



**SELINUS UNIVERSITY**  
OF SCIENCES AND LITERATURE

# **NUTRITION AND ITS EFFECTS ON IMMUNITY**

By  
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I do hereby attest that I am the sole author of this thesis and that its contents are only the result of the readings and research I have done.

A handwritten signature in blue ink, appearing to read 'Bảo Nguyễn', is written above a horizontal blue line.

Bảo Nguyễn

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## ABSTRACT

This thesis has been to analyze to give the readers a better understanding the effect of nutritional elements on human immune system. Human immune system is composed of a variety of different cell types and proteins. The cells and proteins that wonderful collaboration work together to provide defense against infection. It is regulated by cells and organs in our body like the spleen, thymus, bone marrow, and lymph nodes. When a foreign substance enters the body, these cells and organs create antibodies and lead to multiplication of immune cells (including different types of white blood cells that we need them from our nutritions) that are specific to that harmful substance and attack and destroy it. There are many factors that affect immune system functions, one of those is nutrition. There is a significant correlation between immune system and nutrition, furthermore malnutrition shouldn't be considered as energy and a protein deficiency alone. Due to these reasons, the main aim of nourishment is not merely to gain energy and protein, but to enhance resistance against ailments with some specific nutriment and to turn the inflammatory response in someone's best interests.

## Chapter 1. Introduction

### 1.2 Introduction to the topic

After six years working and observe over thousands of people from sedentary and athletes. Human beings are in close relation with the microorganisms that were common in nature. Immune system is a means of protection against the damaging effects of noxas, which cause infection in our bodies. Immune system is a form of protection consisting of, thymus, spleen, lymph nodes and some specific immunity cells [1]. Immunity, on resistance against microorganisms acts both naturally and acquired in a complex mechanism, but they are mostly in collaboration. One of the factors that affect natural resistance is nutrition.

### 1.2 The aim of the thesis

The thesis aims to inform the readers about of dietary factors that cause harm to immunity functions are either deficient intake of macro-nutrient elements (fat, carbohydrate, protein) or deficiency in some specific micronutrient elements (vitamin, mineral, water). Balanced nutrition, especially in terms of adequate vitamin, mineral and protein intake, enhances the resistance against infections. Research's show that balanced nutrition subsidizes the immune system and carry out vital importance on the system [2].

Nutrition has an impact on body resistance and microbes. Excessive strain, Traumas, Ambustions, etc., could cause protein destruction consequently body resistance decreases. Malnutrition, especially in childhood play vital role in catching illness and mortality. Malnutrition paves the way for infections and their complications. This composed infection distorts the nutrition and abates the immunity [2,3].

The effects of nutritional elements on immune system has been a study case for many research's because there is significant influence on supporting immune system and in deficiency it causes malfunction in immune system [2,3]

### 1.3 . Explantion of Human immune system

The immune system is comprised of both the innate (fast, non-antigen specific) and adaptive (slower, antigen-specific) responses. The innate immune system is comprised of physical barriers that help prevent pathogen entry (e.g., skin, gut epithelium), antimicrobial peptides, the complement system, and a variety of phagocytic and other cells (e.g., neutrophils, macrophages, natural killer cells), that recognize the presence of pathogens via the expression of nonspecific pattern-recognition receptors [9].

The innate system moves quickly to recognize and destroy “non-self” threats, typically via inflammatory processes, and then resolve the inflammation and repair the damage caused by these events [9]. However, innate immunity does not increase efficacy or speed of response with repeated exposure to a pathogen. Subsequent to the innate response, the adaptive response is engaged.

The adaptive response includes antigen-specific cells, e.g., T lymphocytes, subsets of which coordinate the overall adaptive response or kill virally-infected cells, and B lymphocytes, which can be activated to secrete antibodies specific to the infecting pathogen [9]. While slower to respond than the innate system, the adaptive system is responsible for generating immunological “memory”, whereby a repeated infection with the same pathogen will generate a vigorous, fast antigen-specific response [9]. The induction of immunological memory is the mechanism by which vaccines can provide protection against subsequent pathogen exposure. Undoubtedly, public hygiene practices and, when available, vaccinations can be effective mechanisms to provide protection against infectious disease. However, vaccines can take years to create, are

not available against all viruses (including the current coronavirus SARS-CoV-2), and provide varying levels of protection. The morbidity and mortality numbers cited above highlight the need for additional strategies to support the immune system, in order to reduce the impact of respiratory and other infections

Immune system is a common name for structures within our bodies that protects living organisms against harmful substances. Human body possesses many elements in self defence. One of the simplest of those is outer creatine layer on the skin. Another element is biochemical body units [4].

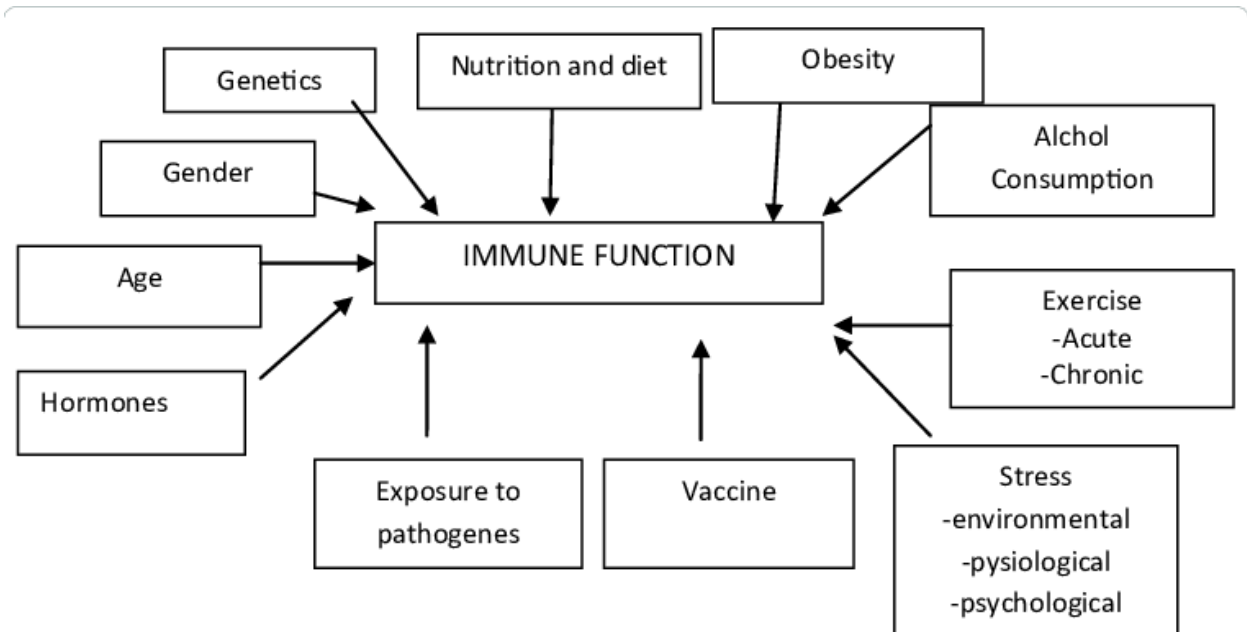
The substance that stimulates the immune system is generally known as nonspecific substance like macrophage and neutrophils that enhance the defence capability of phagocytes. The many of those substances ad here the surfaces of phagocytes and lymphocyte cells and also stimulates the production of interferon, interleukin and sophisticated compositions, consequently activates the immune system [4].

Immune system has a structure that consists of similar neurologic system. One of the most significant traits of immune system is, having the ability of recognizing the millions of different threats and distinguishes them. Thanks to this trait, the functionary cells in immune system, detect the unfamiliar object, memorise it and recognise it when coming across later. These structures are; thymus spleen, lymph nodes and specific immunity cells.

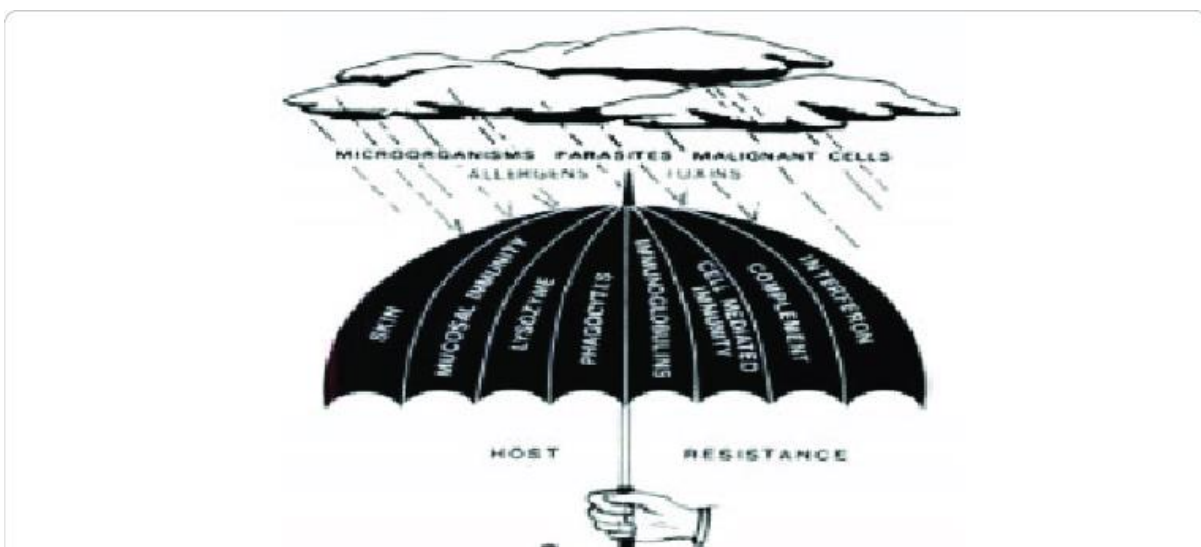
Immune system gets down to work as soon as pathogenic factors entering the body. This defence carried out by immune system against pathogenic called “immune response”[1,5,6].



