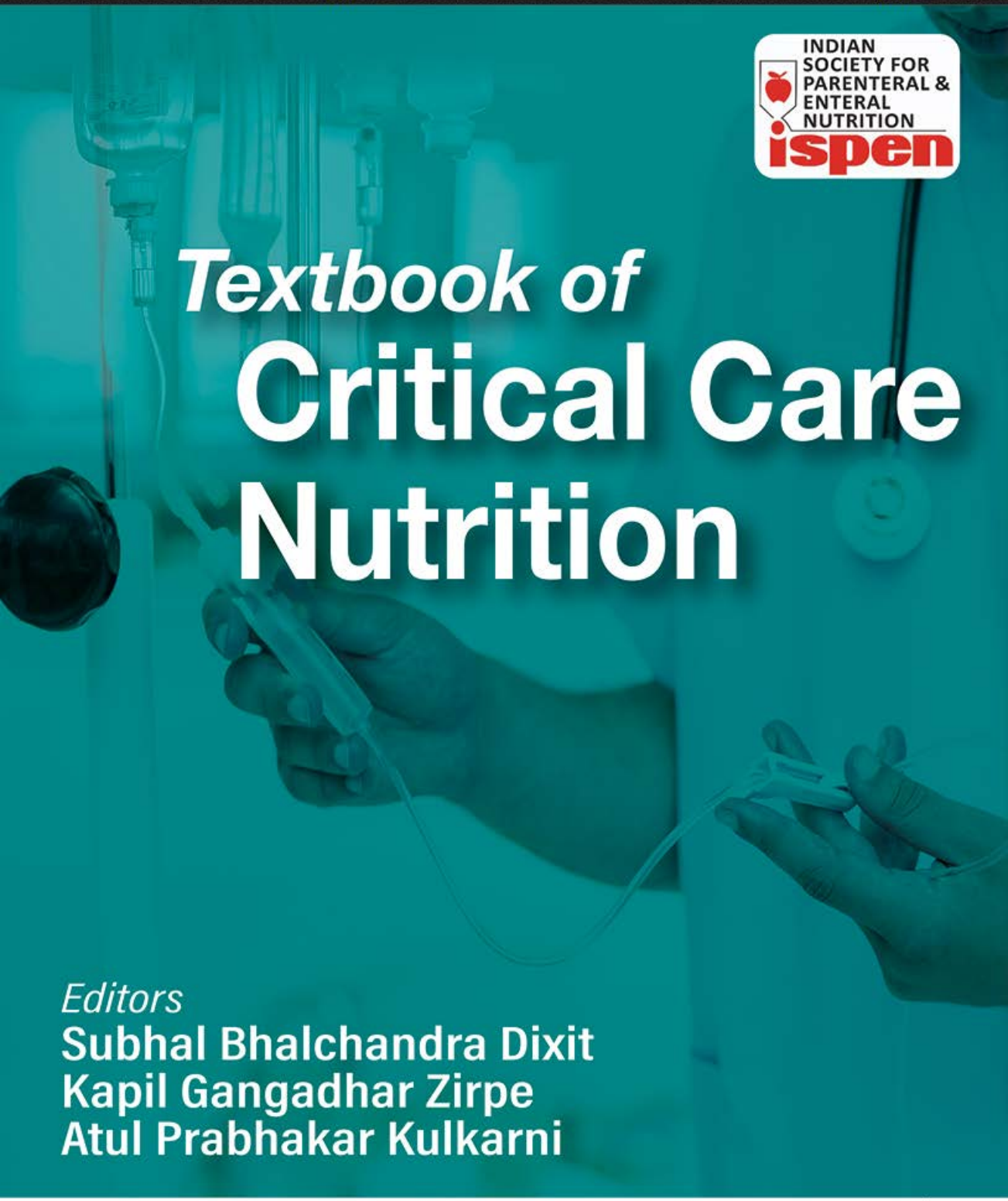
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Textbook of Critical Care Nutrition



Editors
Subhal Bhalchandra Dixit
Kapil Gangadhar Zirpe
Atul Prabhakar Kulkarni

Associate Editors
B Ravinder Reddy
Khalid Ismail Khatib

Forewords
Jean-Louis Vincent
Varsha T

JAYPEE

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CHAPTER 3

Immune Responses and Immunometabolism: An Overview

B Ravinder Reddy

The greatest discoveries often lie not in finding new things, but in seeing familiar things in new ways.

