Immunometabolism: new insights and lessons from antigen-directed cellular immune responses

Renata Ramalho 1 · Martin Rao 2 · Chao Zhang 3 · Chiara Agrati 4 · Giuseppe Ippolito 4 · Fu-Sheng Wang 3 · Alimuddin Zumla 5 · Markus Maeurer 2,6

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Abstract
Modulation of immune responses by nutrients is an important area of study in cellular biology and clinical sciences in the context of cancer therapies and anti-pathogen-directed immune responses in health and disease. We review metabolic pathways that influence immune cell function and cellular persistence in chronic infections. We also highlight the role of nutrients in altering the tissue microenvironment with lessons from the tumor microenvironment that shapes the quality and quantity of cellular immune responses. Multiple layers of biological networks, including the nature of nutritional supplements, the genetic background, previous exposures, and gut microbiota status have impact on cellular performance and immune competence against molecularly defined targets. We discuss how immune metabolism determines the differentiation pathway of antigen-specific immune cells and how these insights can be explored to devise better strategies to strengthen anti-pathogen-directed immune responses, while curbing unwanted, non-productive inflammation.

Keywords Infection · Cancer · Immunometabolism · Immunotherapy · Inflammation · Microbiome · Tuberculosis · MTB · T cell · Innate immune cell · Cytokine · Nutrition · Mitochondria

Introduction
Clinical immunologists have (re)discovered that the profile of cellular metabolism shapes the outcome of cellular development and immune functions: immunometabolism [1–3]. This prompted cross-fertilizing preclinical and clinical research between immunology, nutrition, and biochemistry [4]. The field of immunometabolism is marked by the impact of metabolic reprogramming on the immune response as well as studying the fate of immune cells [5, 6]. The immunometabolic profile of cells influences their activation, their proliferative capacity, their quiescent state in tissues and in the systemic circulation. The functional specificity of each immune cell subset determines its biochemical requirements which is associated with different metabolic phenotypes [2, 7, 8]. These phenotypes are linked with variations in nutrient and oxygen availability, pH, as well as fluctuations during immune cell trafficking [2]. Thus, a well-founded understanding of molecular interactions between nutrient availability, biochemical requirements, and cellular metabolism is crucial to recognize how these components jointly affect immunodynamics in pathological conditions and ultimately shape the host immune response [9, 10]. We review therefore here more recent insights in
immunometabolism in infections and cancer—a timely exercise since (i) nutrients are often limited in resource-constrained countries, (ii) immunonutritional concepts are often not considered in vaccine or adjuvant treatment protocols in patients with infections, (iii) similar molecular pathways are functional in “chronic antigen stimulation” in patients with bacterial and viral infections or cancer. Insights from curbing immunopathology and eliciting protective immune responses in patients with cancer will therefore cross-fertilize the advancement of new treatment concepts of patients with infectious diseases—particularly where nutrients are limited. We would also like to point out that such a review provides the platform of discussing individual mechanistic concepts. However, although a more individual approach in patient management is scientifically sound, the clinical reality is often different: individuals have a different genetic background, they have been exposed to different pathogens/commensals and may suffer from different infections—at the same time or in different orders that may shape the quality and quantity of immune responses. A more recent, prominent example [11] is the acquired capacity of the organism—in early life—to differentiate between commensal bacterial that colonize the skin versus potential pathogenic bacterial species, where antigen-specific regulatory T-cells (Tregs), tolerance mechanisms, and the IL-1-receptor–IL-1β axis play a prominent role. It is obvious that age, the country, nature of exposure to commensals and potential pathogens plays a pivotal role. The need to integrate these variations in different networks—and to extract biologically and clinically relevant concepts—is appreciated and fueled the discussion to obtain better models that integrate anatomical and biological diversity [12].

The study of metabolism has revealed six core biochemical pathways which impact on immune cell reprogramming: glycolysis, tricarboxylic acid (TCA) cycle, fatty acid oxidation (FAO), fatty acid synthesis (FAS), pentose phosphate pathway (PPP), and amino acid synthesis (AAS) [13, 14]. Additional pathways have been described as modulators of the complexity of the immune response, mainly those leading to the biosynthesis of polyamines, cholesterol, hexosamines, and nucleotides [15]. The biochemical demands of each immune cell type are intrinsically linked to its function, especially those related to quiescence/memory and activation/proliferation [14, 16]. That said, different immune cell functions are, in fact, associated with distinct metabolic configurations: resting immune cells utilize energetically efficient processes such as the tricarboxylic acid (TCA), linked to the generation of ATP via oxidative phosphorylation (OXPHOS), whereas activated cells prefer glycolysis to generate adequate levels of energy storage to support survival and produce numerous biosynthetic intermediates to allow for cellular growth and proliferation [14]. CD8+ T-cells are believed to be dependent on FAO in regard to immune effector functions and tissue homing, yet more recent evidence suggests that memory T-cells may use alternate pathways for these immune effector functions [17–22]. This plasticity of immune cells modulates metabolic reprogramming from an inflammatory to anti-inflammatory or immunomodulatory phenotype or vice versa [7, 8, 23], which is of special interest for exploitation as an anti-tumor immune-based strategy [24]. In fact, cancer cells behave more like activated immune cells with increased biochemical demands and rely on glycolysis for survival [25–27].

Nutrients play a pivotal role in the context of immune cell metabolic phenotypes, further supported (and influenced) by gut microbiota and gastrointestinal organs such as the pancreas, colon, and liver [28, 29]. Immunonutrition is a growing biomedical discipline [30] that aims to affect immune cell functions directly by delivering signaling metabolites by regulating nutrient availability [31]. Figure 1 summarizes different metabolic pathways and biological cell functions.

Integration of metabolism and immunity

Cellular metabolism of immune cells

As stated earlier, the main metabolic pathways involved in immune cell survival, proliferation, and activation are glycolysis, TCA cycle, PPP, FAO, FAS, and AAS (particularly those of glutamine, arginine, and tryptophan). Glycolysis occurs in the cytosol and generates two ATP molecules by substrate-level phosphorylation and pyruvate that enter mitochondria and are converted to acetyl–coenzyme A (acetyl CoA). Glycolysis is a relatively inefficient pathway for the generation of cellular ATP but is involved in several processes due to its capacity of being rapidly activated via the induction of key enzymes such as pyruvate kinase, glyceraldehyde 3 phosphate dehydrogenase, aldolase, and enolase [32, 33]. Cells requiring rapid production of ATP will switch to glycolysis as increased cell growth kinetics demand an equally (if not higher) turnover of biosynthetic intermediates [13, 34–36]. For example, glycolysis inhibition by modulation of pyruvate kinase M2 induces the polarization of macrophages towards an alternatively activated phenotype (M2 macrophages) in terms of gene expression, in addition to boosting IL-10 production [32, 37, 38]. It has been recognized that activating cell signals such as cytokines may lead to the generation of ATP, which will support the TCA cycle in providing intermediates for PPP, glycosylation reactions, and the biosynthesis of key biomass constituents like serine, glycine, alanine, and acetyl-CoA [13, 33]. This is true for macrophages (phagocytosis, inflammatory cytokine production) [39, 40], dendritic cells (Ag presentation) [41], as well as T-cells (effector cytokines, IL-17 for Th17) [42].

PPP is a metabolic pathway parallel to glycolysis. It generates NADPH, pentoses, and ribose 5-phosphate [43]. This pathway involves oxidation of glucose but is an anabolic
pathway rather than a catabolic one [43]. NADPH is generated during the oxidative phase, whereas pentoses are produced during the non-oxidative phase of PPP. NADPH will, therefore, be used to generate ROS during respiratory burst and as a counterbalance to generate glutathione and other antioxidants. This is used by macrophages differently according to their phenotype [44, 45].

The TCA cycle (also known as the citric acid cycle or Krebs cycle) is a metabolic pathway for generating ATP and carbon dioxide through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins [46]. Additionally, the TCA cycle also provides NADH to be used in diverse biochemical reactions while TCA cycle-derived citrate, uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), itaconic acid, and succinate are important for immune cell physiology [46]. The TCA cycle operates both in normoxia and hypoxia [33, 38].

Fatty acid (FA) metabolism consists of both (energy-generating) catabolic and anabolic processes necessary for the synthesis of important biological building blocks such as triglycerides, phospholipids, secondary messengers (arachidonic acid and free fatty acids), hormones, and ketone bodies. When compared to other macronutrient classes, FAs generate the most ATP on an energy per gram basis when completely oxidized to CO₂ and water by beta oxidation and the TCA cycle. Many immune cells that are not inflammatory in nature and exhibit increased cellular lifespans (M2 macrophages, regulatory T-cells (Treg), memory CD8+ T-cells) have been demonstrated to rely on FAO, as previously mentioned [20, 47, 48]. Nevertheless, FAS seems to positively regulate the generation and function of pro-inflammatory innate and adaptive immune cells [49]. The efficacy of lipid oxidation for energy generation and the necessity of lipid synthesis for biosynthesis and cell growth suggest that pro-inflammatory and regulatory immune cells show fundamental differences in their reliance on ATP generation for growth [20].

Glutamine, arginine, and tryptophan are the most well-studied amino acids affecting the immune system. Insufficient supply of glutamine has been related to increased mobilization from muscles and low plasma levels [50, 51]. Human studies have demonstrated that these low plasma
levels of glutamine are related to reduced B-cell differentiation [52], decreased IL-2 production (and IL-2R expression), downregulation of HLA class II expression on and reduced antigen presentation by macrophages [51, 53]. Glutamine can be used by macrophages for NADPH production [53]. Murine macrophages and neutrophils involved in pinocytosis have, in fact, been shown to prefer/require NADPH supplied by glutamine metabolism rather than PPP, since glucose supplied by the latter pathway is used for fat storage [54]. In murine T-cells, glutamine is used as a resource in nucleic acid synthesis and as an energy source [55]. Pertaining to arginine metabolism and immune cells, arginase-1 is responsible for the breakdown of arginine to ornithine and plays a role in the immune function regulation of activated T-cells through depletion of arginine in the local microenvironment (as controlling arginine bioavailability allows control of nitric oxide production), which has been described in experimental models of cancer and tuberculosis [56–58]. Arginine depletion has been related to T-cell suppression, mainly by reduced expression of the CD3-ζ chain (and concomitant lower expression of the TCR complex) as well as downregulation and subdued enzymatic activity of the cyclin D3/CDK4 complex which is known to regulate cell cycle progression [59, 60]. Interestingly, elevated levels of arginase-1 have been found in the splenocytes of tumor-bearing mice [61]. Moreover, cancer and postoperative patients present with a lack of the CD3-ζ chain, dysfunction and reduced number of T-cells, and increased arginase-1 activity [62–64]. Idoleamine-2,3 dioxygenase (IDO), which oxidatively degrades tryptophan in the kynurenine pathway, has been considered a key enzyme in host immune function [65]. The properties exhibited by some innate immune cells, i.e., human CD123+ DC subset (CD11c+ CD8α+ DC subset in mice) and macrophages to induce IDO, have been demonstrated to be responsible for the modulation of not only T-cell function mainly via tryptophan depletion but also IDO-cytotoxic metabolites [65–67], although the latter mechanism requires further elucidation.