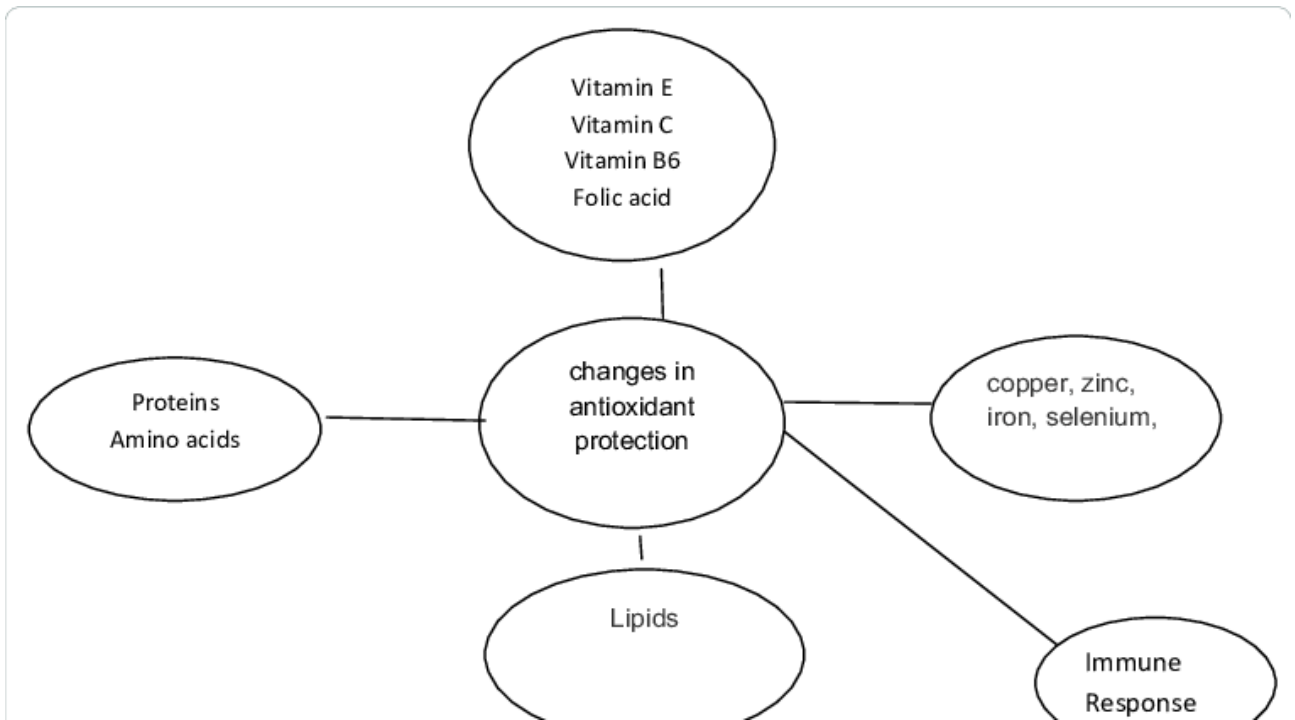
Immune system is a moliminous mechanism in fighting against diseases and sanitation. The possible response of immune system against body cells is called autoimmune reactions and consequently autoimmune disorders occur [7-13] (Figures 1 and 2).



**Figure 1:** Factors effecting immune function



**Figure 2:** The correlation between immune system and distorting health elements [2].



**Figure 3:** Nutritional elements and immunity response relation [5].

## Chapter 2. Effects of nutrition on immune system

Often missing in public health discussions around immunity and infection are nutritional strategies to support optimal function of the immune system. This is surprising, given that the importance that nutrition plays in immune function is well established. Several vitamins, including vitamins A, B6, B12, C, D, E, and folate; and trace elements, including zinc, iron, selenium, magnesium, and copper, play important and complementary roles in supporting both the innate and adaptive immune systems. Deficiencies or suboptimal status in micronutrients negatively affect immune function and can decrease resistance to infections [10–12]. Indeed, with the exceptions of vitamin E and magnesium, each of these micronutrients has been granted health claims in the European Union for contributing to the normal function of the immune system [13]. Other nutrients such as omega-3 fatty acids also support an effective immune system, specifically by helping to resolve the inflammatory response [14]. The mechanistic roles that micronutrients play to optimize immune function have been well-described recently [10,12]. Most micronutrients exhibit pleiotropic roles in supporting immune function. With respect to innate immunity, the vitamins and minerals listed above collectively function to support the development and maintenance of physical barriers; production and activity of antimicrobial Nutrients 2020, 12, 1181 3 of 10 proteins; growth, differentiation and motility/chemotaxis of innate cells; phagocytic and killing (e.g., oxidative burst) activities of neutrophils and macrophages; and promotion of and recovery from inflammation (e.g., cytokine production and antioxidant activity). They also support adaptive immunity, via lymphocyte differentiation, proliferation and homing; cytokine production; antibody production; and the generation of memory cells. The roles that vitamins C and D play in immunity are particularly well elucidated. Vitamin C affects several aspects of immunity, including supporting epithelial barrier function, growth and function of both innate and adaptive immune cells, white blood cell migration to sites of infection, phagocytosis and microbial killing, and antibody production [10]. Many immune cells have vitamin D receptors that affect their function after ligand binding, and as such vitamin D profoundly influences immunity.

For example, it promotes differentiation of monocytes to macrophages and increases their killing capacity; modulates the production of inflammatory cytokines; and supports antigen presentation. Furthermore, vitamin D metabolites appear to regulate production of specific antimicrobial proteins that directly kill pathogens, and thus are likely to help reduce infection including in the lungs [15,16].

It is known that each year in the world 6 million children die because of infections caused by malnutrition due to breakdown in immune system. Therefore we must make sure we consume adequate protein, especially milk dairy products, eggs which are biologically valuable proteins in order to keep our immune system strong [3].

## 2.1. Carbohydrates (CHO):

Carbohydrate is an important fuel cell for immune system. That anaerobic glycolysis showing an increase on lymphocytes, stimulated in mitogens, indicates the increase of glucose as a fuel. However during the lymphocyte proliferation, usage of carbohydrates for energy decreases. In this case, glycolytic products are directed to purine and pyrimidine nucleotide synthesis for cell growth [2,3,8].

Carbohydrates are nutrients largely found in vegetative foods containing carbon, hydrogen and oxygen molecules [8,16]. They are classified as simplistic (sugar) and complicated (starch). Glucides are found in sugar, fruits and fruit juice. On the other hand complicated starch is found in vegetables, legumes and cereals.

Carbohydrates are situated in human body as glycogen in a small amount. Glycogen is mostly in liver. In other organs and muscles a little amount of glycogen exists. That being present in blood in the form of glucose in certain amount, is very important in respect for provision of continuous energy for tissues [8,17].

It is emphasised that on high CHO diet, consumption of raw CHO sources affects the immune system negatively. The key point that makes CHO an important figure in the immune system is that, it is the most important fuel and its ability to prevent the decrease of number of cells is conjoint to apoptosis [18].

## 2.2. Fats:

Fats are among the most important nutrition sources for our lives. Fats take an active role in some biological functions such as; absorption of vitamins A, D, E and K needed for human and animal nutrition, being a source of omega 3 and omega 6 oil acid, being functional at neuritis functions, provision of permeability and stability for cell membranes [18]. Fats are important energy sources 1 gram fat provides twice the energy as protein and carbohydrate does [16]. Fat acids are powerful modulators of immune response. Studies on animals verify that conjugated linoleic acid available in meat and dairy products stimulates the immune system and prevent breast cancer. Linoleic acid also decreases allergic sensitization. Diets, containing high amount of fats can also decrease cellular inflammatory activity and immune response [19]. It is a well known fact that omega 3 fat acids lower blood pressure and plasma aggregation and inflammatory response [11].

As mentioned above, inflammation is a key component of the immune response. This response is caused by a variety of pro-inflammatory mediators, produced by several different types of cells, resulting in the influx of fluid, immune cells, and other mediators that function to eliminate the infection. Inflammation typically resolves quickly at the end of the immune response, due to activation of specific negative-feedback mechanisms. Among these, the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) present at the site of inflammation are enzymatically converted to specialized pro-resolving mediators (SPMs) known as resolvins, protectins,

and maresins. These molecules, along with others, function together to orchestrate the resolution of inflammation and to support healing, including in the respiratory tract [14,17]. Notably, nutritional deficiencies in these essential fatty acids can result in delayed or suboptimal resolution of inflammation [17]. This could be very important in the context of severe COVID-19 which manifests as uncontrolled inflammation, the so-called cytokine storm [18,19], linked with acute respiratory distress syndrome (ARDS). A number of the SPMs formed from EPA and DHA have been shown in animal models to both protect against and resolve acute lung injury and ARDS [20–24]. Nutritional formulas containing antioxidants and rich in EPA and DHA have been used in several human trials of patients with ARDS. A recent Cochrane review of these trials identified a significant improvement in blood oxygenation and significant reductions in ventilation requirement, new organ failures, length of stay in the intensive care unit and mortality at 28 days [25]. Taken together, these findings suggest an important role for EPA and DHA in ameliorating inflammation and lung injury, perhaps acting via conversion to SPMs.

### 2.3. Proteins:

Proteins make up frame work for cells. They are also framework of body defence systems, enzymes that control body functions, and some hormones [17]. Proteins are nutriments that contain nitrogen, carbon, hydrogen and oxygen in their chemical structures. Many immune mechanisms rely on production of active protein compounds or cell replication. In protein deficiency, functions of immune system decrease. It is thought that the negative effect of protein deficiency on immunity is connected with the effect of immune system regulator for some amino acids. Deficiency in essential amino acid can also cause repression on immune system. Too much consumption of some amino acids can cause diverse effect on immune system functions [19]. The latest studies show that protein metabolism play an important role in formation of natural and acquired immunity against infections. Arginine: Arginine is an amino acid mainly used for hospitalized patient's [20]. It is among the amino acids containing most

nitrogen in the course of growth, illness or metabolic stress, endogenous syntheses remain incapable and it is regarded as conditional essential amino acid. It enhances lymphocytic progress and phagocytosis, and speeds up the wound healing. It enables normalization of T-cell response after serious surgical procedures and traumas. On arginine deficiency, NEK risk arises. It has also antitumor activity. It stimulates anabolic hormone cycle and enhances nitrogen balance [20]. It is required to have a look at studies, done with arginine to determine its location in immune nutrition. Glutamine: It is the most freely amino acid in blood. Besides it is an important nutrient for prolific cells (blood cells, intestinal cells, cancer cells, etc). It ranks among the antioxidants, glutathione pyrimidine nucleotides, gamma amino butyric acid syntheses. In some cases, such as cancer treatment and intestinal injury, it has curative effects for digestive system. By this way, it can prevent micro be contamination to blood from intestines. It also takes part in regularization of acid-base balance. It is precursor of glutathione. In serious illness, it can be given either through vascular access or orally; however presentation orally to those babies with low birth weight can lower the risks of fatality rate. It is also important for nitrogen transport between organs. Patients that are given glutamine, after bone marrow transplant, the number of lymphocyte, T-lymphocyte, CD4+ and CD8+ is upwards [6,20]. Because it is not crucial for an amino acid, which absence in healthy bodies may not be a fail. Therefore, there is no need for daily intake [21]

### Chapter 3. Micronutrients :

#### 3.1. Vitamins

Another effective nutritional element on immune system is vitamin. Vitamins are subbranch of nutritional elements which play important role on growth and development, carrying out neurologic and digestion functions, using nutrimental elements effectively, supporting immune system and keeping sanitary [21-23].