– Alexander Fleming

INTRODUCTION

On an average, humans contain about 37 trillion cells and about 39 trillion bacteria, which marginally outnumber human cells at an estimated ratio of about 1.3:1.[1] The intrinsic human cells also include the different types of immune cells involved in innate defenses and acquired immunity. Configuration of their structural form and the control of the different functions of all these numerous cells occur at molecular level, involving various biochemical reactions. These complex physiological mechanisms enable extraction of energy in the form of a small molecule—adenosine triphosphate (ATP) and other provisions from the nutrients. In addition, these metabolic reactions also enable the biosynthesis and assembly of newer molecules, which in turn act as substrates for production of newer reactants and products for further biochemical pathways. Hence, these dynamic intra- and inter-cellular responses are crucial for various metabolic interactions, supporting the various immune cells and facilitating their responses. Therefore, the interactions between metabolism and immunity, termed as *immunometabolism*, can be described as numerous interactions between the various metabolic pathways that sustain and regulate the diverse immune responses.[2] Immunometabolism, which was first described in 2011, is a rapidly evolving field, linking various disciplines and is presently a leading research topic in the field of metabolism. Immunometabolism forms a major mechanism in preserving homeostasis, in facilitating metabolic signaling, and is involved in the pathogenesis of obesity, diabetes, and various other metabolic disorders, inflammation, autoimmune diseases, cancers, infections, and sepsis.[3]

OVERVIEW OF BASIC METABOLIC PATHWAYS

There are seven interconnected metabolic paths, which are essential for growth, sustenance, and survival:

1. Glycolytic pathway
2. Tricarboxylic acid (TCA) cycle
3. Oxidative phosphorylation (OXPHOS)
4. Pentose phosphate pathway (PPP)
5. Fatty acid oxidation (FAO)
6. Fatty acid synthesis (FAS)
7. Amino acid pathways

1. *Glycolytic pathway:* This occurs within the cytoplasm of all the cells, in aerobic as well as anaerobic conditions. A single molecule of glucose produces seven ATPs (aerobic glycolysis) and two ATPs (anaerobic glycolysis, the only pathway that

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produces ATP in the absence of oxygen). Though this seems like an inefficient pathway, it actually generates essential biosynthetic precursors for cellular proliferation, such as ribose for synthesis of nucleotides, amino acids, fatty acids (FAs), and enzymes, which act as cofactors (known as the Warburg effect). Glycolysis plays a leading role in all the rapidly dividing cells, including activated white blood cells and neoplastic cells.[4]

2. *Tricarboxylic acid cycle:* This occurs in the mitochondrial matrix and is also known as Krebs cycle or citric acid cycle. The "cycle" commences by accepting acetyl CoA (which is produced by all the three macronutrients—glucose, fatty acids, and amino acids). It has both catabolic (each cycle generates 10 ATPs by breakdown of macronutrients) and anabolic (synthesis of new molecules by providing raw materials), hence termed as amphibolic pathway. An important aspect of TCA cycle is the generation of reducing equivalents, flavin adenine dinucleotide ($FADH_2$), nicotinamide adenine dinucleotide (NADH), and protons (H^+). These energy-rich molecules take part in the electron transport chain (ETC), by moving electrons and enabling oxidative phosphorylation. TCA cycle is an efficient process of ATP generation.[5]
3. *Oxidative phosphorylation:* This occurs in the presence of oxygen, at the inner mitochondrial membrane, and is made up of two components—electron transport chain and chemiosmosis. ETC is made of four extremely complex structures, embedded within the inner mitochondrial membrane (complex I, II, III, and IV). The high-energy electrons, NADH and $FADH_2$ present in the mitochondrial matrix, are transferred serially from one membrane-bound complex to the other (enabled by coenzyme Q10 and cytochrome c), in a series of redox reactions, releasing protons (H^+), and produce energy at each step. This energy is used to pump these protons (which are at a higher concentration in the matrix of the mitochondria) against the concentration gradient into the intermembrane space. Subsequently, by the process of chemiosmosis, these protons within the intermembrane space of mitochondria flow down the concentration gradient through a complex molecule called ATP synthase, producing ATP. Finally, the high-energy protons interact with oxygen and form water. An important by-product of the serial transfer of electrons (e^-) is the generation of reactive oxygen species (ROS), which aid in cell signaling to maintain homeostasis and also contributes to the oxidative stress. On an average, one molecule of glucose generates 30–36 ATPs, thus oxidative phosphorylation is an extremely efficient metabolic process in the generation of energy.[6]
4. *Pentose phosphate pathway:* Like glycolysis, PPP too occurs within the cell cytoplasm and is also called phosphogluconate pathway or hexose monophosphate shunt. A key function is enabling the synthesis of various molecules, by using substrates from glycolytic pathway, to generate nucleic acids, nucleotides, amino acid precursors, FAs, cholesterol, and glutathione. It also plays a major role in the cell defenses by production of the small antioxidant molecules and antioxidant enzymes. PPP has several functions, the most important of which are cell proliferation (anabolic)