Aerobic glycolysis appears to be a characteristic feature of many rapidly dividing cells, including cancer and immune cells, even when sufficient oxygen is present to support OXPHOS [8, 35]. In proliferating cells, the increase in lactate production may result from the contribution of growth factor-mediated increases in glucose uptake, increased ATP consumption associated with cell growth, and low NAD+/NADH ratio secondary to oxidative biosynthesis [68–70]. The advantage of this metabolic phenotype in proliferating cells is to help meeting the biochemical requirements of biosynthesis and allow differentiation [71]. Aerobic respiration produces a larger fraction of cellular ATP from mitochondrial OXPHOS, while glycolytic cells produce relatively more ATP from glycolysis [72]. Some immune cells transition between OXPHOS and glycolytic metabolic phenotypes over the course of an immune response; manipulation of this dichotomy can have an effect on the regulation of host immunity [73]. Increased glycolysis (the Warburg effect) has been described as a feature of inflammatory as well as cancer cells (for adaptation [74]), whereas cells involved in immunoregulation or in the resolution of inflammation display FAO and an intact TCA cycle as hallmarks of their metabolism [33, 75], inevitably affecting their cellular phenotypes as will be discussed in the following subsection.

Systemic metabolism and immune cell ontogeny

Macrophages and metabolism

Macrophages have several functions in tissue homeostasis and inflammation, with their metabolic characteristics reflecting functionality [76]. Immunometabolism has been recently studied in macrophages, as metabolic pathways not only provide energy but also regulate macrophage phenotype and function [77, 78]. In this regard, comparison between classically activated, pro-inflammatory macrophages (M1) and alternatively activated, anti-inflammatory macrophages (M2) with reparative capacity, reflecting functional polarity, is of special relevance [73, 76]. The expression of toll-like receptors (TLRs) on the surface of macrophages promotes a M1 phenotype (mainly TLR2 and TLR4), whereas IL-4 and efferocytosis promote a M2 phenotype [79, 80]. These two phenotypes are distinct in their function as well as the preferential biological mediators produced. M1 macrophages are known for their ability to produce pro-inflammatory cytokines (IL-1β, IL-18, IL-12, TNF-α, IL-6) and reactive oxygen species (ROS), while M2 macrophages release anti-inflammatory cytokines (IL-4, IL-10, TGF-β) and promote angiogenesis and fibrosis [73, 81].

The differences between the M1 and M2 macrophage phenotypes are also evident in their cellular metabolic profiles. In general, M1 macrophages are highly glycolytic, whereas M2 macrophages use FAO metabolism and OXPHOS [37, 49, 80, 82]. In M1 macrophages, glycolysis would allow for rapid ATP production to fuel activation during acute inflammation [80, 82], while in M2 macrophages, OXPHOS occurs during the lengthy process of resolving tissue inflammation and repair or in promoting anti-parasite immunity [80, 82, 83].

Metabolomic and transcriptomic data have provided useful insights into revealing the metabolic changes in macrophage polarization. In fact, the presence of two breaks in the TCA cycle of M1 macrophages has been described [73], thereby suggesting an “interrupted” TCA cycle for this phenotype. One of the breaks was described at the isocyanate dehydrogenase step and the other after the succinate step, with evidence for a variant of the pathway: the aspartate-arginosuccinate shunt [41, 84]. This disruption in the TCA cycle in M1 macrophages leads to the accumulation of citrate and nitric oxide (NO) production [41]. Jha and colleagues showed that the
TCA cycle in M1 macrophages is rather a fractionated than an undisrupted cycle [73]. Interestingly, inhibition of aspartate aminotransferase (a key enzyme in the TCA shunt pathway) suppressed IL-6 and NO production, revealing the importance of the arginosuccinate shunt for M1 macrophage function [73]. M1 macrophages convert arginine into NO through inducible NO synthase (iNOS) activity [85], while in M2 macrophages, arginine is metabolized by arginase-1 [86]. Despite the core belief that glycolysis is merely associated with inflammation and OXPHOS with anti-inflammatory responses, it is now accepted that this dogma is more fluid that previously perceived and demands revision [39, 77, 79, 80]. Macrophage metabolism remains a very interesting field especially in modalities with an urgent need for novel therapeutic targets, i.e., cancer. This subject will be discussed later.

**T and B cells and metabolism**

Oxidative metabolism is preferred by resting lymphocytes, where glycolysis or aerobic glycolysis meets their cellular demands after stimulation [87]. Resting precursor T-cells require energy and active replenishment of basic biological building blocks for survival and migration as they continually migrate through lymphoid tissue for immune surveillance [88]. These ATP-intensive functions are mainly achieved by FA β-oxidation as well as pyruvate and glutamine oxidation via the TCA cycle [87]. It is also known that mature resting T-cells exhibit a dynamic regulatory pattern rather than fixed metabolism [89].

During activation, and to sustain rapid clonal proliferation, the increased metabolic needs of T-cells are met by converting glucose to lactate through aerobic glycolysis—that increases glucose and glutamine metabolism while decreasing lipid oxidation as cell proliferation requires the activity of mammalian target of rapamycin (mTOR)-dependent pathways [55, 90]. It is known that OXPHOS can still be used by activated T-cells as a source of energy; however, strong evidence supports the induction of the glycolytic pathway as a lineage-decisive event for Th1, Th2, and Th1 development [89]. These lineages display a strong bias towards glycolysis over mitochondrial metabolism; Th17 development, for instance, involves hypoxia-inducible factor 1 alpha (HIF-1α), which is an oxygen-sensitive transcription factor also responsible for glycolytic gene expression regulation in Th17 cells [47, 91]. Conversely, induced Treg lineage displays a mixed metabolic signature involving glycolysis, lipid oxidation, and OXPHOS [91]. Also, blocking glycolysis during Th17 differentiation may favor Tregs over Th17 development [91], which may be detrimental in early stages of infections [92, 93] and potentially in patients with cancer [94, 95]. Interestingly, decreased T-cell proliferation and activation, T-cell anergy or cell death may be observed if inadequate nutrient supply or metabolic inhibition occur during T-cell ontogeny [89].

Much less is known about how metabolism directs the fate of normal B cells. As these cells develop into specialized antibody-secreting plasma cells and memory cells [9, 96], specific metabolic and nutritional requirements may be at play. Anergic human peripheral blood B-cells, following LPS stimulation, have been shown to only moderately increase their glycolytic rate, while unstimulated B-cells exhibited a balanced upregulation of lactate production and aerobic glycolysis concomitant with a steady increase of glucose transporter 1 (Glut1) expression following LPS or B-cell receptor (BCR) activation [97]. Indeed, BCR-mediated B-cell proliferation is stunted following inhibition of glycolysis [96], reminiscent of the scenario in activated T-cells. How B cell subsets are metabolically regulated in different human diseases and stages warrants further investigation using appropriate clinically welldefined samples.

**Dendritic cells and metabolism**

The activation of DCs implies phenotypic, secretory, and functional modifications that cause an increase in glucose uptake and lactate production; however, a metabolic reprogramming from OXPHOS towards glycolysis occurs after DC activation by TLRs [7, 98, 99]. During cellular activation, ATP is generated by OXPHOS, and therefore, lactate production does not reflect commitment to the Warburg effect [100]. Moreover, the need for citrate by activated DCs for fueling FAS involved in ER and Golgi apparatus turnover seems to be biochemically supported by glycolysis [100]. This glycolytic metabolism is dependent on the activation of HIF-1α and PI3K/Akt pathways and indicates a possible role for mTOR downstream of PI3K/Akt [99, 101], whereas induction of the OXPHOS mediator AMPK antagonizes the glycolytic pathway, inhibiting DC maturation [102]. Nevertheless, DCs with immunogenic (promoting effector T-cells) and tolerogenic (promoting suppressive Tregs) functions have different metabolic profiles that reflect their function [103]. Tolerogenic DCs are predominantly catabolic and rely on OXPHOS and FAO for ATP production, with low glycolytic potential [103]. In contrast, immunogenic DCs exhibit anabolic metabolism and are mainly glycolytic, with reduced OXPHOS and FAO. Anabolic demands of DC activation require rapid induction of glycolysis as an integral component of TLR signaling, where the TAB1, IKKε, and Akt kinases seem to be essential for engaging the mitochondrial glycolytic enzyme HK-II [104]. The rapid loss of mitochondrial OXPHOS by TLR-triggered inflammatory DCs may be explained by the NOS-2-mediated NO production, which accompanies the glycolytic switch that is able to direct inhibit the mitochondrial ETC in an autocrine as well as paracrine manner [105]. Conventional DCs, on the other hand, do not express NOS-2 nor are they amenable to NOS-2 induction by TLRs or inflammatory cytokines [105]. An interesting insight
into energy and mitochondrial homeostasis in DC, supporting immune activation, was highlighted by Thwe et al. in mouse DC cultures [106]. In their research, early glycolytic metabolism was observed during DC activation, supported by utilization of intracellular glycogen reserves [106]. Moreover, the authors also saw that glycogen-derived carbons preferentially contributed to the TCA-dependent citrate pool, when compared to glucose directly catabolized by mouse DCs [106]. IDO1 phosphorylation and subsequent cellular signalling in CD11c⁺, IL-4, IFN-γ or TGF-β activated DCs has been shown to be dependent on prior expression of Arg1 and Arg1-dependent production of polyamines [107]. The latter are either produced by DCs or released by Arg1⁺ myeloid-derived suppressor cells (MDSCs) and may skew DCs towards an IDO1-dependent, immunosuppressive phenotype (via Src kinase activation) [107]. DC metabolism and its potential edit the quality and quantity of immune responses are likely to influence the design of immunotherapeutic strategies.

Cancer, the tumor microenvironment, and metabolism

Immune cell competition for nutrients

In a more molecular perspective, we can objectify the relationship between nutrients and immune cells through the role of the former in the control of cellular responses of the latter. In fact, there are immune microenvironments where some degree of nutrient limitation is present, which provide the opportunity to study changes in signal transduction driven by nutrients and to understand the relevance of nutrient availability in regulating immune responses (elegantly reviewed in [108]). As the concept of unequal nutrient availability to immune cells is emerging [6], competitive nutrient uptake in immune microenvironments seems to be of major importance for immune responses, hinting at nutrients’ role in regulating the fate of immune cells. As will be discussed later, competition for nutrients can be observed in the tumor microenvironment (TME) and at sites of pathogen infection [108]. Solid tumors exhibit an increased demand for glucose to support growth and proliferation, despoiling extracellular levels of glucose by increasing blood supply into the TME via neovascularization [108]. There is also evidence that in some tumors, competition for glutamine may lead to limiting glutamine resource levels in the TME. This restriction of glucose and glutamine supply in the tumor seems to inhibit immune cell infiltration, as observed in local resistance to to adoptive T-cell therapy [108, 109], which will be revisited later in this review. A similar competition for nutrients has been observed in virus-infected cells, which are reprogrammed for increased glucose metabolism, glycolysis, and glutaminolysis (glutamine breakdown) and decreasing extracellular concentrations of these nutrients in the surrounding microenvironment [108, 110, 111].