Besides the important functions on metabolism, they are on duty for keeping normal cellular function in order [9,11]. In the course of inadequate intake, a break down occurs in growth and body functions. Most vitamins are not synthesized in human body, therefore they should be taken with the diet [10].

Vitamins distinguish as fat-soluble (A,D,E,K) and water-soluble (B,C) [14,22] and the effects of these vitamins on immune system, have been study case for many research [9,23,24]. Ailments, related to vitamin deficiency occur, as a result of vitamin deficiency. Vitamin deficiency causes repression in production of immune cells and cause malfunction [12,23]. It has been established that, vitamins that are considerably important in general metabolism, are very functional at resistance and immune mechanism and vitamin A, vitamin C, pyridoxine, pantothenic acid and thiamine are very effective against infections.

In vitamin A and C deficiency, repression in studies stating that [20,23]. Using vitamins A, E, C beta, carotene, and folic acid along with B12 as a supplement is very effective on cardiac vascular complaints and cancer mortality and morbidity. However some prospective trials suggest that  $\beta$  carotene supplements have little positive effect. Nevertheless it has been reported that vitamin C have positive effect on atherosclerosis. Vitamin C supplementation for cancer patients enhances the life quality and life time [21,25,26]. Water soluble vitamins:

- Vitamin B: It is a water soluble vitamin. B-complex vitamins are thiamine, riboflavin, niacin, vitamin B6, pantothenic acid and biotin [13]. Apart from these, folic acid and B12 are among the group B vitamins [22,23,25]. It is thought that, riboflavin, vitamins B6 , B12 and folic acid are effective on immune system [14,26]. Vitamin B6 , is the most needed one for immune system among other group B vitamins [21,22]. B12 and folic acid, play important role on protein, DNA and RNA synthesize. For this reason they are closely related to immune system. In vitamins B6 deficiency, production of immune body and lymphocyte decreases. Same deficiencies emerge in folic acid deficiency



[21,23].

Vitamin B12 also in close relation with folic acid and deficiency of it effects protein and nucleic acid synthesis negatively [22,23].

- Vitamin C: The effects of vitamin C on immune system have been argued for many years however many people have been consuming it in order to avoid flu and catarrh. It has been seen from the studies that supplementation of vitamin C, enhances the production of white blood cell, and immune body and helps their proceedings. However the studies of the effects of Vitamin C on catarrh and upper respiratory infections show that it doesn't reduce the infection rate however it reduces the time and stress of incidents [12]. It is claimed that vitamin C protects the body against infections and bacterial toxins. During the infections, the amount of vitamin C in the body decreases 12. Vitamin C also contributes to iron absorption; it is also known as anticancer element. The functions of group B vitamins are so multifarious. For instance, thiamine take charge in carbohydrate metabolism riboflavin in protein and fat metabolism lastly niacin takes charge in all metabolic functions [12,22,23,27].

- Vitamin A: Vitamin A is a fat soluble vitamin. Vitamin A that is needed for body is supplied from retinol and caratenoids [23,28]. It is mostly available in yolk, liver and milk fat. Especially in children, pneumonia and diarrhoea progress slowly. If there is any vitamin A deficiency then course of illness having vitamin A makes the disturbance gentler. In vitamin A deficiency production of immune body decreases, if vitamin support is made immune body production increases. It is thought that vitamin A may have anti inflammatory effect. There are many cases indicate that vitamin A support decreases the inflammatory response in acne bronchopulmonary dysplasia and same cancer cells [29,30]. A fat soluble vitamin A, take charge in formation the epithelial tissues, which spreads over the body, visual function and provide continuity in immunity functions [30].

- Vitamin D: Vitamin D which is derived from fish and fishy oil and synthesized endogenously by isolation has [14,23] many responsibilities in providing the usual calcium and phosphorus level in blood absorbing calcium to the bones [31], muscle contraction, nerve conduction and other cellular functions [32-34]. After determination of vitamin D receptor in cells, it has been understood that it has many other functions apart from already known classical functions [23,32]. It has been concluded in consequence of the studies conducted that vitamin D might have immunomodulatory affects [7,13]. It is thought that, in adequate intake (50 mcg is recommended) of it, it can be effective in carrying out optimal immune functions, reduction in autoimmune disease incident and enhancing the clinical picture [7,33,35]. In the same time, it is a powerful immune system regulator [7,33].

- Vitamin E: Vitamin E shows inhibitory activity to formation of immunomodulator and platelet [22] on the grounds that it is a fat soluble antioxidant, it enhances the immune response. Having taking vitamin E, stimulates the enhancement of white blood cell, helps them to destroy foreign cells, helps destruction of microbes by special cells and enhance resistance against infectious agents. It also enhances immune body productivity. Even though different results have been obtained, it has been seen that it lessened multiple infections while it has no effect on respiratory tract infections in elderly.

Vitamin E is effective in strengthening immune system. It enhances the body resistance against catarrh and other infections and prevents vitamin A getting oxidized. It has important to consume good sources of vitamin E such as vegetables, hazelnut, walnut and legumes adequately [36,37]. Its antioxidant functions make vitamin E primarily effective against infections [22].

- Vitamin K: Vitamin K, which is a crucial vitamin for normal coagulation and modification of protein that are dependent to it, is thought to be in relation with some immune cells [38]. Protein S one of a dependent protein to vitamin K [14], is thought to

be related to C4B binding protein (C4BP) and this relation indicates us positive results in favour of B cells [39].

### 3.2. Minerals:

Minerals are colourless substances found in nutrients and are vital for cellular functions [16] minerals are substances that can't be self created by body. Minerals generally collaborate with vitamins and provide vitamins transportation to the most needed areas. At the same time, they play important role in blood pressure cardiac rhythm, muscular functions, keeping the fluid balance, fertility and many more functions. The scientific studies show that mineral loss and deficiency affect our health directly [17]. There are identified at least 13 vitamins as well as improperly distributed in tissues they all are available in fish [40]. Fish, as well as being a good source of poly unsaturated fatty acids (omega3) calcium, phosphor, selenium and iodine minerals for the development of brain functions, it also helps strengthen the immune system [36]. Aquatic products are magnificent calcium and phosphor course, containing between 15 to 200 mg calcium in every 100 g and 100 to 400 mg in every 100 g in some species. Fish is recommended to those who need sodium died with the containable 60 mg sodium in 100 g muscle. Potassium which functions as a catalyser in carbohydrate and protein metabolism, eurhythmy, nerve transmission, muscle contraction is found in fish meat in the ratio of between 250-500 mg in every 100 g. Again fish meat is a good source of magnesium which functions as a catalyser in enzyme systems [40]. Trace elements:

- Selenium (Se): It is a crucial element which is needed for the progression of both natural and acquired immune system. In serious diseases, deficiency in selenium increases the fatality rate considerably.

Glutathione peroxidise which formed during daily metabolism and which is catalyzing hydrogen peroxide and organic peroxidises is determined to selenium. It ensures the integrity of cell membrane and prevents DNA damage. It reduces the fatality rate in sepsis treatment, infections rate in ambitions; consequently it reduces the antibiotic

usage. In default of it, antibody formation decreases, transportation of white blood cells slows down and injuriousness of some viruses' increases, Selenium support enhances the antibody level in blood. There are far more traits to be discovered about selenium [19]. Selenium possesses important immunity functions in protection of cells against oxidative damage. Selenium is mostly found in aquatic products, kidney, heart and liver and also in whole wheat [41-43].

- Zinc (Zn): Zinc has features stimulating the immune system. Zinc helps prevention of infections in the long term. Beside this, it has been seen that, zinc pastilles speed up the viral diseases and are very effective in relieving the symptoms. It is needed for many enzyme activation including DNA and RNA synthesis. It has also antioxidant effect. In deficiency, malfunction in cellular immunity, deterioration in acrodermatitis and enteropathica, increase, in fungus, virus, bacterial infections; decrease in thymus gland and lymphocytes and changes in rations, diarrheal, malabsorption and slowdown in growth occurs. The effects of zinc on immune system functions take place with immunity support. Adequately zinc intake improves the anticancer effect of vitamin A and helps newly developed cancer cells by strengthening defence system. The best zinc sources are giblets like liver, meat aquatic products, eggs, cheese, walnut, hazelnut, whole wheat and whole wheat bread [40-44].

- Copper (Cu): Copper plays an important role in immune system development and continuation. Even though, both deficiency and superabundance cause some negative effects on immune system, in take with food is generally sufficient and immunity problems relating to copper deficiency aren't encountered [43,44].

- Iron (Fe): Both deficiency and superabundance have an effect on immune system. Virus and bacteria need iron for proliferation. There for during acute infectious diseases, giving iron should be avoided. In iron deficiency, transportation of white blood cells

toward infectious areas decreases and destruction of microbes that entered in cells abates. Fertility of lymphocyte, in charge of defence, is affected negatively in deficiency of iron. However, cells, in charge of production of antibody, what is called humoral immunity aren't affected by iron deficiency. It can be emphasised that, in areas wide spread of malaria; iron support to children can increase the complications [22,23,43].

Prebiotics and probiotics: Probiotic products are beneficiary microorganism added nutrients.

Intestines are known as the biggest immune organ in body. Intestines bacteria are always in interactivity with the immune system bacteria in intestines. This interactivity is very important for immune system development.