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and detoxification and neutralization of intracellular ROS (survival), especially in the immune cells.[7]

5. *Fatty acid oxidation:* This process occurs within the mitochondria and utilizes numerous enzymes to generate ATPs and energy-rich NADH and $FADH_2$. It begins within the cytoplasm where the inert FAs are converted into an energy-dense derivative called acyl-coenzyme A ("activation"). It is then transported to mitochondrial matrix by conjugating with carnitine. The medium- and long-chain FAs need carnitine (carnitine shuttle) to be transported into the mitochondria, whereas the short-chain FAs (having less than six carbon atoms) diffuse easily into the mitochondrial matrix. Subsequently, each of the activated FA acyl-coenzyme A undergoes a complex and a repeated process called beta-oxidation, resulting in production of enormous amounts of ATP. For example, palmitic acid, a common form of saturated FA, yields 106 ATPs. FAs are calorie-dense nutrients and have the potential to generate significant amounts of energy when metabolic demands are high.[8]
6. *Fatty acid synthesis:* This occurs in the cell cytoplasm using substrates and metabolic products from other pathways, such as glycolysis, TCA, and PPP, by a complex mechanism. The major source of FAS is by glycolysis, which provides carbon atoms. Glycogen, the stored form of carbohydrates, is limited to about 500 g in the muscles (range from 300 to 700 g) and about 80 g in the liver (range from 0 to 160 g). Therefore, excess glucose undergoes glycolysis, providing the acetyl coenzyme A and NADH + H^+, which are utilized as substrate and generate FAs in a complex biosynthetic pathway. In addition, mechanistic target of rapamycin (mTOR), a molecule that controls growth and metabolism, also controls synthesis of FAs. FAS enables production of lipids, which are essential for growth and proliferation.[9]
7. *Amino acid pathways:* Amino acids are critical for cell and tissue growth, proliferation, and homeostasis. They are essential for locomotion, organ functions, interorgan cross talk, and provide substrates for gluconeogenesis and in inflammatory and immune responses. They are crucial for intra- and extracellular cell signaling and also for the mTOR pathways, which sense the availability of essential amino acids, which in turn control protein synthesis.[10] Additionally, amino acids act as reservoirs and reactants for many diverse molecular, metabolic, and biochemical reactions. Though all of the 20 amino acids are needed for various homeostatic processes, certain amino acids such as glutamine, arginine, and tryptophan play a significant role in immune cell activation and immune responses and serve as immunometabolites and immunotransmitters. Glutamine has multiple roles, noteworthy of which are—it acts as substrates for synthesis of purines and pyrimidines, fuel for immune and other proliferating cells, substrate for neoglucogenesis, expression of heat-shock proteins, ATP production, and FAS. Arginine acts as a substrate for production of nitric acid, nitric oxide, polyamines, and has an essential role in wound healing, releasing of hormones and T cell, and other immune functions. Tryptophan has a positive role in cell proliferation and anabolism and is utilized in different biochemical reactions.