Role of nutrients metabolism in the TME

The metabolism of proliferating cells is quite different from that of non-proliferating ones (which obtain energy fromOXPHOS) [112]. Proliferating cells, like cancer cells, show increased requirements of energy and nutrients for rapid growth and dissemination (metastasis) and exhibit an increase in the uptake of glucose, amino-acids, fatty acids, minerals, and vitamins [113]. In fact, a central feature of nearly all cancers is impaired cellular energy metabolism [112]. To respond to the high energy demands of active proliferation, cancer cells convert great amounts of glucose into pyruvate (aerobic glycolysis), in a low-efficiency pathway – albeit their dependence on glucose for survival and growth [114]– thus the Warburg effect [115, 116]. Cancer cells use glucose catabolism via glycolysis as a major energy-generating pathway, generating several biosynthetic molecules and NADPH. Depriving cancer cells of glucose can, in fact, promote mutations in the KRAS pathway which, in turn, induces increased sensitivity to glucose in transformed cells, leading to GLUT1 upregulation and enhanced glucose uptake from the immediate microenvironment [117]. The Warburg effect can be described as a state of mitochondrial dysfunction, as cancer cells are unable to undergo mitochondrial OXPHOS [112]. Metabolic reprogramming of cancer cells can be viewed as an enhancer of adaptation to intratumoral metabolic stress and immune surveillance, contributing to maintaining “cancer stemness” [118]. This has been considered indispensable and to the advantage of the pathological biological processes occurring in cancer cells [119].

The TME is also characterized by extracellular acidosis resulting from lactate accumulation [119–121]. This is due to the synergy between HIF-1α and Myc in promoting expression of glycolytic enzymes driving glucose influx and lactate production in response to the (i) poor clearance of acid accumulation outside the TME (generating a low pH within the TME) and (ii) upregulation of monocarboxylate transporter (MCT) 4, favoring the migration of extracellular lactate to the extracellular matrix [114, 119]. MCT4 upregulation is especially relevant, as it is transcriptionally upregulated by the hypoxia-driven HIF-1α enzyme, and tumor cells usually localize in hypoxic environments [122]. While not applicable to the entire TME, there may be distinct hypoxic areas due to aberrant neovascularization and subsequent impaired access to nutrients, metabolic changes that may promote disease progression [27]. Vascular endothelial growth factor (VEGF), the cardinal mediator of angiogenesis, is aberrantly expressed in several cancers and is clinically
targeted cancers of different histology [123]. Nevertheless, it has been shown in patients with breast cancer that VEGF blockade with bevacizumab—under hypoxic conditions—leads to reoxygenation of the TME but also promotes acute hypoxia in treatment-resistant patients [124]. Anti-angiogenic therapy would deprive the tumor of nutrients necessary for survival—which would inevitably also affect the immune cell compartment therein. In fact, to escape from anticipated senescence or death, tumor cells engage autophagy to survive the potentially hostile TME [125, 126]. Thus, overexpression of GLUT and downstream glycolytic enzymes (pyruvate kinase isozymes M2, serine hydroxymethyltransferase, carbonic anhydrase 9) [118] has been observed in several cancers [127–131]. Oncogenes (Akt, PI3K, mTOR, Ras, Raf) [132] and loss of tumor suppressor genes (VHL, PTEN, p53) also contribute to the increasing growth and metabolic activity of tumor cells [132]. Glucose can either be used in glycolysis or metabolized by PPP, promoting production of glutathione, FAs, sterols and nucleic acids, which are considered relevant for reducing oxidative stress and increasing DNA repair in cancer cells, conferring resistance to cancer treatments [133, 134]. Figure 2 presents a schematic compilation of stressors in TME.

The TME also hosts tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), and endothelial cells involved in tumor stroma formation [135]. Evidence suggests that TAMs and CAFs interact in a reciprocal manner [136, 137], have a role in tumor progression [138, 139], and are associated with cancer invasion and metastasis [135, 140]. Also, the TME is infiltrated by T-cells (tumor-infiltrating T lymphocytes, TILs), whose functions are impaired, often in association with the volume of the tumor lesion. Generally, TILs are considered a pro-inflammatory and/or cytotoxic population of T-cells able to recognize tumor antigens and, therefore, mediate tumor regression, constituting a critical clinical biomarker of prognosis [141, 142]. The complex cellular composition of the TME, along with the hostile conditions of nutrient deprivation caused by intense energy requirements of cancer cells, imposes an important question: how do cancer

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**Fig. 2** Stressors, e.g., (increased) potassium, reduced oxygen and nutrient access in tissue environment, act on T cells (Li et al., Immunity, 51, 491–507, 2019). One of the key factors modulating tissue resident T cells’ activity is the transcription factor Bhlhe40 (top) in infections and cancer. Reduced Bhlhe40 leads to reduced capacity to contain infections or cancer in preclinical models, in part via effecting mitochondrial activity—that impacts on the T-cell epigenome. OXPHO (oxidative phosphorylation) and TCA activity are associated with memory immune cells. HDAC inhibitors and the fatty acid acetate replenish mitochondrial function and cytokine production. This is a simplified sketch and clinical outcomes of HDAC treatment that may be different depending on the pathogen, previous exposures of immune cells to drugs, viral and bacterial species, as well as the nominal T-cell receptor repertoire available in the microenvironment.
cells obtain enough “food” in these adverse conditions? This appears to be achieved by despoiling neighbor cells of energy and nutrients to survive and proliferate [143]. Some of these afore-mentioned nutrients, i.e., amino acids, acetate, and lactate are used as alternative fuels by cancer cells and are summarized in Table 1.

Some of these nutrients become crucial for cancer cells, which sometimes exhibit some degree of “addiction” [144, 145]. To prevent inadequate tumor perfusion due to low nutrient availability, cancer cells resort to multiple scavenging strategies to take up nutrients from cells in the immediate microenvironment [146]. These strategies include integrin-mediated scavenging, receptor-mediated scavenging of albumin, and scavenging via micropinocytosis and entosis [147], as a way of obtaining final products for ATP generation and anabolism [146].

The despoiling of neighboring cells nutrients is of special concern for TILs, which is evidenced by the negative impact by the TME on TIL metabolism and its contribution to functional exhaustion of TIL, also marked by the induction of programmed cell death 1 (PD-1) expression by T-cells [148]. PD-1 is a co-inhibitor that blocks CD28-mediated activation of the mTOR pathway and reduces glycolysis but enhances FA metabolism [149]. The increase in PD-1 may facilitate the metabolic switch of energy production to TCA cycle and OXPHOS, which is observed in continuous antigen-driven stimulation during chronic infections [150]. In cancer, therapeutic targeting of PD-1+ (immunologically “exhausted”) TIL has revolutionized oncotherapy and established the newly coined field of immuno-oncology [151]. Additionally, TILs must deal with the hostile environment of glucose deprivation and hypoxia, which alters their anti-tumor activity. The absence of glucose has profound effects on CD8+ T-cells, as this nutrient is crucial for the differentiation of naïve CD8+ T into effector subsets [152]. Although differentiation may still occur in this situation, effector clones present reduced effector functions [153, 154]. In this context, TILs have additional challenges as the TME is a glucose-deprived environment, and regardless of high expression of GLUT1 by TILs, tumor cells are more efficient at consuming glucose [153]. Also, high concentrations of lactate in the TME lowers pH, which inhibits PPK and consequently reduces TILs glycolysis [155]. Thus, hypoglycemia in the TME leads to reduced glycolysis, leaving TILs relying on OXPHOS. Further challenges arise with oxygen restriction; TILs face severe hypoxic conditions when infiltrating tumors from well-oxygenated peripheral blood vessels [148]. In this condition, HIF-1α is activated and performs two important functions: it adjusts metabolism by enhancing TIL glycolysis due to lactate dehydrogenase A induction and increases PDK1 expression preventing OXPHOS [156–158]. Consumption of glucose is, therefore, increased to allow glycolysis to proceed. It has been demonstrated that in hypoxic conditions, T-cell activation is inhibited, with their proliferation and capacity to cytokine production reduced [159]. In fact, oxygen deprivation negatively impacts metabolism and function of TILs, as

### Table 1 Non-glucose nutrients used by transformed cells as alternative fuels

| Non-glucose nutrients | Essential uses by cancer cells for survival and proliferation | References |
|-----------------------|---------------------------------------------------------------|------------|
| Glutamine             | Carbon and nitrogen source                                   | [374–381] |
|                       | c-Myc activation                                              |            |
|                       | Inhibition of Akt-mediated glycolysis                         |            |
|                       | Lipid biogenesis by direct supply of acetyl-CoA in hypoxic conditions or in presence of IDH1 mutation |            |
|                       | Redox homeostasis                                             |            |
| Asparagine            | Regulation of mTORC1 activation and autophagy                 | [382, 383] |
|                       | Regulation of serine uptake and metabolism gene expression    |            |
| Leucine               | Exchanging with extracellular essential amino acids           | [384]      |
| Arginine              | Autophagy regulation                                          |            |
| Methionine            | Maintenance of viability by stability of checkpoints (mainly G1 checkpoint) | [385]      |
| Cysteine              | Reduction of cell death by oxidative stress                   | [387, 388] |
| Serine and glycine    | ROS detoxification                                            | [388, 389] |
| Acetate               | Activation of PKM2, supporting aerobic glycolysis and lactate production | [390–392] |
|                       | Activation into acetyl-CoA, used as a crucial central metabolite for TCA cycle, as a source of acetyl groups used for DNA acetylation modifications and for regulation of histone acetylation and gene expression program |            |

CoA coenzyme A, mTORC1 mammalian target of rapamycin complex 1, PKM2 pyruvate kinase muscle isozyme M2, ROS reactive oxygen species, TCA tricarboxylic acid
hypoxia is immunosuppressive and induces ROS accumulation in association with the apoptosis of activated TILs [160]. Thus, hypoxia in the TME inhibits OXPHOS by TILs and reprograms their metabolism to use glycolysis; however, most solid tumors combine both hypoglycemia and hypoxia to render TILs inactive in the TME. How TILs survive in these adverse conditions is still being investigated. It has been proposed that TILs may resort to using ketone bodies, similar to other cells under the same conditions [148, 161]. What seems certain is that these conditions are unfavorable for TILs—impairing immune cell function, immune exhaustion and reducing anti-tumor reactivity. As cancer cells also rely on alternative nutrients for their metabolism, they affect not only the use of glucose by TILs but also other nutrients, i.e., amino-acids and FAs [162, 163]. Overall, low availability of these nutrients impairs both differentiation and cytokine production, which in turn reduces effector cytotoxic functions [164], as summarized in Table 2.