Probiotics are effective on systemic immune response as well as strengthening the immune system is gastrointestinal system. Probiotics can activate the effects mentioned above [10,34,43]. Non-pathogenic microorganisms, which regulate mucosal and systemic immunity when taken with foods, are separately and which regulate the nutritional and microbial balance, are called probiotics [31,34,43]. Probiotic consumption has some immune inflammatory diseases e benefits; immune system stimulation, regulation, protection against enteric infections, and immune inflammatory diseases (inflammatory bowel diseases) mitigation of lactose intolerance symptoms, reduction in blood cholesterol level and prevention of cancer [11,45-47]. It has been stated that, probiotics strengthen the mucosa defence systems and affects on immune stimulation. Probiotic bacteria stimulate the immune system of host, by effecting specific immunity and natural immunity. It has also been stated that, the presence of probiotic bacteria in viable cell's intestines, stimulates and strengthens the immune system [44,46-48]

### 3.3. Antioxidants:

In the course of metabolic functioning a large number of oxidant substances develop. These are so reactive free radicals and they should be neutralized by antioxidants for not to be harmful to cells. However free radicals develop on normal body conditions, it can also develop by radiation smoking, pollution, foods and medicines. Free radicals are use full to body, for they are used for killing microbes. However, surplus and needless ones should be neutralized at once. In the course of neutralization of free radicals, Se, Zn, Cu and Mn needed for enzymes to function. Vitamin E, vitamin C, vitamin D, alfa tokoferol, beta-carotene, uric acid, transferrin, seruloplazmin, flavonoids, lycopene (tomato) are elemental antioxidant substances. There is no need to take extra antioxidants for a person who has health food regularly. The more refined food consumption in daily consumption the fewer intakes of antioxidants [23,28].

Vitamin A, C, E and enzymes such as beta carotene zinc, selenium, copper, glutathione superoxide dismutase and glutathione peroxidase have this anti oxidant functions [11]. Vitamin A, C, E, zinc and selenium are called “war quintette” because of their power full antioxidant traits [23].

## Chapter 4. Diet and immune funtion

### 4.1. Malnutrition and immune system

Malnutrition breaks down the immunity functions by repressing immune system. Repressive immune systems cases have been increasing recently [13]. The dietary factors that cause malfunction in immune system could be insufficient intake of energy and macronutrients (CHO, protein, fats) or deficiency of specific micronutrients [8].

As mentioned above, inflammation is a key component of the immune response. This response is caused by a variety of pro-inflammatory mediators, produced by several different types of cells, resulting in the influx of fluid, immune cells, and other mediators

that function to eliminate the infection. Inflammation typically resolves quickly at the end of the immune response, due to activation of specific negative-feedback mechanisms. Among these, the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) present at the site of inflammation are enzymatically converted to specialized pro-resolving mediators (SPMs) known as resolvins, protectins, and maresins. These molecules, along with others, function together to orchestrate the resolution of inflammation and to support healing, including in the respiratory tract [14,17]. Notably, nutritional deficiencies in these essential fatty acids can result in delayed or suboptimal resolution of inflammation [17]. This could be very important in the context of severe COVID-19 which manifests as uncontrolled inflammation, the so-called cytokine storm [18,19], linked with acute respiratory distress syndrome (ARDS). A number of the SPMs formed from EPA and DHA have been shown in animal models to both protect against and resolve acute lung injury and ARDS [20–24]. Nutritional formulas containing antioxidants and rich in EPA and DHA have been used in several human trials of patients with ARDS. A recent Cochrane review of these trials identified a significant improvement in blood oxygenation and significant reductions in ventilation requirement, new organ failures, length of stay in the intensive care unit and mortality at 28 days [25]. Taken together, these findings suggest an important role for EPA and DHA in ameliorating inflammation and lung injury, perhaps acting via conversion to SPMs. It is not surprising, then, that deficiencies and even suboptimal status of these nutrients can impair immune functions. Depending on the deficient nutrient or nutrients, there can be decreases in the numbers of lymphocytes, impairment of phagocytosis and microbial killing by innate immune cells, altered production of cytokines, reduced antibody responses, and even impairments in wound healing [12]. These functional impairments are, presumably, what lead to the clinical immune-related manifestations of deficiency. Indeed, people deficient in vitamin C are susceptible to severe respiratory infections such as pneumonia [10,26]. A recent meta-analysis reported a significant reduction in the risk of pneumonia with vitamin C supplementation, particularly in individuals with low dietary intakes [27]. In older patients, disease severity and risk of death were reduced with supplementation,

particularly in the case where initial plasma levels of vitamin C were low [27]. Vitamin C supplementation has also been shown to decrease the duration and severity of upper respiratory tract infections, such as the common cold, and significantly decrease the risk of infection when given prophylactically in people under enhanced physical stress [26,28]

Likewise, vitamin D deficiency increases the risk for respiratory infection. Observational studies report an association between low blood concentrations of 25-hydroxyvitamin D (the major vitamin D metabolite) and susceptibility to acute respiratory tract infections [29,30]. Consistent with these findings, several recent meta-analyses have concluded that vitamin D supplementation can reduce the risk of Nutrients 2020, 12, 1181 4 of 10 respiratory tract infections in both children and adults [11,31–35]. In 2017, Martineau and colleagues performed a systematic review and meta-analysis of individual participant data (n = 10,933) from 25 randomized, double blind, placebo controlled trials of vitamin D supplementation with a specified outcome of acute respiratory tract infection (ARI). They found a 12% reduction for experiencing at least one ARI irrespective of dosing schedule [11].

They found a 19% reduction in individuals taking a daily or weekly dose without bolus doses and no benefit with bolus dosing. Among those receiving a daily or weekly dose, they observed a 25% reduction for those with baseline 25(OH)D levels  $\geq 25$  nmol/L (12 ng/mL) and a 70% reduction for those with baseline levels  $< 25$  nmol/L [23]. They concluded that daily or weekly vitamin D supplementation protected against ARI overall and that it was safe.

Clinical outcomes also demonstrate a role for vitamin E in respiratory tract infections. In a randomized controlled trial of 617 nursing home residents, daily supplementation for one year with 200 IU vitamin E reduced the risk of upper respiratory tract infections, but not lower respiratory tract infections [36]. Vitamin E enhances T cell-mediated immune



function in the face of age-related decline [37]. In one study, supplementation of older adults with vitamin E improved natural killer cell activity, neutrophil chemotaxis and phagocytosis, and mitogen-induced lymphocyte proliferation [38]. In a second study, vitamin E supplementation improved T cell-mediated immunity as measured by increased production of antibodies to hepatitis B virus and tetanus vaccines [39]. Finally, marginal zinc deficiency can also impact immunity. Zinc is important for maintenance and development of cells in both the innate and adaptive immune systems. Zinc deficiency results in impaired formation, activation and maturation of lymphocytes, disturbs the intercellular communication via cytokines, and weakens the innate host defense [40,41]. Those deficient in zinc, particularly children, are prone to increased diarrheal and respiratory morbidity [42,43]. Furthermore, data from animal models and epidemiological studies in people indicate that deficiency in specific nutrients, particularly selenium and vitamin E, can lead to reproducible genetic mutations and increased virulence of certain viruses, including coxsackievirus, poliovirus, and murine influenza [44,45]. In a double-blind placebo controlled study, an increase of selenium intake by otherwise healthy subjects with relatively low levels of plasma selenium concentrations improved cellular immunity. Subjects receiving selenium cleared an oral live attenuated poliomyelitis vaccine more rapidly and sequence analysis of the viral genome showed lower numbers of mutations as compared to those receiving the placebo. These data suggest that suboptimal nutrient status in the host population could lead to the emergence of more pathogenic strains of viral diseases, thereby increasing the risks and burdens associated with these illnesses. Given the current situation, it may be beneficial to further pursue this line of investigation

#### 4.2. A well-functioning immune system

Optimal intake of all these nutrients ideally would be achieved through the consumption of a well-balanced and diverse diet, but this can be difficult to accomplish for the general population. Indeed, it is generally accepted that nutrient inadequacies and deficiencies are widespread [46–50] (and references therein). Biochemical markers of nutrient status are particularly useful in assessing inadequacy or deficiency, and lead

to the conclusion that intakes often are not sufficient. For example, extensive data have been published, using blood 25-hydroxyvitamin D levels to assess vitamin D status. A systematic review involving 195 studies in forty-four countries reported that 37.3% of the studies found mean values lower than 50 nmol/L [51]. The US Institute of Medicine (IOM) committee that reviewed Dietary Reference Intakes (DRI) for vitamin D has suggested that those with concentrations less than this level are at risk for inadequacy, while those with concentrations between 50–75 nmol/L are considered sufficient [52,53]. Interestingly, while the highest vitamin D levels were reported in North America, data from the United States still indicate that 8% of the non-infant population was at risk for vitamin D deficiency, and 17% exhibited concentrations below the 25(OH)D level that is associated with desirable intake [53]. Other studies based on 25(OH)D levels indicate that vitamin D inadequacy or deficiency are also prevalent in Europe and China [54–56]. Similarly, a recent systematic review involving 132 studies of serum alpha-tocopherol status indicated that 13% of the values were below the threshold of deficiency (12 μmol/L). Deficiency was noted in the Americas, Asia Pacific, Europe, Nutrients 2020, 12, 1181 5 of 10 the Middle East and Africa [57]. The situation with vitamin C is similar. Currently, the most commonly used vitamin C cutoff levels are approximately  $\leq 23\text{--}28$  μmol/L for hypovitaminosis C and  $\leq 11$  μmol/L for deficiency [58]. The evidence indicates that vitamin C insufficiency or deficiency is common in low and middle-income countries (e.g., Mexico, Brazil, India), and not uncommon in high income countries (e.g., US, Singapore, New Zealand), particularly in at-risk subpopulations [53,59–67]. Furthermore, the WHO and the Food and Agriculture Organization (FAO) of the United Nations have described that, based on blood markers, vitamin A and iron deficiencies are widespread and of significant global concern [46,49,50]. Status data in the general population or specific subpopulations also reveal inadequacies or deficiencies in various countries, including in developed nations, for vitamins B6, B12, and folate, as well as zinc and selenium [53,59,60,68–73]. Finally, a global survey of EPA + DHA status in the blood, from 298 studies, found “low” or “very low” status (i.e., levels associated with increased risk of cardiovascular related mortality) of EPA + DHA in most of the countries assessed [74]. Collectively, the totality of these data strongly suggest

that micronutrient and omega-3 inadequacies or deficiencies are prevalent around the globe. It should also be noted that optimal nutritional support for the immune system can require intakes above the RDA for some micronutrients, while at the same time infections and other stressors can reduce micronutrient status in the body. Vitamin C levels, in particular, decrease during times of infection and higher intakes are required to restore normal blood levels [10,75]. These higher intakes and blood levels are associated with improved clinical outcomes. For example, supplementation of pneumonia patients with  $\geq 200$  mg/d vitamin C restored depleted plasma and cellular vitamin C levels, and resulted in decreased respiratory symptom scores and a dose-dependent decrease in hospital length of stay [76,77]

The nutrients which support and stimulate the immune system are called “Immuno nutritional elements” and some effective vitamins are included in this group [15]

(Figure3).

Studies of immune system metabolism (“immunometabolism”) segregate along two paths:

The first investigates the effects of immune cells on organs that regulate whole body metabolism, such as adipose tissue and liver.