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Therefore, amino acids are mandatory for several intracellular and intercellular functions, which enable immune cell activation, differentiation, proliferation, and a robust immune response.[11]

OVERVIEW OF IMMUNE CELLS AND RESPONSES

The following is a brief overview of immune cells and immune responses.

The immune system comprises diverse group of extremely intricate cells, each having a specific nutrient and energy requirements, obtained either from a highly efficient process of OXPHOS or from a process of glycolysis, which has a low efficiency of extraction of energy, but is a major source of substrates for biosynthesis of cellular components and various other molecules. They also have distinct types of proteins, which aid in the many dynamic and complex responses. These processes are extremely efficient in the protection and defense against various microbes and their toxins, from developing malignant tumors, other cancerous conditions, and from foreign substances. They also play a pivotal role in immune tolerance, repair of tissues, and in homeostasis. However, disturbances and dysregulations of immune cells have the potential to induce and provoke abnormalities and various complications ranging from allergies, hypersensitivity, anaphylaxis, autoimmunity, severe and excessive inflammations, infections, and overwhelming sepsis.

Immune cells form an important component of the immune system and originate from the bone marrow hematopoietic precursor cells. Under the influence of specific cytokines, they differentiate either into myeloid series (erythrocytes, monocytes, neutrophils, eosinophils, basophils, and platelets) or lymphoid series [dendritic cells (DCs), natural killer (NK) cells, and T and B lymphocytes], and depending on the types, their lifespan ranges from a few hours or days to several months.[12] The other essential components of immune system comprise a host of distinct proteins that make up the cytokines (small soluble proteins), the complement system (soluble and membrane-bound proteins), antibodies (polypeptide chains), and the innumerable assortment of receptors (intricate proteins), some of which are present on their surfaces in a very precise manner, and some of which are known as cluster of differentiation (CD). Therefore, the myriad types of immune responses depend on the type and the individual characteristics of immune cells, tissues, and organs and include physical barriers such as skin and mucus membranes. A characteristic feature of immune system is the rapid shift of the immune cells from inactive to highly activated state and depend on the availability of energy and the metabolic pathways that occur in these complex arrays of immune cells.[13] Some of the prominent features of the important immune cells, such as neutrophils, macrophages, DCs, NK cells, and lymphocytes, are as follows:

- *Neutrophils:* These short-lived lymphocytes constitute about 50–60% of white blood cells and have multilobed nuclei with abundant cytoplasmic granules. Quiescent neutrophils are activated by interleukin (IL)-1, which prolongs their lifespan from 24 hours to about 5 days and enable their rapid migration to the sites of injury and infections; they play a pivotal role in host defenses by initiating inflammation and phagocytosis. Microbial killing occurs by degranulating their lytic enzymes, generation of hydrogen peroxide, and ROS. They also release extracellular net-like traps, called

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neutrophil extracellular traps (NETs), made up of their mitochondrial DNA, due to lysis of mitochondria, secondary to increased ROS within them. These NETs trap and bind the microbes to expose them to a high concentration of microbicidal factors. NETs have the potential to cause tissue damage in the vicinity of their formation, which can lead to untended inflammatory cell recruitment and responses.[14]