Nutrient availability also impacts metabolic pathways in TAMs, which affects their functions as well as TIL immune surveillance competence. TAMs display different phenotypes which go beyond the conventional M1/M2 dichotomy. Ultimately, five TAM phenotypes are present in the TME: activated (IL-2**, MCHIIhi, iNOS**, TNF-α, CD80/CD86), immunosuppressive (Arg1*, MARCO**, IL-10*, CCL22*), angiogenic (VEGFR1*, VEGF*, CXCR4*, TIE2*), invasive (WNT signaling, EGF*, MMP9, CCL3), and metastasis-associated (VEGFR1*, VEGF*, CXCR4*, CCR2*) macrophages [165]. The nature of the TME may edit TAMs in order to compete for nutrients, mostly glucose, which reprograms TAMs towards a phenotype consistent with tumor growth, progression and metastasis [23, 166, 167]. The central features of this metabolic reprogramming have been identified as activation of glycolysis, modifications of TCA cycle that include fueling with alternative non-glucose nutrients, FA synthesis, and altered nitrogen cycle metabolism. In cell cultures, cancer-cell stimulated macrophages have exhibited upregulation of glycolysis, increased expression of hexokinase-2, activation of AKT1/mTOR, and increased lactate receptors. Upregulation of REED1, with consequent inhibition of mTOR and glycolysis, has been observed in TAMs during hypoxic conditions. This can be linked to an augmented angiogenic response and the development of vascular leakage. Lipids and amino acids have important roles in sustaining the altered TCA cycles of TAMs. TAMs exhibit increased FA biosynthesis, uptake and storage (with important intensification of arachidonic acid metabolism), while glutamine seems relevant for macrophages polarization, especially towards a M2-like phenotype although the role of different amino acids in TAMs metabolism remains poorly studied [168, 169]. Arg1 is upregulated in TAMs, consuming arginine for NO production and protein synthesis (reviewed in [170]). In terms of lipids, polyunsaturated (PU) FA linoleic acid (18:3) and saturated FA (SFA) stearic acid (18:0) have been considered relevant for macrophage polarization and function in TME. In fact, linoleic acid-enriched, as opposed to stearic acid-enriched TAMs, appear to exhibit cytotoxicity against some cancer cells [168]. Thus, TAMs also compete with TILs for nutrients, functionally impairing the latter (Table 2). MDSCs also play relevant roles in the TME and in modulating the efficacy of anti-cancer therapies (recently reviewed by Yan et al. [171]). Tumor-infiltrating MDSCs, as opposed to their circulating (peripheral blood) counterparts, appear to have preference for FAO as energy source in comparison, suggesting that they undergo metabolic reprogramming—like macrophages—in the TME [171]. Also, the switch from glycolysis to FAO demands an increase in lipid uptake that is associated with tumor progression and suppression of T-cells [171]. Targeting lipid metabolism in MDSCs may, therefore, be a potential target in anti-cancer strategies and warrants further investigation.

All aspects of the TME, including empowering anti-cancer ability of TILs, have been considered potential therapeutic targets for more rationally designed cancer treatments. For example, metformin treatment may improve memory CD8+ T-cell responses by targeting AMPK (inducing activation) as well as mTOR (inhibitory effect leading to c-Myc and HIF-1α downregulation) [17, 172, 173], which manifest in improved FA metabolism in CD8+ T-cells leading to memory

### Table 2: Competition between cancer cells/TAMs and T-cells for non-glucose nutrients: effect of nutrient despoiling on cellular functions

| Deprived by cancer cells and/or TAMs | Effect on T-cells | References |
|-------------------------------------|------------------|------------|
| Glutamine                           | Reduced proliferative capacity and cytokine production | [55, 162]  |
| Arginine                            | Reduced effector function and survival            | [57]      |
|                                    | Impaired memory subsets differentiation           |           |
|                                    | Impaired TCR                                     |           |
| Cystine                             | Reduced proliferative capacity and cytokine production | [162]    |
| Tryptophan                          | Downregulation of CD3-ζ chain in CD8+ T cells    | [393–395] |
| PUFAs                               | Inhibition of Th17 differentiation                |           |
|                                     | Absence of memory                                | [17]      |

*PUFAs* polyunsaturated fatty acids, *TAMs* tumor-associated macrophages, *TCR* T cell receptor
| Target | Drug | Mechanism | Type of cancer | Situation (Ref.) |
|--------|------|-----------|----------------|------------------|
| Hypoxia and acidosis | Panzem (2-methoxyestradiol, 2ME2) + temozolomid | Inhibition of HIF-1α and HIF-2α protein synthesis | Recurrent glioblastoma multiforme | Phase 2: NCT00481455 |
| | Topotecan | Inhibition of HIF-1α expression, angiogenesis, and tumor growth in human xenograft models | Ovarian and small cell lung cancers | Phase 1: NCT00117013 [396] |
| | Metformin | Oxygen concentration improvement in cancer tissue | Head and neck SCC cancer | Proof of principle: NCT03510390 (completion for 12/2020) |
| | Everolimus (RAD001) | Inhibition of tumor cell HIF-1 activity, VEGF production, and VEGF-induced proliferation of endothelial cells | Advanced renal cell cancer | Phase 4: NCT01206764 (completed, first data posted 24/06/2019) |
| | Everolimus (RAD001) + lenvatinib | Inhibition of tumor cell HIF-1 activity, VEGF production, and VEGF-induced proliferation of endothelial cells | Renal cell carcinoma | Phase 2: NCT03324373 (completion for 4/2021) |
| | Digoxin (DIG-HIF1) | Inhibition of VEGFR1,2 and 3; FGFR1, 2, 3, and 4; PDGFRα, KIT, and RET | Operable breast cancer | Phase 2: NCT01763931 (completion for 7/2020) |
| Angiogenesis | Pazopanib | Inhibition of VEGFR, PDGFA and -B receptors and e-Kit; Blockade of HIF-1α | Advanced renal cell carcinoma and soft tissue sarcoma | Approved for clinical use |
| | Sunitinib | Inhibition of c-kit activity | Several | Approved for clinical use |
| | Sorafenib | Inhibition of tyrosine kinase and Raf kinase activity | Several | Approved for clinical use |
| | LY01008 + bevacizumab | Anti-VEGF; inhibition of neovascularization | Non-small cell lung cancers | Phase 3: NCT03533127 (completion for 12/2020) |
| | Cediranib | Anti-VEGF; inhibition of neovascularization | Ovarian | Phase 3: NCT03278717 (completion for 12/2023) |
| | Ramucirumab (LY3009806) | Anti-VEGF; inhibition of neovascularization | Gastric and gastroesophageal cancers | Phase 3: NCT02898077 (completion for 8/2020) |
| | Everolimus (RAD001) | Inhibition of VEGF production, and VEGF-induced proliferation of endothelial cells | Advanced renal cell cancer | Phase 4: NCT01206764 (completed, first data posted on 24/06/2019) |
| | Aflibercept | Anti-VEGF; inhibition of neovascularization | Large choroidal melanoma | Phase 3: NCT03172299 (completion for 12/2024) Phase 3: NCT02885753 (completion for 6/2023) |
| TAMS, MDSCs | Pexidartinib | Inhibition of CSF1R, recruitment blockade | Giant cell | Phase 3: NCT02371369 (completion for 12/2019) |
| | PDR001 + M-CSF110 | Inhibition of CSF1R, recruitment blockade | Gastric | Phase 2: NCT03694977 (completion for 12/2019) |
| | ARRY-382 + pembrolizumab | Inhibition of CSF1R, recruitment blockade | Advanced solid | Phase 1b/2: NCT02880371 |
| | Emactuzumab | Anti-CSF1R, recruitment blockade | Advanced squamous cell | Phase 2: NCT03708224 (completion for 11/2025) |
| | Cabiralizumab | Anti-CSF1R, recruitment blockade | Metastatic pancreatic | Phase 2: NCT03697564 (completion for 12/2021) |
| | | | Biliary tract | Phase 2: NCT03768531 (completion for 1/2023) |
| | Vemurafenib | Inhibition of BRAF kinase, recruitment blockade | Metastatic melanoma | Approved for clinical use [397] |
| Aerobic glycolysis | Dichloroacetate | Inhibition of glycolysis, by PDK inhibition | Head & Neck SCC | Phase 2: NCT01386632 (completion for 10/2019) |
| | AZD3965 | Inhibition of glycolysis, by MCT1 inhibition | Several advanced | Phase 1: NCT01003769 (completion for 6/2020) |
generation. Table 3 shows a non-exhaustive list of approved drugs and candidates in clinical trials targeting some TME characteristics as well as immunometabolism for patients with solid cancer as a paradigm how these repurposed drugs can be used in the treatment of patients with infectious diseases (reviewed for pulmonary infections in reference [174]).

**Nutritional status, nutrient metabolism, and susceptibility to infection**

Infections and parasitic diseases are the most common cause of death [175] in low-income countries, where malnutrition appears to be the precipitating factor [176]. Children and adolescents with lower BMI-for-age, as well as underweight adults, are at higher risk for infections and infection-associated morbidity and mortality [175–177], e.g., for malaria and pulmonary tuberculosis [178, 179]. Nutrition, infection(s), and subsequently altered immune function(s) affect each other [180]: changes in nutritional status (especially energy and protein depletion) are associated with alterations in the systemic metabolism that affects immune cell regulation, immune competence, and disease susceptibility. Host factors associated with infectious diseases lead to increased metabolism (catabolism) paired with decreased appetite and subsequently to malnutritional [179]. However, the nutritional status favors maintenance of T-cells with “stem cell-like features” that are important for long-term immune memory [181].

Although malnutrition remains a concern in low-income countries, it is also present—in a “different format” in higher-income countries. Economic disparities within a country (poverty, malnutrition, and obesity) represent a major challenge for twenty-first century societies and health professionals. Obesity is no longer considered to be a consequence of the abundance of food, but rather a result of poor education, lower income, and access to affordable high-energy-dense food along with the lack of physical activity [182] and, possibly, the composition of the microbiome [183]. In general, changes in the nutritional status of populations shape immune competence, the ability to resist, fight off infections and to productively respond to vaccinations [184–186].

The relationship between malnutrition and immunity will be discussed in detail below; immunometabolism and the implications for protective immune responses and host-directed therapies have been extensively reviewed in Rao and co-workers [174].