The second explores the role of metabolic pathways within immune cells and how this regulates immune response outcome.

Distinct metabolic pathways diverge and converge at many levels and cells therefore face choices in how to achieve their metabolic goals. There is interest in fully understanding how and why immune cells commit to particular metabolic fates, and in elucidating the immunologic consequences of reaching a metabolic endpoint by one pathway versus another. This is particularly intriguing since metabolic commitment is

influenced not only by substrate availability, but also by signaling pathways elicited by metabolites. Thus metabolic choices in cells enforce fate and function and this area will be the subject of this review.

The immune system encompasses a heterogeneous population of cells that for the most part are relatively quiescent in the steady state, but share the ability to rapidly respond to infection, inflammation, and other perturbations. Responses are regulated by a broad range of cell type specific, and/or shared, activating and inhibitory receptors that are responsive to pathogen-derived or immune system intrinsic signals.

The response that is mounted by immune cells typically involves changes in the expression of large numbers of genes and results in the acquisition of new functions, such as the high output production of cytokines, lipid mediators, tissue remodeling enzymes, toxic gases, and the ability to migrate through tissues and/or undergo cellular division. There is a growing appreciation of the fact that transitions between quiescent and activated states require the apportioning of nutrients into different pathways and therefore there is a strong interest in how metabolic pathways are regulated to support or direct functional changes.

The need to produce ATP to provide energy for cellular function is of course essential in both quiescent and activated cells. Glucose can be used to fuel this process through two integrated pathways.

The first of these, glycolysis, involves the conversion of glucose to pyruvate in the cytoplasm. In this pathway, phosphates are transferred from glycolytic intermediates to ADP to generate ATP.

The second pathway, the tricarboxylic acid (TCA) cycle, generates the reducing equivalents nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH<sub>2</sub>), which donate electrons to the electron transport chain to fuel oxidative phosphorylation (OXPHOS), the process by which ATP is generated in the mitochondria.

Glycolysis and the TCA cycle can be integrated when pyruvate is converted into acetyl-CoA, which enters the TCA cycle. To differing degrees, cells also have the flexibility to metabolize other substrates, such as glutamine, via glutaminolysis, or fatty acids, via  $\beta$ -oxidation, to replenish the TCA cycle and fuel OXPHOS. Under hypoxic conditions cells can produce ATP solely by the breakdown of glucose via glycolysis, with pyruvate being diverted primarily towards lactate rather than acetyl-CoA.

In some cases cells preferentially use glycolysis for ATP generation even when oxygen isn't limiting, a process known as aerobic glycolysis or Warburg metabolism. Thus, as might be expected, cells have several options for producing ATP, and activity between different metabolic pathways will be influenced to a great extent by the relative availability of glucose, glutamine, and fatty acids, and whether there is sufficient oxygen to utilize OXPHOS. As has been pointed out before, in sufficiently fed metazoan organisms in the steady state nutrient availability is regulated centrally, and the ability of any given cell type to access nutrients will depend on their ability to express appropriate transporters and enzymes within the metabolic pathways that permit utilization of that nutrient ([Thompson, 2011](#)). The regulated expression and posttranscriptional control of pathway specific genes and/or proteins therefore assume key roles in dictating the metabolic profile of a cell under specific circumstances. In the immune system, this level of regulation is imposed by growth factor cytokines and by key activating receptors such as toll-like receptors (TLRs) on myeloid cells, and co-stimulatory receptors on T cells.

Interconnections between metabolic pathways are notoriously complex and it is therefore the case that superficially simple choices between aerobic glycolysis, or the oxidation of various substrates in the mitochondria for ATP production will have enormous ramifications on the outcome of key ancillary metabolic processes such as the pentose phosphate pathway (PPP, an offshoot of glycolysis that generates reducing equivalents in the form of nicotinamide adenine dinucleotide phosphate, NADPH, and ultimately is important for the synthesis of pentose sugars), the synthesis of fatty acids,

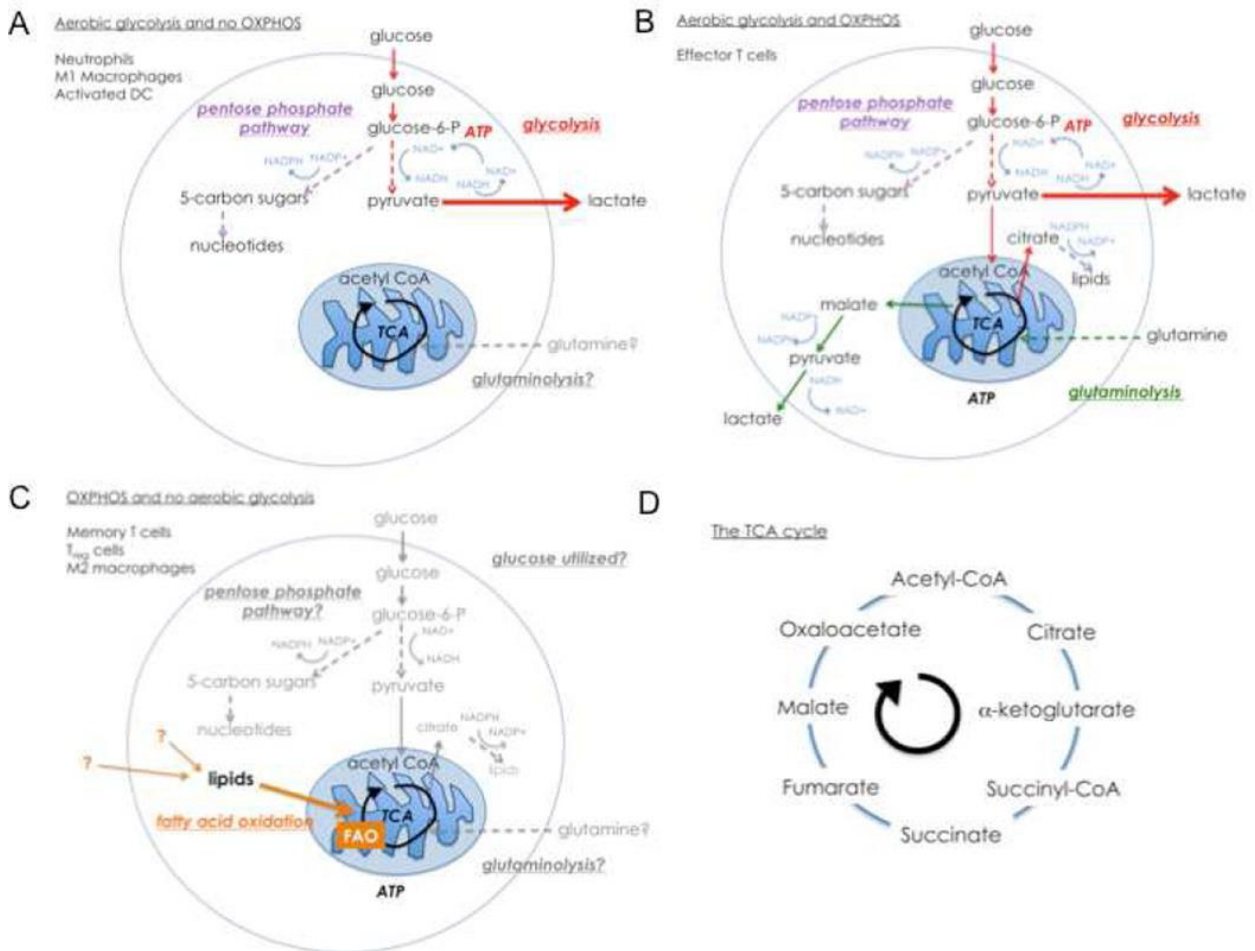
and the production of lipid ligands for nuclear hormone receptors. Thus regulated changes in metabolism are key to function.

## GRANULOCYTES

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There is a general view that myeloid cells primarily use glycolysis as a source of ATP ([Kominsky et al., 2010](#)). A fine example of this axiom is provided by neutrophils, short-lived granulocytes whose primary function is to rapidly enter sites of infection and initiate microbial killing. Studies dating back to 1950s have shown that neutrophils are highly dependent on glucose for ATP production via aerobic glycolysis ([Fig. 1A](#)) ([Sbarra and Karnovsky, 1959](#); [Valentine and Beck, 1951](#)). Consistent with this, neutrophils have few mitochondria and consume little oxygen ([van Raam et al., 2006](#)).

Upon activation by TLR agonists, or phagocytosis of antibody-coated particles, neutrophils increase their consumption of glucose and oxygen ([Borregaard and Herlin, 1982](#)). However, this is not a reflection of increased oxidation of glucose in the mitochondria, but rather it is a reflection of the Warburg effect and increased activity through the PPP ([Fig 1A](#)), which generates NADPH, an essential cofactor for the NADPH oxidase, which consumes oxygen to produce the important neutrophil microbicidal product H<sub>2</sub>O<sub>2</sub> ([Dale et al., 2008](#)).



**Figure 3: Cell fate and function in the immune system is supported by engagement of metabolic pathways**

In this diagram colored arrows represent pathways that have been shown to be used in the cell types indicated, grey arrows indicate pathways that might be used, but have yet to be clearly defined, and dashed arrows indicate multiple steps shown in a single arrow. A.

In activated neutrophils, M1 macrophages and iNOS expressing DCs stimulated with TLR agonists, Warburg metabolism dominates. ATP production and cellular survival are dependent on glycolysis, with the majority of pyruvate being converted to lactate. In this pro-glycolytic state, the PPP is active and provides NADPH for key microbicidal pathways regulated by NADPH oxidase. Under these conditions, there is little evidence

for OXPHOS, but maintenance of mitochondrial potential and integrity are needed to maintain cell survival. B. Activated T cells engage OXPHOS and glycolysis.

Most pyruvate is excreted as lactate, but some also enters the TCA cycle. Glutaminolysis is an important pathway in these cells as glutamine replenishes TCA cycle intermediates as they are withdrawn for biosynthesis. Metabolizing glucose in the PPP can yield both nucleotides and NADPH for lipid synthesis. C. Memory T cells, Treg cells, and alternatively activated macrophages use FAO for survival and to support function. Other pathways are depicted in grey as the extent to which they are used in these cells, if at all, has not been established. D. Overview of the TCA cycle.