- *Macrophages:* These immune cells are large and distributed in all body tissues and are derived from monocytes. They are tissue specific, which include alveolar macrophages (lungs), Kupffer cells (liver), microglial cells (central nervous system), and splenic macrophages, Langerhans cells (skin and mucosa), lamina propria macrophages (intestines), histiocytes (connective tissues), osteoclasts (bones), synovial A cells (joints) and peritoneal macrophages (proinflammatory), or by alternate pathways, involving anti-inflammatory cytokines, IL-4 and 13, called M2 macrophages. M1 macrophages secrete proinflammatory cytokines and are involved in recognition, phagocytosis, and destruction of microbes and tumor cells. In overactivated states, they have the potential to cause tissue damage. M2 macrophages induce anti-inflammatory effects and are essential for wound healing and repair.[15]
- *DCs:* These are highly specialized leukocytes present in all the tissues, which constantly sample their immediate environments for antigens and other molecular patterns by diverse group of structures on their surface, called pattern recognition receptors (PRRs). In the presence of foreign antigens and microbial products, DCs mature rapidly and coordinate innate and adaptive responses (which are further described below in the section of activation of T lymphocytes), in addition to recognizing the self-antigens and promoting immune tolerance.[16]
- *NK cells:* These cells, which are a part of the innate immune system, are granular lymphocytes, and respond very rapidly to a wide variety of immune challenges. They are also called group I innate lymphoid cells (ILCs) and belong to the same family as T and B lymphocytes and mount a direct toxicity, as well as by antibody-dependent cytotoxicity. They have a crucial role in the immune defense, immune-surveillance, and by targeting tumor cells and especially those infected with viruses.[17]
- *T and B lymphocytes:* These lymphocytes form a crucial component of acquired immune system. Though morphologically similar, they have distinct functions, with T cells being involved in cell-mediated B cells, which produce antibodies and form plasma cells that are involved in humoral immunity. Based on the CD found on their surfaces, T cells are further subclassified into $CD4^+$, $CD8^+$, gamma delta ($\Upsilon\delta$) T cells, and regulatory T cells (T_{regs}). Both T and B cells exist in inactive (or naïve) state and get activated on exposure to various antigens, which can be present either on the surface of infected cells (T cells), or by the antigens present on the surface of bacteria and viruses (B cells). Upon activation, they form the highly efficient effector cells and memory cells.[18]
- *Immune responses:* Immune defenses commence as soon as the physical barriers are breached, either by pathogens or tissue damage by injuries or trauma, and result in specific molecular patterns—pathogenic-associated molecular

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patterns (PAMPs) or damage-associated molecular patterns (DAMPs), both of which are recognized by receptors called PRRs, which are present on the surface of the immune cells. In addition, PRRs are present within the cell cytoplasm, cell vesicles, as well as in the soluble forms within the body fluids and blood. Depending on the nature of molecular patterns (PAMPs/DAMPs), phagocytic responses, cytotoxic activation, or biochemical cascades are initiated.[19] Those which occur immediately are the innate immune responses, whereas those that develop a few days after the initial invasion or infection are the acquired or adaptive immune responses, which is an adapted response and more specific to the particular pathogen or a situation.

Innate immunities are quite efficient in eliminating pathogens and initiating the process of repair and regeneration. They include the phagocytes (neutrophils, macrophages, and DCs), NK cells, mast cells, eosinophils, and basophils. On the other hand, when innate responses are insufficient and inadequate, acquired immune responses are induced and activated to provide an effective protection, in the form of cell-mediated responses by T lymphocytes and humoral immune responses by B lymphocytes. The primary or central lymphoid organs, bone marrow and thymus, are involved in the production and processing of lymphocytes. Both T and B lymphocytes have highly specific receptors and other complex molecules on their surfaces, which allow them to recognize a wide spectrum of antigens and result in activation of dormant or quiescent lymphocytes.

- *Activation of T lymphocytes:* The proteins from the pathogenic microbes (and their toxins) are taken up and processed to smaller peptides by specialized cells called antigen-presenting cells (APCs). Important APCs are DCs, macrophages, and B cells. DCs form extremely efficient APCs. On the surface of these APCs are tiny, intricate complexes which are part of major histocompatibility complex (MHC). There are two types of MHCs, class I and II. DCs, which are the prominent form of APCs, have class II MHC molecules. Once the foreign proteins are processed by DCs, they are displayed on its surface, in conjunction class II MHC and are recognized by T cells. It is important to note that T-cell receptors (TCRs) recognize a specific antigen on the APCs, only if presented by class II MHC molecules, and are activated, generally within the draining lymph nodes. In bloodstream infections, the splenic APCs process and present the antigens. Lymph nodes, spleen, and lymphoid tissues associated with gut and other mucosal membranes [gut-associated lymphoid tissue (GALT) and mucosa-associated lymphoid tissue (MALT)], which constitute the peripheral and secondary lymphoid organs also enable antigen processing and presentations. Once activated, the T cells undergo a swift polarization into specific subsets of T helper (Th) cells—Th1, Th2, and Th17. Th1 cells form the core component of cell-mediated immunity and activate neutrophils, macrophages, $CD8^+$ cells, which initiate the process of identification and destruction of intracellular microbes (bacteria and viruses) by inducing cytolysis. They are also essential for the generation of memory T cells. Th2 cells are involved in the eradication of extracellular microbes and parasites,