**Nutritional immunology**

**Definition and historical aspects**

Beginning with J.F. Menkel’s notes on thymic function and adequate nutrition in the nineteenth century, malnutrition has been related to alteration(s) in organs of the immune system [187]. However, the publication *Interactions of nutrition and infection* by Scrimshaw et al [188] in 1959 postulated the first steps pertaining to nutritional immunology. Almost a decade later, the World Health Organization (WHO) released the first edition of an extended monograph with a similar sounding concept [189]. The name of Professor Nevin Scrimshaw (1918–2013) will, thus, remain forever associated with nutritional immunology, not only due to these two publications but also owing to other works devoted to understanding the interrelationship between nutrition and infection, and the evidence of higher mortality in malnourished populations [190–198]. Since the 1969 WHO monograph, the hallmark of nutritional immunology as a discipline has been the recognition that almost any specific and sufficiently severe nutritional deficiency can interfere with
immunological functions, affecting infection-associated morbidity and mortality [191, 199].

**The synergistic relationship of nutrient reserves and immune responses**

Early observations following the advent of nutritional immunology showed that malnourished patients were more susceptible to infection and presented with an increased risk of mortality due to sepsis [200]. In fact, the impact of malnutrition on immune defense constituted, for many years, the core of and justification for immunonutrition in immunosuppressed patients—inclusively referred to as nutritionally acquired immune deficiency syndrome. The new challenges faced by humanity, mainly overnutrition, aging, and stressors, are redirecting research in the field of nutritional immunology and rewriting the applications of immunonutrition.

Nutrition and immunology have a multi-level synergistic interaction that has been described in conjunction with the 4 “Is”—Infection, Immunity, Inflammation, and Injury [31]. However, as stated above, the relationship between nutrition and immunology was first confined to the effect of poor nutrition due to the risk of infectious diseases as well as recovery after a bout of infection [191]. This was understandable in a context where nutrition was seen merely as protein and energy, and nutritional problems as “protein-energy” malnutrition (PEM). In fact, malnutrition was always a considerable clinical issue at hospital admission. Epidemiological evidence that malnutrition screening at admission and nutritional intervention during hospitalization positively impact patients’ quality of life, reduce hospital stay, increase resistance to infection, and reduce costs have been instrumental recognizing the impact of nutrition in preventing and recovering from infection [201, 202]. The relationship between PEM and infection, especially the impact on immune cells and non-cellular components are summarized in Table 4.

A relationship between nutrition and immunity was established following recognition of multiple micronutrient deficiencies which affect immune cells and other components of the immune system, for example ascorbic acid deficiency and scurvy accompanying states of malnutrition. In fact, the idea that proper nutrition also nourishes the immune system gained scientific credibility [203]. Vitamins and minerals exert profound effects on immune cells—in terms of physiology and ontogenesis—that should be considered when treating a patient. Also, the acknowledgement that nutrition may be used to re-establish immunity provides a new perspective for this adjuvant therapy. Table 5 summarizes the main effects of selected vitamins and minerals on the immune system, with significant knowledge arising from studies undertaken to obtain a better picture of nutritional deficiencies in relation to immunity.

| Table 4 | Relationship between protein-energy malnutrition (PEM) and infection: effects of PEM on immune cells and non-cellular components |
|---|---|
| Innate immunity | Adaptive immunity | Organs |
| Mucus: reduced production and altered structure | WBC counts: increased or maintained | Thymus, lymph nodes, spleen, tonsils: reduced weight |
| Intestinal mucosa: reduced integrity | CD3⁺ proliferation: reduced | |
| Complement: reduced C3 concentration in blood | CD3⁺CD4⁺: reduced counts and IL-2 and IFN-γ production | |
| NK cell: reduced activity | CD3⁺CD8⁺: reduced counts | |
| Neutrophils: reduced respiratory burst and bacterial killing | Antibodies: increased or maintained concentration in blood; decreased or maintained response to immunization; reduced concentration of IgA in saliva and tears | |
| Acute phase proteins: reduced concentration in blood | | |
| Monocytes/macrophages: reduced production of TNF, IL-1, and IL-6 | | |

C3 complement protein C3, PEM protein-energy malnutrition, WBC white blood cells

The increase in prevalence of chronic non-communicable diseases and the recognition of adipose tissue as a metabolic organ with the capacity to produce specific cytokines (adipokines) and infiltrated with specialized macrophages marked the era of inflammation research. In the inflamed visceral adipose tissue, a phenotype switch in macrophages occurs, establishing the prevalence of classically activated (M1) over alternatively activated (M2) subsets. This increase in HIF-1α and iNOS, thus, provides a propitious environment to metabolize L-arginine into NO, increasing hypoxia and insulin resistance and altering the expression of adhesion molecules responsible for the homeostasis of the vascular endothelium [204–208]. This low-grade chronic inflammation underlies several pathological conditions and is considered a hallmark of obesity, diabetes, coronary arterial disease, chronic infections (tuberculosis) [209, 210], to some extent, sequelae associated with cancer [206, 211]. The central role of inflammation and metabolism in chronic non-communicable diseases has strengthened the relationship between nutrition and immunology. “Classical” obesity and the paradigm of sarcopenic obesity have been gradually replacing PEM as major problems at hospital admission, independently of the underlying pathology [212–214]. Cachexia and sarcopenic obesity are relatively common in patients with cancer and are extremely challenging for clinicians and researchers. Skeletal muscle morphology is now recognized to reflect a relevant prognostic factor for these patients, as the role of skeletal muscle mass (SMM) and metabolism in health and
Table 5

| Vitamins/minerals | Innate immunity | Adaptive immunity |
|-------------------|-----------------|-------------------|
| **A** | Generation of antibacterial and anti-fungal immune responses  
Killing through NK cells, macrophages, and neutrophils  
Maintenance of ILCs homeostasis, balancing ILC2 and ILC3 subsets  
Differentiation of pre-μDCs into CCR9+ plasmacytoid DCs and conventional DCs subsets, preferentially developed into intestinal CD103+ conventional DCs [398, 399] | Promotion of gut-associated immunity by facilitating induction of IgA-producing B cells, gut-tropic CD4+ and CD8+ T cells, Th17, γδ T cells  
Generation of mucosal and splenic CD11b+ DC subsets with important role in the generation of Th2, Th17, and antibody responses  
Balancing of Th1/Th2 subsets, favoring Th2 polarization |
| **C** | Enhancing chemotaxis and phagocytosis and thereby promotes microbial killing  
Protection of phagocytes against ROS-induced damage  
Reduction endothelial cell expression of the adhesion molecule ICAM-1 in response to TNF-alpha  
Suppression of systemic neutrophil extravasation during bacterial infections  
Inhibition of p38 MAPK pathway and endothelial NF-kappa B activity  
Suppression of endothelial permeability and vascular leakage | Enhancing of differentiation and proliferation of T cells, particularly enhancing the selection of functional TCRαβ after the stage of β-selection  
Balancing of Th1/Th2 subsets, favoring Th1 and Th17 differentiation  
Increasing the induction of CTLs due to production of IL-15 and IL-12 by DCs  
Regulation of Treg function via epigenetic regulation of Foxp3? |
| **D₃** | Increasing cathelicidin transcription (VDRE, C/EBPα, SWI/SNF complex) in monocytes/macrophages, keratinocytes, IECs, placental trophoblasts, and LECs | Suppression of IL-2 transcription in Th1, by blockade of NFAT/AP1 complex and sequestration of Runx1  
Suppression of IFN-γ transcription in Th1  
Induction of Fox3p transcription in Treg (VDRE in the conserved non-coding region of the Fox3p gene)  
Suppression of IL-17 transcription in Th17, by blockade of NFAT binding, sequestration of Runx1, and inhibition of RORγt |
| Selenium | Improving NK cell activity | Increasing of lymphocyte proliferation  
Increasing expression of IL-2R  
Balancing of Th1/Th2 subsets, favoring Th1 |
| Zinc | Increase of phagocytosis, NK cell activity | Cytosolic defense against oxidative stress  
Induction of DTH and antibody response  
Induction of CTLs |
| Iron | Differentiation of NK cells, monocytes, and macrophages and enhancing of cytotoxic activity | Differentiation and proliferation of Th1, IL-2 production, increasing in immunoglobulin levels |

AP activator protein, DC dendritic cell, Foxp3 forkhead box P3, ILCs innate lymphoid cells, C/EBPα CCAAT/enhancer-binding protein alpha, CTL cytotoxic T-cell, DTH delayed type hypersensitivity, ICAM intercellular adhesion molecule, IEC intraepithelial cell, LEC lymphatic endothelial cell, MAPK mitogen-activated protein kinase, NFAT nuclear factor of activated T-cells, ROR retinoic acid receptor-related orphan receptor, SWI/SNF SWItch/sucrose non-fermentable, TCR T-cell receptor, TNF tumor necrosis factor, VDRE vitamin D response element

Disease is being established [215–218]. SMM loss, as observed in sarcopenia and cancer-related cachexia, is driven by the increase of systemic inflammation [219–221]. Intracellular signaling responsible for muscle wasting is regulated by IL-6, TNF-α, and transforming growth factor beta (TGF-β) in response to several distinct stimuli [219–222]. These cytokines have been mechanistically linked to SMM wasting and disruption of metabolic homeostasis in cancer-related cachexia [223]. Evidence also suggests that these pro-inflammatory cytokines can reduce mitochondrial biogenesis by decreasing the activity of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which in turn has an effect on nuclear respiratory factor 1 (NRF-1) and sirtuin 1 (Sirt-1) expression in cells [220]. Cachectic muscle shows increased autophagy (through induction of microtubule-associated protein light chain 3 (LC3B) Beclin-1, p62, Atg 5, and Bnip3, and dysregulated dynamics (increased FIS-1 and Drp-1 and decreased MFN-1, MFN-2, and OPA-1 expression). These factors contribute to decreased mitochondrial function and ATP synthesis in skeletal muscle. Mitochondrial damage induced by mild oxidative stress can be repaired by mitophagy (targeted autophagic clearance of mitochondria), whereas high levels of oxidative stress lead to mitochondrial fission and ultimately enhanced ROS production [224]. The evidence that loss of SMM is present even when patients seem well nourished (sarcopenic obesity) is sparking more extensive research into the area of body muscle composition as compared to classical assessment based on an individual’s physical stature. In patients with cancer, recovery of SMM has been related to weight maintenance, as sarcopenia is associated with delayed recovery and longer hospital stays postsurgery [225], increased susceptibility to toxicity of
chemotherapy, and reduced quality of life and survival [226]. Therefore, SMM reflects a negative prognosis for patients with cancer and warrants greater attention in treatment regimens.