The presence of non-functional mitochondria can be dangerous because loss of mitochondrial membrane potential can lead to the release of cytochrome c into the cytoplasm, and the initiation of apoptosis ([Galluzzi et al., 2012](#); [van Raam et al., 2006](#)). However, despite the fact that they are not functioning to produce ATP, neutrophil mitochondria maintain their membrane potential through the glycerol-3-phosphate shuttle, a pathway that allows the receipt of electrons from glycolysis by Complex III of the electron transport chain ([van Raam et al., 2008](#)). In this way the mitochondria simultaneously contribute to redox balance and promote flux through the glycolytic pathway while avoiding commitment to the apoptotic process. This extreme commitment to Warburg metabolism may underlie the ability of neutrophils to temporarily remain viable during netosis, the process of releasing extracellular traps of mitochondrial DNA and embedded microbicidal products ([Remijssen et al., 2011](#)). The importance of glycolysis in the microbicidal functions of neutrophils is emphasized by the fact that netosis is NADPH oxidase-dependent ([Kirchner et al., 2012](#)).



Available evidence, albeit scant, indicates that eosinophils and basophils are metabolically similar to neutrophils ([Sher et al., 1983](#); [Sumbayev et al., 2009](#); [Venge et al., 2003](#)). A unifying feature of granulocytes is that they are terminally differentiated, and largely incapable of proliferating in the periphery. It is interesting to speculate that this aspect of their biology is directly connected to their relative lack of mitochondrial function.

## DENDRITIC CELLS

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Dendritic cells (DCs) are heterogeneous and can be categorized into a large and growing number of subsets ([Satpathy et al., 2012](#)). These cells are functionally united in standing at the checkpoint between innate and adaptive immunity since activated DCs participate in the initiation of inflammation and play an essential role in priming of T cell responses ([Banchereau et al., 2000](#)). Activation can be driven via an array of receptors for pathogen associated molecular patterns (PAMPS) and alarmins that allow DCs to respond to infection or other changes in the environment ([Bianchi, 2007](#)). As is the case for macrophages ([Geissmann et al., 2010](#)), during inflammation DCs can arise from monocytes, and consistent with this, there are metabolic similarities in the way that monocyte-derived dendritic cells and macrophages respond to certain stimuli. Aspects of this area have been reviewed recently elsewhere ([O'Neill and Hardie, 2013](#)).

Many studies on DC biology have utilized cells derived from bone marrow by culture in granulocyte macrophage-colony stimulating factor (GM-CSF) as a model for monocyte-derived and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and inducible nitric oxide synthase (iNOS) producing (TiP) DCs. At rest, these cells oxidize glucose in the mitochondria, engage OXPHOS, and consequently produce relatively little lactate. However, after stimulation with TLR agonists they undergo a remarkable metabolic transformation in which they become dependent on Warburg metabolism for survival ([Krawczyk et al., 2010](#)).

Signaling through phosphatidylinositol 3-OH kinase (PI3K) and Akt is central to the regulation of glycolytic metabolism ([Locasale and Cantley, 2011](#); [Shaw and Cantley, 2006](#)) and consistent with this, PI3K and Akt play an essential role in sustained commitment to glycolysis in activated DCs ([Krawczyk et al., 2010](#)). In cells that have been activated for >12 h, despite the fact the glucose consumption increases, glucose carbons no longer enter the TCA cycle and mitochondrial oxygen consumption ceases ([Everts et al., 2012](#); [Krawczyk et al., 2010](#)).

Rather, lactate production increases substantially and cells survive by aerobic glycolysis alone ([Fig. 1A](#)). The reason for the collapse of mitochondrial respiration in these cells is that activation leads to the expression of iNOS, which produces the toxic gas NO from arginine at a high rate ([Everts et al., 2012](#)). NO inhibits mitochondrial electron transport by nitrosylation of iron-sulfur containing proteins, including complex I (NADH-ubiquinone oxidoreductase), complex II (succinate-ubiquinone oxidoreductase), and complex IV (cytochrome c oxidase) and therefore blocks oxygen consumption and coupled ATP production ([Beltran et al., 2000](#); [Cleeter et al., 1994](#); [Clementi et al., 1998](#)). The general connection between reduced respiratory rate and inflammation has been recognized for some time and high output NO production by cells such as monocyte derived DCs and macrophages (described below) is the underlying cause since NO, which diffuses rapidly, is able to affect bystander cells within inflamed tissue ([Rees et al., 1998](#)). At low doses, in brain, liver, kidney and muscle cells, NO stimulates mitochondrial biogenesis, which ultimately results in an overall increase in mitochondrial ATP output ([Nisoli et al., 2004](#)). Whether dendritic cells are capable of a similar response to low NO concentrations is unknown. However, it is clear that the commitment to glycolytic metabolism in activated DCs occurs only in DC subsets that express iNOS, and that it is a direct consequence of the inhibition of OXPHOS by NO, and serves a vital survival function to provide ATP in the absence of mitochondrial ATP generation ([Everts et al., 2012](#)).

While aerobic glycolysis is clearly important for prolonged survival of activated DCs, it seems additionally likely that a rapid, early increase in flux through this pathway following stimulation with TLR agonists is important for initiating activation. We base this on the fact that 2-Deoxy-D-glucose, which inhibits glycolysis, is able to profoundly prevent early (<6 h, which is prior to the initiation of NO production) manifestations of activation when present at the time of DC stimulation ([Krawczyk et al., 2010](#)). It will be important to determine whether rapid changes in metabolism are important in other DC subsets in addition to those derived from cultured bone marrow cells.

DCs also play an important role in maintaining tolerance. This is exemplified by the situation in the gut, where regulation of potential responsiveness to the microbial flora is controlled to a considerable degree by the production of retinoic acid (RA), a small lipid metabolite of vitamin A, by gut associated lymphoid tissue (GALT) CD103<sup>+</sup> DCs ([Coombes et al., 2007](#)). RA is produced from vitamin A by a process that is dependent on retinal dehydrogenases (RALDH), and is a ligand for the nuclear receptors RA receptor (RAR) and retinoid X receptor (RXR) ([Nagy et al., 2012](#)). In the steady state RA strongly promotes both transforming growth factor- $\beta$  (TGF- $\beta$ ) dependent inducible T regulatory (Treg) cell development ([Coombes et al., 2007](#); [Mucida et al., 2007](#); [Sun et al., 2007](#)), and the production of IgA by B cells ([Mora et al., 2006](#)), which helps maintain intestinal barrier integrity, and therefore plays an important role in immune homeostasis in this organ. These processes are consolidated by the fact that RA induces expression of the gut homing molecules  $\alpha 4\beta 7$  and CCR9 in a variety of immune cells, and thereby plays a role in their retention within the intestine ([Iwata et al., 2004](#)). Paradoxically, in inflammatory environments RA also plays an important role in promoting the development of effector T cells ([Hall et al., 2011](#)). This may reflect the superimposition of inflammation-induced signals onto RAR and RXR signaling, or possibly functionally important differences in the composition of RAR and RXR heterodimers in T cells in steady state vs. inflammatory conditions.

## MACROPHAGES

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Macrophages are a key cell type in the immune system. They exist throughout the body as resident components of most tissues. These cells are embryonically derived, seeded into tissues in utero, and maintained by in situ proliferation ([Geissmann et al., 2010](#); [Schulz et al., 2012](#)). During inflammation additional macrophages of hematopoietic origin develop from monocytes recruited from the bone marrow ([Geissmann et al., 2010](#)). Macrophages play crucial roles in innate immunity and can respond to local immune- and/or pathogen-derived signals to adopt different activation states. Interferon- $\gamma$  (IFN- $\gamma$ ) in combination with TLR agonists promotes M1 (or classical) activation, whereas the cytokines IL-4 and IL-13 promote M2 (or alternative) activation ([Benoit et al., 2008](#); [Gordon, 2003](#); [Murray and Wynn, 2011](#)). From the host defense standpoint, M1 macrophages are inflammatory, secreting mediators such as IL-12, which promotes IFN- $\gamma$  production by NK cells and T cells, TNF- $\alpha$ , which activates other immune cells, and NO, which is directly cytotoxic; they are implicated in the clearance of many types of microbial infections. In contrast, M2 macrophages make a range of molecules that serve to modulate inflammation, promote tissue repair, and regulate adaptive immunity. M2 activation dominates the response to helminth parasites, and is linked to resistance to these metazoan pathogens ([Anthony et al., 2007](#)). Intriguingly, M2 macrophages play another crucial role, linked to metabolic homeostasis, particularly within adipose and liver tissues ([Biswas and Mantovani, 2012](#); [Odegaard and Chawla, 2011](#)). In lean animals, resident macrophages in these tissues express genes associated with M2 activation. Functionally, M2 macrophages serve to promote insulin sensitivity by inhibiting M1 activation and associated inflammation. In obese mice with insulin resistance, liver and adipose macrophages are M1-like and M1 products such as TNF- $\alpha$  are instrumental in causing insulin resistance. This area is discussed in detail in the accompanying review.

M1 and M2 activation are characterized by distinct metabolic states, which differ from those of resting macrophages ([Rodriguez-Prados et al., 2010](#)). This metabolic difference is most evident in the differential and defining difference in arginine use by these two

types of cell, with M1 cells using this amino acid as a substrate for iNOS (expressed in M1, but not M2 cells), while M2 macrophages use it as a substrate for Arginase1 (which is expressed in M2, but not M1 cells) ([Murray and Wynn, 2011](#)). Metabolically, M1 macrophages have a very glycolytic metabolism and therefore are similar to activated bone marrow derived dendritic cells ([Fig. 1A](#)). Remarkably, reduced mitochondrial respiration serves an important role in the production of reactive oxygen species (ROS) for host defense. Normally we would expect NADPH oxidase to play the dominant role in this process, but it has been shown recently that in macrophages activated by TLRs expressed at the surface membrane, mitochondria are recruited to phagolysosomes in a TNF receptor associated factor 6 (TRAF6) dependent fashion, and produce ROS that are important for killing phagocytosed bacteria ([West et al., 2011](#)). The link between inhibition of OXPHOS and this process is emphasized by the fact that treatment of macrophages with the electron transport chain inhibitors rotenone and antimycin-A, mimics the effects of TLR agonists in promoting mitochondrial ROS production ([West et al., 2011](#)). Mitochondrial stress that leads to increased ROS production also plays a key role in the activation of the nucleotide-binding domain and leucine rich repeat pyrin-3 (NLRP3) containing inflammasome. In macrophages infected with certain bacteria or viruses, or exposed to danger signals such as monosodium urate or extracellular ATP, or adjuvants such as alum, there are coordinated increases in mitochondrial ROS, IL-1 $\beta$ , and caspase-1 production ([Sorbara and Girardin, 2011](#); [Tschopp and Schroder, 2010](#)). The key role of mitochondria in this process has been demonstrated by the inhibition of inflammasome activation, and IL-1 $\beta$  and caspase-1 production, by inhibitors of mitochondrial ROS, but not by inhibitors of NADPH oxidase-dependent ROS ([Bulua et al., 2011](#); [van Bruggen et al., 2010](#); [Zhou et al., 2011](#)). Taken together, these findings point to an important role for mitochondria in inflammation and host-defense, a concept further supported by the (metabolically enigmatic) findings that mitochondria are a platform for the retinoic acid induced gene-1 (RIG-I) and mitochondrial anti-viral signaling (MAVS) initiated induction of type 1 interferon production in response to viral infection ([Koshiba, 2013](#); [Sun et al., 2006](#)).