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production of anti-inflammatory cytokines, and in the activation of B cells. Th17 cells form the main core of defending the mucosal barriers and surfaces and are also implicated in the pathogenesis of autoimmune diseases. $CD8^+$ are the effective T cells against tumor cells and intracellular microbes (viruses and bacteria). γδ T cells (so called because their receptors are made of γ and δ chains) form a smaller subset of T cells, which are present within the epithelial cells of intestines and lungs, and initiate protective effects by producing proinflammatory mediators upon activation. T_{regs} play a crucial role in homeostasis by moderating and regulating the excessive immune responses.[20,21]

- *Activation of B lymphocytes:* B cells, which constitute an essential part of acquired immune responses, produce antibodies upon activation. Antibodies, in addition, also form part of the B-cell receptors (BCRs). Different types of biochemically distinct antigens are recognized by BCRs. The antigens include a variety of proteins, lipids, carbohydrates, and other molecules, which are present in soluble forms, as well as cell-associated antigens. This process too occurs in the draining lymph nodes and also within the other components of peripheral lymphoid organs and tissues. B cell can be activated directly when antigens bind to BCRs. Complement proteins with their bound antigens accelerate the process. In addition, they can also be activated by a cell-to-cell interaction with an activated T cell. Therefore, B cells can be activated directly by antigens and also by T-cell-dependent activation. Large quantities of antibodies are secreted by activated B cells (plasma cells).[22]

Though T and B cells have about billions of receptors for numerous antigens, each of them has a highly specific receptor for a specific antigen. Soon after activation, they undergo clonal expansion, which is an energy-intense process, and each cell division takes about 8–12 hours. Hence, it takes a few days after the initial or "first" exposure for initiation of acquired immune responses takes. In addition to the effector responses by the activated lymphocytes, some of these activated T and B cells convert to memory T and B cells, which provide long-term immunity.

Therefore, the immune system has a wide reservoir of specialized cells, which interact with various pathogens, antigens, and other abnormal conditions and mount an effective protection and defense. Metabolism forms the core of these complex responses.

Metabolic Pathways in Immune Cells during Various Immune Responses

Glycolytic pathways in immune cells: Glucose is a vital energy source and glycolysis forms a crucial pathway for the activated immune cells, which have a voracious appetite for readily available glucose. The rapid availability of ATP enables phagocytosis, dendritic functions, production of cytokine, interferon gamma (IFN-γ), and other acute-phase proteins, especially by activated neutrophils, M1 macrophages, NK cells, effector T cells, and B cells, especially during clonal expansion of specific subtypes. B cells especially use glycolysis in all phases of maturation, activation, and differentiation. Additionally, glycolysis, by providing biosynthetic molecules, acts as precursors for PPP, and synthesis of nucleotides, amino acids, and fats (by

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providing acetyl coenzyme A) and also in the activation of mTOR pathways. Conversely, a block or reduced glycolytic pathway and uptake of glucose has the potential to result in reduced neutrophil functions, hypoinflammation, and the likelihood of immune supression.[23]

Pentose phosphate pathways in immune cells: Forms an essential biochemical route in the immune cells (including M1 macrophages, etc.) during acute inflammatory conditions and sepsis, as there is an increased demand for ROS, followed by facilitation of an effective antioxidant environment. PPP generates adequate amounts of reduced nicotinamide adenine dinucleotide phosphate (NADPH), which results in an effective production of ROS as well as glutathione, a naturally occurring antioxidant, which counteracts the free radicles.[24]

TCA and OXPHOS in immune cells: TCA and OXPHOS are the main pathways in the naïve and quiescent immune cells, including M2 macrophages. In addition, citrate, an important molecule of TCA cycle, enables production of bactericidal compounds (itaconic acid) in M1 macrophages. Succinate, another molecule from the TCA cycle, is involved in the production of hypoxia-inducible factor-1 (HIF-1) and IL-1β. In hypoxic conditions, HIF-1 regulates and activates various responses to maintain homeostasis, switching on genes to adapt to hypoxia, and also in increasing oxygen delivery. Both, TCA and OXPHOS, are the major metabolic pathways in M2 macrophages.[25]