Knowing that inflammation and body composition (fat mass, SMM, free fat mass, and water) are related, it is important to also understand how nutrients may reverse chronic inflammation. Tocopherols (many with the properties of vitamin E), retinol (vitamin-A1-alcohol), zinc, essential fatty acids (omega-3/omega-6 balance), amino acids and nucleotides are able to modulate the intensity of inflammatory responses, more specifically metaflammation or chronic metabolic inflammation [227]. This may in part be responsible why individuals in countries with a high burden of infectious diseases are more susceptible to severe pathology, as many of those who succumb to infectious diseases under-nourished, particularly children [228]. Perinatal nutrition and supply of micronutrients to neonates, including via breast feeding, has already been discussed in light of their paramount importance in priming innate immune responses against bacterial infections in very early childhood [229, 230]. While nutrition is indispensable for muscle mass anabolism, the regulation and fine-tuning of inflammation and immune cell composition in tissue compartments by micronutrients deserves a closer look in clinical studies. It is, therefore, necessary to design future clinical trials (vaccines, drugs, immunotherapy) and treatment plans with the inclusion of the fundamental aspects of nutrition, metabolism, and inflammation.

The relationship between nutrition and immunology can also be extended to injury. It has been widely accepted that nutrition and wound healing are closely related, so that proper nutrition is required to allow progression through all stages of wound healing: inflammatory, proliferative, and remodeling/maturation phases. PEM or nutrient deficiencies negatively impact wound healing by extending the inflammatory phase, decreasing fibroblast proliferation, and reversing collagen synthesis [231]. Malnourished patients are recognized to be at risk of pressure ulcers, infections, delayed wound healing, and chronic non-healing.

Nutrition has been considered one of the most relevant modifiable factors influencing chronic non-communicable diseases. The importance of nutrition is being increasingly recognized by clinicians as a biologically and clinically factor in clinical performance and recovery [232–234], more well-designed clinical studies are need combining clinical endpoints with biological marker analyses, particularly in patients with cancer [235–239]. Recent data from the PREDyES® study revealed that nutritional risk is present at hospital admission in 33.9% of patients, with an increase at discharge from hospital (36.4%) [239]. In a recent report involving a prospective cohort including 1588 patients with cancer, Byung-Gon Na and colleagues demonstrated that malnutrition appears to be more frequent in patients with esophageal, pancreaticobiliary, or lung cancer (52.9%, 47.6%, and 42.8%), followed by stomach, liver, and colon cancers (29.1%, 24.7%, and 15.9%) [240]. Also, malnourished, patients with cancer who underwent surgical procedures had longer hospital stays and poorer quality of life than those who were well nourished [240].

Nutritional immunology is now considered clinically relevant, to pave the way for novel research paths with the ultimate aim to provide improved nutrition, increased, competent immune function and overall 'better' healthcare.

**The role of the microbiome in regulating nutrient bioavailability and immune responses**

The study of the microbiome is an emerging area of research with an influence on all aspects of health—cancer [241–243], depression [244], metabolic disease [245], and susceptibility to and control of infections [246, 247]. The gut microbiota is directly involved in the metabolism of drugs [248], thus forming an additional layer of pharmacokinetics further to the role of the liver and kidneys in relation to treatment efficacy.

The gut is considered a unique organ in humans due to the sheer diversity of microflora performing a myriad of functions, in addition to its direct exposure to the external environment. A healthy microbiome—also in other mucosal tissues, i.e., lungs, skin, gums—is directly associated with general well-being [249]. There are psychological, environmental, and physical stressors that affect microbiome composition and function (reviewed in [250]). A major nutritional component linked to immune regulation are short- and long-chain fatty acids (SCFAs and LCFAs) produced by gut commensals. These have been shown to influence memory T-cell formation and maintenance as well as activation of effector cell populations in tissue [251]. The biosynthesis of micronutrients such as vitamins and amino acids by gut commensals including lactic acid bacteria (LAB) would—in the first place—affect the physiology of parenchymal tissues, i.e., epithelial-cell functions, for instance [252]. In fact, the microbiome is also responsible for biosynthesis of vitamins like cobalamin, folic acid, biotin, thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, and vitamin K [252, 253]. The potential link between SMM and gut dysbiosi, particularly with respect to aging, is being actively explored. Changes in gut microbiota composition have been related to enrichment of certain bacterial species, i.e., *Bacteroidetes* sp.*, Escherichia* sp.*, and reduced frequencies of *Ruminococcus* sp.*, which have been observed in individuals older than 65 years of age in northern Europe [254, 255]. Also, SMM due to aging has been associated with gut microbiota alterations, which contribute to increased risks of systemic inflammation as well as fat accumulation in skeletal tissue [256]. Consumption of particular types of food have also been investigated as inducers of
predictable alterations in existing host microbiota (reviewed in [257]). All dietary proteins contribute to microbial diversity; however, the sources of the protein seem to determine the effect on specific genera. Animal proteins, particularly red meat, favor Bacteroides, Alistipes, Bilophila, and Ruminococcus, while reducing Bidobacteriag and Lactobacillus and reduce Bacteroides and Clostridium perfringens, which has been associated with increased production of SCFA [257]. Proteins of plant origin favor Bidobacteriag and Lactobacillus and reduce Bacteroides and Clostridium perfringens, which has been associated with increased production of SCFA and an improved gut barrier, Treg induction, and amelioration of inflammation [257]. Unsaturated fat favors Streptococcus, Lactobacillus, and Bifidobacteria that seem to downregulate TLR activation and white adipose tissue inflammation, while saturated fat is associated with increases in Bacteroides, Bilophila, and Faecalibacterium prausnitzii promoting white adipose tissue inflammation, TLR activation and impaired insulin sensitivity [257, 259, 260]. Concerning carbohydrates, natural and artificial sweeteners promote different effects on microbiota composition: natural sweeteners tend to increase Bifidobacteria and reduce Bacteroides, while artificial sweeteners seem to have the opposite effect [257]. There is no doubt that the Western diet is associated with dysbiosis (increase in Bacteroides and Enterobacteria and reduction in Bifidobacteria, Lactobacillus, and Eubacteria) [261], while the Mediterranean diet appears to have opposite and beneficial effects on the gut microbiome [262]. In this context, both obesity and malnutrition (despite the few studies available) have a severe impact on gut microbiota as well as individual micronutrient deficiencies [263]. Malnutrition results in persistent impaired maturation of the intestinal microbiota that seems difficult to revert even with refeeding [264]. As such, this topic deserves further investigation in multicohort clinical studies. A healthy “microbiome” does not sufficiently describe the commensal–host relationship and different layers of shaping immune responses. Analysis of the “dark viral matter,” i.e., known and not yet known viral sequences in the gut revealed that a healthy gut microbiome is defined by integrated prophages versus the shift from lysogenic to lytic replication, associated with inflammatory bowel disease [265, 266].

Pertaining to individual micronutrients, vitamin D is an interesting but somewhat controversial paradigm. Vitamin D is necessary for the biosynthesis of cathelicidin (human LL-37), a crucial antimicrobial peptide that is also produced in the gut and linked to the IFN-γ, IL-32, and IL-15 signaling axis [267, 268]. Several studies have gone further to show that LL-37 has anti-cancer properties based on its ability to kill cancer cells in vitro (reviewed by Kuroda et al. in [269]). LL-37 bioavailability in the colon, however, can affect gut microbiota viability and potentially perpetrate dysbiosis, as shown in chickens in the context of CATH-2 [270]. However, mice lacking the antimicrobial peptide CRAMP (CRAMP-KO) displayed oral dysbiosis following co-housing with wild-type mice, possibly transferred to the gut of the CRAMP-KO animals due to CRAMP presence in the feces of the latter [271]. Strikingly, CRAMP-deficient mice exhibited compromised intestinal morphology, i.e., reduced crypt length but increased inflammatory events leading to tissue enlargement. Due to the very high likelihood of inter-organ communication pathways, i.e., gut-lung axis, LL-37 produced in the lungs during an acute bacterial infection could translocate to the bowel and eliminate certain commensal populations—a phenomenon which can also occur in vice versa, at least with regard to microbial metabolites and immune cells [272–274]. Further clinical studies in addition to relevant and well-designed translational models are necessary to better understand how antimicrobial peptide biology plays into nutrient uptake and immune response development in humans. For instance, fecal microbiota transplantation (FMT) for the treatment of recurrent Clostridium difficile infections (CDI) leads not only to clinical improvement in patients but also the establishment of a corrective mechanism to introduce gut-friendly commensals which would compete with C. difficile for nutrients and ameliorate pathology [275]. Correcting the local immunoregulatory networks using FMT also appears to be clinically beneficial in patients with ulcerative colitis [276], where prebiotic therapy helps remodel damaged colon tissue, as is likely the case in recurrent CDI. It would be helpful if a more broader, objective appreciation of mucosal dysbiosis could be performed. This could help to devise more robust clinical studies measuring immune-competence and clinical endpoints in patients with infectious diseases or cancer.

Diet is most often seen as having a circular relationship with the microbiome. However, it has been proposed that a distinction be made between the role of the microbiome in mediating the effects of diet on metabolism and the microbiome itself as a modifier of the host response to diet [277].

Future directions: is there a role for tailor-made nutrition in cancer and infections?

Cancer cachexia, muscle wasting, and metabolism

Along with the immunosuppression that results from a reprogrammed TME, patients with cancer experience profound alterations in body composition as a result of wasting disease and anti-cancer directed treatments [278]. These alterations are most evident in SMM, as muscle as well as adipose tissue wasting are common features in cancer (affecting nearly
80% of late-stage patients) and the major causes of morbidity and mortality [279]. As SMM and adipose tissue are depleted during cancer progression, patients experience weakness, frailty, and loss of mobility [280], followed by a rapid decline in total body weight and severe compromise of immune functions [223]. SMM and adipose tissue depletion are closely connected to increased levels of TNF-α, IL-1, and IL-6, the key mediators of cancer-associated cachexia [281–283]. TNF-α has a direct catabolic effect on MM by induction of the ubiquitin-proteasome system (full form), which dictates an increase in gluconeogenesis, proteolysis and a decrease in protein, lipid, and glycogen synthesis [283]. A comprehensive review of the metabolic changes during cancer cachexia was published recently [284]. However, besides the knowledge that patients with cancer present with hypermetabolism induced by cachexia [285], the effective role of metabolism in muscle consumption deserves further investigation. Patients with cancer exhibit altered glucose metabolism clearly marked by sluggish glucose uptake, reduction of the conversion rate of glucose to glycogen, lactate or CO₂, and suppression of enzymes that support glycolysis and glucose oxidation [284]. Lipogenesis has been found to be lower in preclinical cachexia (murine) models. However, lipolysis and FAO rates seem similar in patients with cancer and healthy controls during fasting [286, 287]. Not only protein synthesis and degradation contribute to muscle atrophy, yet also age-related defects in autophagy signalling [288, 289]. In fact, p38β MAPK was identified as a key mediator of cancer-induced autophagy activation in SMM of tumor-bearing mice [290]. The authors demonstrated that this occurs through ULK1 activation and upregulation of C/EBPβ-controlled LC3b and Gabarapl1 genes [290]. Fukawa and colleagues also demonstrated, using human muscle stem cell-based models and human cancer-induced cachexia models in mice, that progressive muscle wasting was associated with excessive FA catabolism triggered by complex pro-inflammatory factors, increased oxidative stress, and activation of the p38 signaling pathway [279]. Mitochondrial dysfunction also seems to underlie SMM consumption in cancer [220], with mitochondrial dynamics and mitophagy signaling being identified as aberrant checkpoints of the muscular-mitochondrial quality control axis associated with cancer cachexia [291].