The importance of the commitment to a glucose based metabolism in activated M1 macrophages is emphasized by the fact that expression of carbohydrate kinase-like protein (CARKL), which inhibits flux through the PPP, is repressed following stimulation with TLR agonists ([Haschemi et al., 2012](#)). The PPP is essential for M1 macrophages not only because it generates NADPH for NADPH oxidase, which is important for ROS production but also because NADPH is required for NO synthesis ([Aktan, 2004](#)), and moreover reduces glutathione, which then plays a crucial role minimizing auto-oxidative damage by ROS.

Hypoxia inducible factor-1 (HIF-1) plays an important role in the commitment to glycolysis by orchestrating the decision to commit pyruvate to acetyl-CoA or to lactate ([Kim et al., 2006](#); [Papandreou et al., 2006](#)). In order to maintain flux through the glycolysis pathway it is essential that NAD<sup>+</sup> be regenerated from NADH. This can occur in one of two ways. In normoxic conditions when OXPHOS is active, the malate aspartate shuttle provides a means for regenerating NAD<sup>+</sup> in the cytoplasm while at the same time producing NADH in the mitochondrial matrix to help fuel OXPHOS. However in conditions where OXPHOS is inhibited, the conversion of pyruvate into lactate becomes an essential means of regenerating NAD<sup>+</sup> ([Locasale and Cantley, 2011](#)) ([Fig. 1](#)). HIF-1 $\alpha$ , which is induced by hypoxia, but also by TLR agonists and proinflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$ , supports this process by promoting the expression of lactate dehydrogenase, which is responsible for the production of lactate from pyruvate, and of pyruvate dehydrogenase kinase, which phosphorylates and thereby inhibits pyruvate dehydrogenase, an enzyme complex that converts pyruvate into acetyl CoA ([Imtiyaz and Simon, 2010](#)). Thus under conditions where OXPHOS is inhibited, HIF-1 $\alpha$ , promotes aerobic glycolysis. As discussed above, increased glycolytic flux is essential for macrophage and DC activation and consistent with this, HIF isoforms have been shown to be crucial for activation in both cell types ([Imtiyaz et al., 2010](#); [Jantsch et al., 2008](#)).

In addition to changes in core ATP generating pathways, TLR-initiated signaling induces alterations in macrophage lipid metabolism that are of interest because they are both extensive and integral to the induction and resolution of inflammation ([Andreyev et al., 2010a](#); [Andreyev et al., 2010b](#); [Anthony et al., 2007](#)).

For example, M1 activation leads to increased metabolism of arachidonic acid, with the production of eicosanoids including the generally inflammatory leukotrienes and prostanoids (prostaglandins, prostacyclins and thromboxanes) ([Greene et al., 2011](#)). TLR agonists also lead to increased metabolism of eicosapentaenoic and docosahexaenoic acids with the synthesis of nonclassic eicosanoids like resolvins and lipoxins, which tend to have anti-inflammatory properties ([Serhan et al., 2011](#)). The eicosanoids exert their diverse effects on other cells via G-protein coupled receptors (GPCRs) that are differentially expressed ([Hirata and Narumiya, 2012](#); [Serhan et al., 2011](#)). IL-4 can counter some of these effects by inhibiting, for example, the TLR agonist induced expression of cyclooxygenase-2 (COX2), which along with constitutively expressed COX1 catalyzes one of the first steps in prostanoid synthesis ([Endo et al., 1998](#); [Raetz et al., 2006](#)). Thus a balance of external signals, coupled with temporal changes in the pattern of expression of different mediators from lipid substrates, will have profound effects on immune cell functions and the successful initiation and conclusion of inflammation. The magnitude of the effects mediated by these pathways is attested to by the clinical importance of drugs that target them for the treatment of, for example, pain and asthma (reviewed in ([Greene et al., 2011](#))). Recent insights have revealed additional effects of lipid metabolism on inflammation induced by TLR agonists. In M1 macrophages there are increases in the concentration of the cholesterol precursor desmosterol. Suppression of expression of DHCR24, which catalyzes the synthesis of desmosterol, is found to result in increased expression of inflammatory genes associated with M1 activation in mice fed a high fat diet ([Spann et al., 2012](#)). Desmosterol is a ligand for the nuclear receptor LXR, and the intrinsic anti-inflammatory effects of desmosterol has been found to be at least in part LXR-dependent. This is consistent with earlier reports that LXR can inhibit TLR4-initiated macrophage activation by preventing epigenetic remodeling of TLR4-responsive regulatory elements ([Ghisletti et al., 2007](#); [Kidani and Bensinger, 2012](#)).

M2 macrophages are the ying to the M1 yang. They have higher basal mitochondrial oxygen consumption rates than either resting macrophages or, of course, M1 macrophages. This reflects IL-4 and signal transducer and activator of transcription-6 (STAT6) driven expression of PGC-1 $\beta$ , an important transcriptional regulator of oxidative metabolism genes ([Vats et al., 2006](#)). Consistent with the induction of OXPHOS by IL-4, M2 macrophage development is profoundly prevented by inhibition of mitochondrial OXPHOS, and specifically by inhibition of fatty acid oxidation (FAO). Thus M2 metabolism is skewed heavily towards the use of FAO and mitochondrial respiration to meet functional needs ([Vats et al., 2006](#)) ([Fig. 1C](#)). A fundamental difference between M1 and M2 macrophages is that, under certain circumstances, M2 macrophages are able to proliferate ([Jenkins et al., 2011](#)), and although the issue has not been addressed experimentally, it makes sense to consider the metabolic differences between the two activation states as being instrumental in this divergence of function. As discussed in more depth below, mitochondrial ROS are important for antigen-driven T cell proliferation, and a similar relationship between proliferative capacity and mitochondrial activity in M2 macrophage proliferation would be consistent with the differences in OXPHOS between these and M1 cells. Additionally however proliferating macrophages must face metabolic demands specific to the requirements of daughter cell production, which clearly would require anabolic pathways. It is currently unclear how this fits with the facts that: 1) M2 macrophages primarily use catabolic pathways such as FAO, and 2) IL-4 induces the expression of CARKL, which inhibits flux through the PPP ([Haschemi et al., 2012](#)). This is an interesting area for future study.

There has been considerable interest in the role of peroxisome proliferator-activated receptors (PPARs) in M2 macrophages. PPARs are a family of nuclear receptors for fatty acid ligands. They heterodimerize with RXR and interact with transcriptional coactivators to control the expression of genes involved in fatty acid metabolism ([Nagy et al., 2012](#)). Consistent with the noted importance of FAO in M2 macrophages, PPAR $\delta$ , which is responsible for promoting the expression of genes involved in substrate oxidation and oxidative phosphorylation, has been found to be essential for M2 differentiation ([Kang et al., 2008](#); [Odegaard et al., 2008](#)).



Expression of this PPAR is increased in M2 macrophages from mice exposed to parasitic helminths, and these cells additionally contain high amounts of PGI<sub>2</sub>, an eicosanoid ligand for PPAR $\delta$  ([Thomas et al., 2012](#)). It seems therefore that M2 activation can be consolidated metabolically through the production of endogenous ligands for PPAR $\delta$ . Moreover, PPAR response elements are abundant and over-represented in genes induced in M2 macrophages, supporting the view that PPARs are important transcription factors that drive this activation state ([Thomas et al., 2012](#)).

## T CELLS

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Given the critical nature of T cells in clearing or controlling infections and cancer, as well as mediating protective immunity over the long-term, it is logical that a considerable effort is made to target these cells for therapeutic purposes. However, while metabolism underlies the fate and function of T cells, or of any immune cell for that matter, metabolic interventions for manipulating immunity are rare and can be considered to represent a largely untapped opportunity. T cells differ from innate cells in many aspects, but perhaps their ability to extensively and rapidly proliferate upon activation is what sets them apart from other immune cells, at least for the purposes of this discussion. These attributes of activated T cells has led to their ‘metabolic’ comparison with tumor cells, as both cells types have been shown to engage Warburg metabolism when proliferating ([Fox et al., 2005](#); [Jones and Thompson, 2007](#); [van Bruggen et al., 2010](#); [Vander Heiden et al., 2009](#)) (in contrast to most innate cells which engage Warburg metabolism upon activation, but do not proliferate). Another characteristic specific to cells of the adaptive immune system is their ability to generate long-lived antigen-specific memory cells that mediate protection against re-infection or tumor re-emergence. Memory T cells have a very different metabolism from their activated effector T cell counterparts in that they do not use aerobic glycolysis, but rely on mitochondrial FAO for development and persistence ([Figure 1](#)) ([van der Windt et al., 2012](#)).

When a naïve T cell recognizes antigen in the context of proper co-stimulation it undergoes a developmental program characterized by rapid growth, proliferation, and acquisition of specialized effector functions. This is an energetically demanding process that requires metabolic reprogramming. For cells to grow and proliferate they must change from a catabolic metabolism to an anabolic metabolism because unlike in a resting cell, nutrients will no longer be utilized for maintenance and homeostasis, but rather will be incorporated into biomass for new daughter cells. Similarly, T cells destined to become memory cells must maintain, or adopt, a catabolic metabolism, a feature that underlies their quiescence and longevity, and may even serve to impede their terminal differentiation. There is a growing appreciation for the importance of metabolic reprogramming in immune cells. How molecules like mammalian target of rapamycin (mTOR), P13K, Akt, Myc, and HIF link immune signals and metabolic cues for the activation, development, function, and maintenance of T cells, has been reviewed in-depth elsewhere ([Hirata and Narumiya, 2012](#); [Seth et al., 2006](#); [Waickman and Powell, 2012](#); [Wang and Green, 2012a, b](#)). More specifically, metabolic pathways can influence the development of various T helper subsets and this has also been the subject of several reviews ([Chi, 2012](#); [Gerriets and Rathmell, 2012](#); [Zemirli and Arnoult, 2012](#)). For example, Treg cells predominantly use OXPHOS and mitochondrial FAO for development and survival ([Michalek et al., 2011](#)), while the generation of T helper-17 (Th17) cells requires glycolysis ([Shi et al., 2011](#)). While these findings are well documented, it remains unclear precisely why these cells must adopt these very different metabolic phenotypes for their differentiation. In this discussion we hope to provide insight into why changes in metabolism occur in T cells, the challenges to consider, and what remains unanswered in this developing field.