FAO in immune cells: FAO is a common catabolic pathway and provides energy and substrates for TCA cycle and genesis of other molecules. FAO occurs in immune cells, which have a longer lifespan, such as M2 macrophages, T_{regs}, and cells involved in immune memory and immunological tolerance. Reduced FAO leads to abnormal accumulation of FAs, especially within the cardiac myocytes, leading to septic shock. Their accumulation in the macrophages (foam cells) plays a role in the development of atherosclerosis and also induces potent inflammatory responses by expressing IL-1β.[26]

FAS in immune cells: FAS has opposing actions (to FAO) within the immune cells involved in various responses. They provide subunits for synthesis of phospholipids, triglycerides, and some hormones. In the presence of inflammation and sepsis, FAS pathways are enhanced in the macrophages, DCs, and T and B cells, to support their activation, differentiation, and effector functions. A reduction in FAS has been shown to be associated with increase in immature neutrophils (band forms). Thus, FAS is a common pathway in the effector cells of the immune system to support their increased growth and metabolic needs.[27]

Amino acid pathways in immune cells: Proliferating immune cells have an increased demand for protein synthesis and opt for ways that enhance the production of ATPs, especially during activation and differentiation. Additionally, metabolites from the amino acid pathways are involved in activation of mTOR, which has a pivotal function in regulating metabolic functions, by modulating elements of glycolysis and OXPHOS. They are also essential for the generation of cytokines, enzymes, and various cofactors, and especially in providing substrates necessary for meeting the increased demand for all the rapidly proliferating immune cells. Metabolism and metabolites of amino acids are central to the various immune responses, prominent

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of which are glutamine, branched-chain amino acids, arginine, tryptophan, amongst others. Glutamine (along with glucose) is especially essential for phagocytosis, cytotoxic functions, induction of cytokines (IL-1, etc.), generation of nitric oxide (by enabling arginine synthesis), enhances succinate production (by promoting TCA cycle), and also promote functions of M2 macrophages. Deficiencies of essential amino acids, glutamine, and arginine are associated with decreased levels of immunoglobulins, immunosuppression, and immunoparesis, leading to overwhelming infections. Immune cell metabolism of amino acids plays a central role in immune responses.[28,29]

IMMUNOMETABOLISM IN SEPSIS

The immune system has a primary role in preventing, defending, and limiting serious infections. However, abnormal immune responses lead to sepsis as a result of disturbed and disrupted metabolism in the immune cells. Sepsis-3 defines sepsis as a life-threatening organ dysfunction caused by a severely dysregulated host response to infection.[30,31] The disorder begins with failure of the innate immune responses to clear the pathogenic organisms, which results in a massive release of inflammatory mediators by overactivity of the acquired immune responses, resulting in a serious condition called "cytokine storm." This is thought to be due to severe disruption of the interactions between metabolism and all the prominent types of immune cells. Neutrophils and M1 macrophages show an enormous shift from OXPHOS to glycolysis, with an increase in the expression of glucose transporters (GLUT 1 and 3), and an increase in PPP pathways. There is a massive expansion in the production of immature innate immune cells, the myeloid-derived suppressor cells (MDSCs). Glycolysis, glutaminolysis, and metabolism of amino acids are increased, and FAO is inhibited within the MDSCs, resulting in an increase in anti-inflammatory molecules and immunosuppression. Elevated levels of pro- and anti-inflammatory mediators lead to significant dysregulation of metabolism in the various subsets of T cells, leading to increase in apoptosis ($CD4^+$, $CD8^+$, and ϒδ T cells), B cells, and DCs. There is an increase in resistance to apoptosis in T_{regs}. Along with the increase in MDSCs, the persistence of T_{regs} contributes significantly to immune suppression. Being an energy-intense process, the amplification of these immunometabolic dysregulations lead to paucity of energy supply and defective supply of building blocks, causing ineffective effector immune responses and imperfect memory cell functions. As a consequence, there is a breakdown in the processes of pathogen eradication, with a rapid progression of the disease, reduced tissue perfusion, organ dysfunctions, and overwhelming sepsis and septic shock.[32]

CONCLUSION

The most remarkable aspect of each and every biologic function depends on cell metabolism. A highly regulated metabolism in the immune cells is a mandatory process for their normal production, differentiation, proliferation, activation, and effective function. An abnormally aberrant metabolism is the basis of dysregulated immune responses, resulting in the pathogenesis of various diseases, including sepsis. Immunometabolism, an interaction between immunology and metabolism, is a developing field of investigation evaluating the metabolism within immune cells and immune responses. Understanding the

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interplay of immunometabolic pathways offers a tremendous potential to strategize therapeutic interventions in various diseases, including critical illness and sepsis.