Chemotherapy-induced cachexia was recently associated with metabolic dysregulation [292]. In a murine Colon26 adenocarcinoma xenograft model, the authors compared the metabolic derangements associated with cancer-induced cachexia with a chemotherapy-induced cachexia model using FOLFIRI (5-fluorouracil, irinotecan, and leucovorin) [292]. Using metabolomic techniques, FOLFIRI-induced cachexia perpetrated slightly higher amino acid catabolism and carbon flux through the TCA cycle and β-oxidation pathways, as compared with cancer cachexia per se [292]. This study highlights the heterogeneity of cachectic phenotypes induced by cancer and chemotherapy may be considered in future study designs. Other clinical studies and reviews drawn a link between chemotherapy and cachexia induction [293–295] as well as overall body composition [296–299]. This reveals that cancer- and treatment-induced cachexia is complex, multifactorial, and personalized for each patient, especially in respect of the circulating mediators secreted and pathways disrupted. The understanding that this complexity and singularity makes each patient unique, strongly argues for nutrition as an integral component of personalized cancer treatment.

**Immunonutrients: cancer and infection**

Attempts to manipulate the complex network of cells and circulating molecules of the human immune system have been made throughout modern medical history. Considering nutrition as part of these attempts, publications on the dietary manipulation of inflammatory responses date back to the late 1980s and early 1990s [300–303]. Nutrients studied for their possible role on modulating immune responses were considered “immunonutrients,” wherein important contributions have been made by Robert F. Grimble (main reviews [200, 301, 304, 305]). Immunonutrients have been historically divided into omega 3 PUFAs (EPA and DHA), sulfur-containing amino acids, their precursors and other thiol compounds (methionine, cysteine, N-acetyl cysteine and l-2-oxythiazolidine-4-carboxylate lipoic acid), glutamine, arginine, and nucleotides [200]. Other nutrients such as antioxidants can also be used for this purpose [306]. These immunonutrients have been studied in supra-physiological doses, administered enterally or parenterally, to achieve some degree of immune response modulation in different pathological conditions [200, 301]. The role of nutrients for immune cell function and competence was discussed earlier in this review. Therefore, profound metabolic and immunological alterations characteristic of cancer provide a unique opportunity for the study of nutritional modulation, especially in the age of personalized precision medicine.

Currently, the nutritional recommendations for patients with cancer, among other aspects, require the following: (i) provision of adequate nutrition to prevent malnutrition, (ii) avoidance of dietary provisions that restrict energy intake in patients with or at risk of malnutrition, (iii) avoidance of supplementation with branched-chain or other amino acids as well as metabolites to improve fat-free mass, and (iv) supplementation with EPA and DHA or fish oil to stabilize or improve appetite, food intake, lean body mass, and body weight [307]. However, some research questions were raised in these guidelines: the influence of fasting or diets mimicking the effects of anti-cancer drugs, the effect of leucine or hydroxy methylbutyrate in unwanted weight loss assessed by large randomized clinical trials (RCTs), the effect of EPA and DHA on body composition and clinical outcome in patients.
with cancer undergoing treatment, and the effect of omega 3 on quality of life (QoL) and clinical outcome in cachexic patients with cancer. These recommendations, nevertheless, are in need of well-designed clinical trials to obtain solid real-world evidence for clinical practice. Another important issue is the missing link between the nutritional and immunological variables in most clinical studies. Commonly, nutritional publications on the effect of nutrition in clinical outcomes do not account for immunological profiles or immune response parameters. Published studies describing the effect of a single nutrient on immunity or inflammation frequently fail to consider the evaluation of dietary intake or body composition. This is also true for studies evaluating the effect of immunonutrition in cancer.

Three fundamental aspects should be addressed when considering immunonutrition administration and its effect on the overall result: (i) route and (ii) timing of administration as well as (iii) genetic variation among patients [200, 308]. Immunonutrition may be delivered enterally or parenterally, as single nutrient(s) or combinations of two or more immunonutrients. In the early days of immunonutrition, enteral or parenteral formulas were the preferred route for administration of immunonutrients, as the need to resort to artificial nutrition was an opportunity to test the usefulness of these nutrients [309, 310]. Enteral delivery of immunonutrients may be achieved by tube feeding or using oral nutritional supplements (ONS). Currently, oral formulations as capsules are also used, alone or in combination with ONS [311, 312].

The major difference between parenteral and enteral routes is that when the latter route is used, metabolic processing by the liver is bypassed, affecting clinical outcome [200]. Although debated for several years now, there is no consensus on the best route for immunonutrition administration [31, 200, 313, 314]. Regarding timing, preoperative administration of immunonutrition has been studied in the context of surgical critical care, cancer surgery [315–320], as well as perioperative administration [321–323]. Whether immunonutrition should be delivered at the peak of or prior to an inflammatory response remains to be answered. Genetic variation is also an important factor to be considered when evaluating immunonutrition efficacy [324–326]. Hundreds of genes may shape host response to nutrition, contributing to some degree of variability in results with immunonutrients [327–329]. Among others, single-nucleotide polymorphisms (SNPs) have been associated with lipemia owing to dietary lipids and the ability of fish oil to abate TNF production [330–332].

Studies on the effect of single immunonutrients or immunonutrition formulas are heterogeneous pertaining to the routes of administration, time of initiation and duration of immunonutrition treatment, the number and characteristics of patients, cancer diagnoses, as well as the outcomes evaluated. Gastrointestinal (GI) malignancies are prevalent worldwide with a vast impact on nutritional status [333–336]. Table 6 presents a compilation of clinical trials on the effect of immunonutrition on GI cancers addressing body composition and immunological parameters/immune responses as outcomes published for the 10 years. Besides several ongoing clinical trials with immunonutrients in cancer, an interesting phase 2b clinical trial on the effect of omega 3 supplementation before radical prostatectomy on prostate cancer proliferation, inflammation, and QoL (NCT02333435) is expected to be concluded in due course [337]. Once again, this study does not address whether immunonutrition may contribute to modulation of immune cell phenotype, especially in the TME. In-depth immunological analyses are desirable in future clinical studies assessing complete dietary evaluation and full nutritional status assessment of patients prior and after intervention.

Beyond classical immunonutrients, other dietary interventions are currently under investigation for their potential to modulate the TME. One example is fasting, fasting-mimicking diets, and ketogenic diets [338]. Metabolic pathways are activated in response to caloric restriction, promoting inhibition of the mTORC1 pathway to contribute to reduced cancer growth. Additionally, modulation of the ATP/ADP and NADPH/NADP+ ratio, reduction of acetyl-CoA, and decreased serum insulin, glucose, and IGF-1 levels have been associated with caloric restriction [338]. Although not yet recommended for clinical practice (as already discussed here), research in this area is aligned with open questions raised by scientific societies [307].

Fasting, long-term fasting, fasting-mimicking diets, and ketogenic diets are currently under investigation in lung (NCT03700437; NCT01419587), breast (NCT03595540, NCT03162289, NCT01304251; NCT03962647; NCT03535701; NCT02092753), colorectal (NCT03595540), ovarian (NCT03162289), pancreaticobiliary (NCT03510429; NCT02964806), pancreatic (NCT01419483), head and neck (NCT01975766), and prostate (NCT02710721) cancers, as well as malignant CNS tumors (NCT03451799; NCT03278249; NCT03075514; NCT02983942; NCT02939378; NCT02302235; NCT02046187; NCT01865162; NCT01754350; NCT01092247; NCT00575146) and studies involving multiple indications (NCT03340935, NCT01954836, NCT01175837, NCT00936364; NCT03162289; NCT03160599; NCT00936364; NCT01175837; NCT01716468; NCT02516501).

Apart from restriction in total calorie intake, restricting specific nutrients may also be an interesting addition to therapeutic strategies. It has been proposed that specific nutrient deprivations, for example K+, may allow TILs to persist in the TME in a less differentiated status associated with strong anti-tumor responses, rather than contribute to T-cell limitation as it is observed for other nutrients [339]. This hypothesis has
| Study (ref.) | Participants | Intervention | Outcomes | Results |
|-------------|--------------|--------------|----------|---------|
| Ida et al., 2017 [400] | Gastric cancer undergoing gastrectomy, N = 63 (46 males), 65.1 (31–79) years | Omega 3 Enteral ONS, 2.3 g EPA | 7 days to 1 day prior to surgery | BW, CRP | No effect |
| Miyata et al., 2017 [401] | Esophageal cancer, N = 31 (27 males), 64.5 ± 8.4 years | Omega 3 Enteral ONS, 900 mg EPA + DHA | After CT initiation from day 3 to day 12 (total: 10 days) | Caloric intake BW, IL-6, TNF-α Toxicity | Reduced toxicity |
| Sorensen et al., 2014 [402] | CRC undergoing surgery, N = 74 (44 males), 69 ± 11 years | Omega 3 Enteral ONS, 2 g EPA 1 g DHA | 7 days before surgery | 5-HEPE, 5-HETE, LTB5, LTB4 | Reduction in LTB4 production, Increase in LTB5 and 5-HEPE production |
| Mocellin et al., 2013 [403] | CRC undergoing CT, N = 6 (3 males), 55.2 ± 7.7 years | Omega 3 Oral Capsules, 350 mg EPA 240 mg DHA | 9 weeks | IL-1β, IL-10, IL-17A, TNF-α, CRP, BW, % BF, LM | Reduction of CRP levels |
| Silva et al., 2012 [404] | CRC undergoing CT, N = 11 (8 males), 50.1 ± 8.2 years | Omega 3 Oral Capsules, 600 mg EPA + DHA 3 mg cholesterol | 9 weeks | TNF-α, IL-1β, IL-6, CRP, BW | Reduction of CRP levels |
| Bonatto et al., 2012 [405] | Gastrointestinal in CT and after surgery, N = 19 (12 males), 53.8 ± 2.4 years | Omega 3 Oral Capsules, 300 mg EPA 400 mg DHA | 8 weeks | Number and function of PMN BW | Maintenance of PMN number and function, Improved BW |
| Trabal et al., 2010 [406] | Advanced CRC in CT, N = 8 (4 males), 61.5 ± 15.8 years | Omega 3 Enteral ONS, 1.6 g EPA | 12 weeks | BW, dietary intake | Improved BW and appetite |
| Rotovnik Kozjek et al., 2011 [407] | Rectal cancer receiving RT, N = 14 (no reference to gender distribution), 60.5 ± 4.2 years | AA Oral Powder, 30 g glutamine | At start of RT and for subsequent 5 weeks | IL-6, blood count CRP | Reduction of IL-6 |
| Martin et al., 2017 [315] | Pancreatic cancer undergoing surgery, N = 44 (30 males), 60 (27–61) years | Combined Enteral ONS, 12.6 g t-arginine 3.3 g EPA + DHA 1.29 g RNA | 5 days prior to surgery | BW, NRI | Decrease in NRI |
| Seguin et al., 2016 [408] | Liver cancer undergoing surgery, N = 18 (14 males), 68 ± 6 years | Combined Oral Powder, 11.4 g t-ARGININE 3 g EPA 1.2 g RNA | 10 days prior to surgery | CD3+, CD4+, CD8+, NK, B cells, phagocytosis capacity | Increased phagocytosis capacity in monocytes |
| Marano et al., 2013 [409] | Gastric cancer undergoing surgery, N = 54 (34 males), 66.6 (55–78) years | Combined Enteral Tube feeding, 24 g t-arginine 3.3 g EPA + DHA 2.3 g RNA | From 6 h after surgery to 7th day | CD4+, CD8+, leukocyte count | Less impact of surgery on CD4+ |
| Okamoto et al., 2009 [410] | Gastric cancer, N = 30 (20 males), 66.9 ± 11.5 years | Combined Enteral ONS, 9.6 g t-arginine 3.1 g EPA + DHA 0.96 g RNA | 7 days prior to surgery | CD3+, CD4+, CD8+, NK, phagocytosis capacity, HLA-DR expression on monocytes, BW | Maintenance of CD3+, CD4+, CD8+, NK |