While the use of heavy-labeled substrates has allowed a first look into how T cells utilize nutrients, much work still needs to be done to understand 1) what specific nutrients are actually providing to the cells, and 2) how substrate utilization occurs in vivo. For example, while it is known that both glucose and glutamine are critical nutrients for T cells, precisely what they provide to the T cell, especially in vivo during an immune response, is not completely understood.

Glucose can be used as an example. As introduced above, the breakdown of glucose in the glycolysis pathway generates ATP in the cytoplasm, but its oxidation in the mitochondria can generate even more ATP through the production of reducing equivalents (NADH and FADH<sub>2</sub>) to power OXPHOS. Once glucose enters the TCA cycle (as pyruvate-derived acetyl CoA), it can also act as a precursor for biosynthesis. For example, glucose-derived citrate can be exported from the mitochondria to the cytosol for the synthesis of fatty acids. In addition, glucose can also enter the PPP at a branch point early in the glycolysis pathway. The PPP is important for the production of 5-carbon sugars for nucleotide biosynthesis, as well as for the production of NADPH, which is a critical coenzyme for fatty acid synthesis, and for the regeneration of reduced glutathione. For the continued breakdown of glucose in the glycolysis pathway NAD<sup>+</sup> is needed. Pyruvate can be excreted as lactate from the cell as way to regenerate cytosolic NAD<sup>+</sup>, which can then be utilized to support the glycolysis pathway. However, NAD<sup>+</sup> can also be exported from the mitochondria via specialized shuttles, and in theory, the continued breakdown of glucose could also be maintained without the excretion of lactate. Therefore, by considering the fate of glucose in the cell, even in this most basic way, it becomes readily apparent that precisely how this substrate is utilized is exceedingly complex. Now if we consider not only how, but also why, a specific substrate is metabolized into a particular pathway the picture becomes even more complicated. For example, glucose may be directed to the PPP for the purpose of NADPH production or for nucleotide synthesis. If nucleotides are not needed, then is NADPH produced because the cell needs to elongate fatty acids, make cholesterol, or to reduce glutathione? We can further layer these types of questions with the complexities that are inherent in vivo during an immune response, such as differences in substrate availability in various tissues, inflammatory signals, competition for substrates from other immune and non-immune cells, and how each of these alters the local balance of nutrients and growth factor signals. Thus, even though the basic principles have been elucidated, the question of how metabolic processes influence functional and developmental outcomes remains far from clear. Given the fact that metabolism controls the function and fate of T cells, continued research in this area is warranted.

In addition to generating energy and reductive power, and supporting biosynthesis, metabolic pathways also control other key cellular processes. In this context, recent studies have shed light on the requirements for mitochondrial processes versus cytosolic metabolic pathways in fueling T cell activation, survival, proliferation, and effector functions. An example illustrating this idea is found in a recent study that shows a critical role for mitochondrial ROS in T cell activation ([Sena et al., 2013](#)). T cells from mice with a T-cell specific reduction in a subunit of the mitochondrial electron transport chain complex III, which leads to a reduction in ROS from this complex, is required for the activation of NFAT and subsequent IL-2 production. Interestingly, T cells in these mice were not able to undergo antigen-specific expansion in response to infection, even though they were able to proliferate in a lymphopenic environment. These observations allowed the authors conclude that cells with reduced mitochondrial ROS are not lacking bioenergetically, as they were able to undergo homeostatic proliferation, but rather lack ROS-dependent signaling mechanisms needed for antigen-specific T cell activation and subsequent clonal expansion. These results highlight how metabolic pathways can act as signaling mechanisms to control cellular processes other than energy production or biosynthesis directly. Emerging work from our groups also suggests that a switch to, or induction of, aerobic glycolysis is not a requirement for T cell activation, and that this process actually requires mitochondrial OXPHOS. The observation that proliferating cells, such as tumor cells and activated T cells (and bacteria and yeast), use aerobic glycolysis has contributed to the idea that engagement of this pathway is a prerequisite for, or occurs hand in hand with, cellular proliferation. However, an overlooked fact is that most cells in the innate immune system adopt Warburg metabolism upon activation, but do not proliferate (as discussed above).

While there has been considerable interest in the metabolic demands of T cell activation, less time has been spent addressing how changes in metabolism contribute to the contraction of antigen-specific cell populations after the peak of the effector response and the generation of stable memory T cells. Our published work has shown that memory T cells rely on mitochondrial FAO for their development and long-term survival ([Pearce, 2010](#); [Pearce et al., 2009](#); [van der Windt et al., 2012](#); [van der Windt](#)

[and Pearce, 2012](#)). In contrast to effector T cells, which use glycolysis and have reduced mitochondrial mass, memory T cells maintain greater mitochondrial mass, which supports their oxidative metabolism ([van der Windt et al., 2012](#)). These findings led us to propose a model in which most effector T cells die during contraction due to their bioenergetic instability, i.e. their lack of mitochondrial maintenance renders them unable to support OXPHOS when infection associated signals that maintain glycolysis decline. One picture that seems to emerge from these findings is that substantial mitochondrial respiratory capacity (due to increased mitochondrial mass, maintenance, or simply the reliance on mitochondrial pathways?) is linked to cellular longevity. Preliminary studies from our laboratory indicate that memory T cells do have more mitochondrial mass than their naïve counterparts and that this enhanced mitochondrial mass imparts memory T cells with a bioenergetic advantage that rapidly fuels subsequent re-activation. These findings would be consistent with the idea that T cell activation requires OXPHOS. Given that memory T cells maintain more mitochondria than naïve T cells it will be interesting to determine where stem cell memory T cells fall in this range ([Gattinoni et al., 2011](#); [Zhang et al., 2005](#)). Stem cell memory T cells are more differentiated than naïve T cells, but less than central or effector memory T cells ([Gattinoni et al., 2012](#)), therefore we might speculate that they have substantial mitochondrial spare respiratory capacity that supports their persistence and ability for self-renewal. If this were the case then increased mitochondrial biogenesis, which is known to occur immediately after T cell activation ([D'Souza et al., 2007](#)) might represent one of the first developmental steps in the generation of stem cell memory T cells, whereas those cells that continue to rapidly differentiate toward the effector state would not maintain mitochondrial numbers or capacity to the same extent or in the same way. In this context, future investigation of mitochondrial dynamics will be needed to determine whether terminal differentiation controls, or is simply marked by bioenergetic imbalance.

When considering these issues it is also worth drawing attention to the fact that effector T cells do also maintain OXPHOS in conjunction with glycolysis, even after full activation is attained ([Sena et al., 2013](#); [van der Windt et al., 2012](#); [Wang et al., 2011](#)).

However, whether this is a requirement for continued proliferation or function is not clear. In addition, it is not known whether OXPHOS is engaged in these cells is only for the ROS signaling that is needed for proliferation ([Sena et al., 2013](#); [Weinberg et al., 2010](#)), or also for other purposes such as powering ATP production directly, the regeneration of NADH to NAD<sup>+</sup> to support TCA cycling and production of biosynthetic precursors, or to maintain mitochondrial integrity. Establishing the all of the reasons why particular metabolic pathways are used will be key to developing techniques that target metabolism for immunotherapy.

## B CELLS

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Our discussion of metabolism in the adaptive immune system has focused on T cells. While B cells do share certain fundamental metabolic characteristics with T cells, such as their increased glucose uptake and induction of glycolysis after activation ([Doughty et al., 2006](#); [Dufort et al., 2007](#)), much less is known about how metabolism directs the fate of normal B cells (a considerable amount of work has been done to investigate metabolic pathways in cancerous B cells). Where gaps do exist in the knowledge about B cell metabolism, one might be able to fill in some blanks by considering parallel events in T cells. For example, can we speculate that short-lived plasma cells and memory B cells have similar metabolic profiles as effector T cells and memory T cells, respectively? Given the similarity in the functional capacity and life span of these cell types this would seem a reasonable assumption. However, during an immune response, B cells can also differentiate into long-lived plasma cells, which survive within the bone marrow for years, continuously synthesizing large amounts of antibody to maintain physiologically relevant concentrations in plasma. Our models of metabolism in immune cells do not easily explain how plasma cells are able to combine longevity and high output biosynthesis in this way, and these cells clearly represent an important, although challenging subject for further work.

## 5. CONCLUSIONS

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Activity and nutrition can affect how fast and how well our energy systems work.

We can make our energy systems more efficient and effective with regular exercise, especially if we directly target individual systems with specific activities (such as training the ATP-PCr system with short-distance sprinting, or the oxidative phosphorylation system with longer-duration, lower-intensity endurance exercise).

Now, remember our hydrogen carriers NAD<sup>+</sup> (nicotinamide adenine dinucleotide) and FAD (flavin adenine dinucleotide)?

These two molecules act as co-enzymes and are derived from the vitamins B<sub>3</sub> (niacin) and B<sub>2</sub> (riboflavin).

So although these B vitamins don't actually give us energy directly, you can imagine how we might need them to help with the transfer of energy and the regeneration of ATP throughout glycolysis, the Krebs cycle, and the electron transport chain.

You can also imagine what might happen if we don't get enough. Indeed, people who are deficient in B vitamins often report that they feel sluggish and tired.

We can thus also improve how our energy systems work by ensuring we eat a varied diet and correcting any nutrient or enzyme deficiencies.

Optimal intake of all these nutrients ideally would be achieved through the consumption of a well-balanced and diverse diet, but this can be difficult to accomplish for the general population. Indeed, it is generally accepted that nutrient inadequacies and deficiencies are widespread [46–50] (and references therein). Biochemical markers of nutrient status are particularly useful in assessing inadequacy or deficiency, and lead to the conclusion that intakes often are not sufficient

It should also be noted that optimal nutritional support for the immune system can require intakes above the RDA for some micronutrients, while at the same time infections and other stressors can reduce micronutrient status in the body. Vitamin C levels, in particular, decrease during times of infection and higher intakes are required to restore normal blood levels [10,75]. These higher intakes and blood levels are associated with improved clinical outcomes. For example, supplementation of pneumonia patients with  $\geq 200$  mg/d vitamin C restored depleted plasma and cellular

vitamin C levels, and resulted in decreased respiratory symptom scores and a dose-dependent decrease in hospital length of stay [76,77].

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