A detailed and a comprehensive description on the basic metabolic pathways, immunity in health and diseases, immunometabolic pathways, and potential therapies to target immunometabolic factors are beyond the scope of this chapter and can be appraised from the list of references and dedicated textbooks.[33]

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Subhal Bhalchandra Dixit MD (Medicine) FCCM FICCM FICP is the Director, Department of Critical Care ICU, Sanjeevan and MJM Hospital, Pune, Maharashtra, India. He has held major posts at the national level including Past President, Indian Society of Critical Care Medicine (ISCCM), and Past Chancellor, Indian College of Critical Care Medicine (ICCCM). Currently, he is Treasurer, Sepsis Forum of India. He has a special interest in critical care and specializes in critical care nutrition, sepsis, and ventilation. He has authored numerous chapters in various textbooks and has many national and international publications and original published research. He is also the Chief Editor of various books in critical care and nutrition.

Kapil Gangadhar Zirpe MBBS MD (Chest) FICCM FCCM FSNCC is the Head, Department of Neuro-Trauma Intensive Care Unit, Grant Medical Foundation, Ruby Hall Clinic, Pune, Maharashtra, India. He has completed MBBS and MD (Chest Medicine) from Dr VMMC Medical College, Solapur, Maharashtra affiliated to Shivaji University, Kolhapur. He was conferred with Fellowship of Indian College of Critical Care Medicine (FICCM) by Indian Society of Critical Care Medicine (ISCCM) in 2013 and Fellowship of American College of Critical Care Medicine (FCCM) in 2016 by Society of Critical Care Medicine (SCCM). He was conferred with Fellowship of College of Neurocritical Care Medicine (FSNCC) by Society of Neurocritical Care (SNCC), India in 2021. He is the President of Association of SAARC Critical Care Societies (ASARCC). He is the Past President of SNCC and the Past President of ISCCM, Mumbai. He was a Council Member of World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM). He is Council Member of Asia Ocean Chapter of Neurocritical Care Society (NCS). He is an Editorial Board Member of Indian Journal of Critical Care Medicine (IJCCM) and Reviewer for IJCCM, Indian Journal of Medical Research (IJMR) and IJCC.

Atul Prabhakar Kulkarni MD (Anesthesiology) FISCCM PGDHHM FICCM is currently Professor and Head, Division of Critical Care, Department of Anesthesiology, Critical Care and Pain, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, Maharashtra, India. A recognized postgraduate teacher for MD (Anesthesiology), he is now a Teacher for DM (Critical Care Medicine). A postgraduate diploma holder in Postgraduate Diploma in Health and Healthcare Management, he has received training in Intensive Care at St George Hospital, Sydney, Australia in 2002–2003. He has participated in many conferences on critical care and anesthesiology at international, national, and state levels. He was the Organizing Secretary for Anesthesia Review Course since 2004 to 2018. He was the Treasurer of Indian Society of Critical Care Medicine (ISCCM) during 2004–2010. He was later General Secretary of ISCCM (2010–2014) before he took over as the President of ISCCM (2015–2017) and the Chancellor, Indian College of Critical Care Medicine (ICCCM). He was a Member of an Editorial Board of Indian Journal of Critical Care Medicine (IJCCM) and Reviewer for IJCCM and Indian Journal of Anesthesia (IJA). He is also the Past President of Association of South Asian Association for Regional Cooperation (SAARC) Critical Care Societies and Secretary General. After serving as the Honorary Secretary General of the Asia Pacific Association of Critical Care Medicine, he took over as the President of the prestigious organization. Currently, he is an Editor-in-Chief of IJCCM.

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