Age is presented as mean ± standard deviation or median (range)

AA amino acids, BF body fat, BW body weight, CRC colorectal cancer, CRP C-reactive protein, CT chemotherapy, DHA docosahexaenoic acid, EPA eicosapentaenoic acid, HEPE hydroxyeicosapentaenoic acid, HETE hydroxyeicosatetraenoic acid, LM lean mass, LT leukotriene, NK natural killer, NRI nutritional risk index, ONS oral nutritional supplements, PMN polymorphonuclear leukocytes, RNA ribonucleic acid, RT radiotherapy
been explored in publications [339–341] and deserves further clinical investigation.

Immunonutrients are less well studied within clinical trials concerning MTB. Experimental studies suggested that EPA and DHA may improve host defense against infections by limiting excessive inflammation and improving immune responses [342]. For example, in an experimental study with guinea pigs infected with M. tuberculosis, McFarland and colleagues demonstrated that omega 3 intake (13% w/w) for 3 or 6 weeks was associated with decreased lymphoproliferative responses and increased lung bacterial load compared to intake of omega 6-enriched diet [343]. Transgenic mice (producing PUFAs endogenously, Fat-1-trangenic mice) were demonstrated to be more susceptible to MTB infection compared to WT [344]. On the contrary, experimental incorporation of amino acids seems to stimulate TNF-α production by M. tuberculosis-infected macrophages along with antibacterial activity [345]. Epidemiological studies on this subject have provided conflicting results. In selected populations as the Inuit, higher intake of fish has been associated to increased MTB incidence [346–348]. Yet in a large cohort of Chinese men and women (63,257 participants aged 45–74 years old), Soh and colleagues observed that marine omega 3 intake was associated with reduced risk of active MTB in a dose-dependent manner [349]. Regarding amino acids and MTB infection, two RCTs were conducted, to the best of our knowledge, and published during the last 10 years. Ralph et al. studied the effect of 6 g/daily of L-arginine hydrochloride for 8 weeks in MTB clinical outcomes of 99 participants, but no effect was observed [350]. Schön et al. studied the effect of daily intake of arginine-supplemented foods (wheat crackers 0.1 g arginine + 30 g peanuts 1 g arginine) for 4 weeks in patients with smear positive pulmonary tuberculosis, with no observed effects on the outcomes addressed [351]. At this point, biologically relevant clinical studies are needed that take the insights of immune cell activation and differentiation into account.

**Immunonutrition as a form of host-directed therapy—ideation for future clinical possibilities**

The vastly expanding fields of personalized nutrition and immunometabolism deserve thorough clinical investigation to allow immunonutrition be part of clinical practice in precision immuno-oncology. A specialized clinical immunonutritionist, as a member of the medical care team, would be able to perform a complete evaluation of nutritional demands for each patient and to draft an immunonutrition scheme tailor-made for each individual. For example, the formulation of molecularly defined immunonutrition recipes—akin to “molecular gastronomy” but built on scientifically and medically sound bases—warrants testing in a patient-specific manner, representing a form of personalized host-directed therapy (HDT). There may also be patient groups who could benefit from a particular immunonutrition package, presenting “off-the-shelf” options. Also the routes and time schedule of administration of such ‘immunonutrition’ has to be considered. Patients may require a certain set of nutrients at a particular juncture and to be given via a particular route (more of one nutrient and less of another and administered in a specific anatomical location). These immunonutrition packages may also be considered at the same time as personalized cancer vaccines are being delivered (potentially with adjuvant-like properties) and/or during the monitoring phase, which may enhance the immune functions of T and B cells and partly compensate for nutrient despoiling by cancer cells [114]. Equally important are well-designed clinical trials evaluating the effect of immunonutrients on phenotypic changes of cells infiltrating the TME during immunotherapy. These can be pursued in translational studies as well as early-phase RCTs at suitable healthcare facilities.

**Novel concepts in long-term memory in protective immune responses and mitochondrial fitness**

TIL that resemble tissue resident memory T-cells are particularly effective against solid cancers as well as against pathogens. Immune checkpoint blockers target this distinct T-cell population [352]. This is of particular interest since pulmonary tissue resident T-cells (Trm) are abundant in the healthy lung and may play an important role in the first encounters of adaptive immune cells and pathogens invading into pulmonary tissue: T-cells that invade into the pulmonary tissue to form the granuloma could therefore stem from Trm, from regional lymph nodes or, not mutually exclusive, from peripheral blood. However, the phenotypes of Trm, i.e., CD8⁺, CD69, CD103⁺, are also shared by exhausted or activated TIL that express as well these markers [353], which makes it challenging to define what is a TIL and what a bona fide Trm. TIL as well as Trm have been studied in the context of cancer and chronic infections—and the key genes responsible for immune protection have been identified. TIL and Trm display both expression of transcription factors such as Hobit, Runx3f and Bhlhe-40 [354, 355], with the latter factor promoting TIL and Trm functions and tissue persistence [354]. Bhlhe-40 favored Th1-type responses and was therefore found to be associated with IFN and granzyme B expression—conversely, Bhlhe-40-deficient mice were shown to be inferior in containing melanoma or influenza infections [354]. TIL and Trm did not only share a similar phenotype but also the response and transcription pattern as compared to peripheral T-cells, described as “mitochondrial” fitness [356]. Mitochondria do
not only provide energy via ATP but also shape the epigenome. Memory T-cells use oxidative phosphorylation (see above), a concept that was corroborated by the observation that skin Trm access fatty acids and fuel them into the tricarboxylic acid cycle (TCA); a feature that is again shared between Trm and TIL, but not by peripheral T-cells. Bhluhe40 is preferentially expressed in TCF-1 low cells (see below) that resemble rather Trm. This reflects an important biological function, it designates stem cell-like antigen-specific T-cells in the tissue, defined by strong TCF-1 and low Tim3 expression. These T-cells appear to respond to ICBs and give rise of PD1 high-positive cells that mediate immune protection [356, 357]. HDAC inhibitors, as well as acetate, have been shown to increase IFN-γ production in TIL where Bhluhe40 was down-regulated [354] or in antigen-specific T-cells in an “immune exhaustion”-rich environment with high potassium [340]. Increased serum acetate, as a response to bacterial infection, is required for CD8+ T-cell memory formation showing that exposure to pathogens does not only lead to immunopathology but also shapes biologically and clinically relevant anti-target-directed cellular immune responses [358].

Similarly to extrinsic factors, i.e., increased potassium in the tumor microenvironment, or increased serum acetate in infections, may shape the quality and quantity of cellular immune responses: Acetylation has been described in the context of histone modification, yet more detailed analysis, using modern proteomic methodologies, showed that other proteins, involved in cellular maintenance are also acetylated in cellular physiology and pathophysiology. This is mediated by enzymatic reactions, i.e., the transfer of an acetyl-group, and also occur via non-enzymatic reactions where acetyl-CoA plays a major role (reviewed in [359]). Acetyl-CoA, present in mitochondria as well as in the cytosol, is produced from a key enzyme in tumor cells, i.e., acetyl-CoA synthetase enzyme, ACSS2, and contributes to (tumor cell) proliferation. ACSS2, via the production of acetyl-CoA mediates the majority of acetate uptake into cells [360, 361] and presents an alternate mechanisms to provide acetate.

*Mitochondrial stress and mitochondrial fitness* versus “mitochondrial health” has also been shown to play a biologically relevant role in TB and protective immune responses [362]. Type I interferons, i.e., IFNα and IFNβ are helpful to curb viral pathogens, yet they may be detrimental in MTB infections [363–365]. In contrast to type I interferons, IL-1 production has been shown to be protective in MTB, in part by limiting type I interferon production [366]. This dichotomy between type I interferon and IL-1 production may be dependent on the timing, whether the infection is newly acquired or chronic. Drug-induced, e.g., zileutin, reduction of IFNβ leads to less pro-inflammatory, negative effects of infections. The use of Zileutin has been explored as an adjunct therapy in addition to standard antibiotic treatments of patients with TB. IFNα and IFNβ are produced during MTB infection dependent on (i) MTB access to the cytosol in hOS-T-cells and (ii) STING (stimulator of interferon ‘signaling’) via mycobacterial DNA (mDNA) binding to the GMP-AMP synthase. A third mechanism has been described [362] where cGAS, a cytosolic DNA sensing structure that binds to dsDNA from stressed mitochondria, leads subsequently to IFNβ production [367]. This links the observation that Bhluhe40 provides “mitochondrial health” and immune cell fitness with the notion that mitochondria are able to sense “danger” as well as to signal “danger” via the release of mitochondrial (mt) DNA and reactive oxygen radicals, which has been corroborated in other diseases, e.g., preclinical autoimmune diseases and viral-associated, type I interferon responses [368–370]. Thus, promoting “mitochondrial fitness” may help to curb non-productive inflammation, via downregulation of type I interferon(s) and to enhanced immune effector functions in antigen-specific tissues—resident T-cells and Trm. Rewiring immune responses by increasing mitochondrial health both in T-cells and (infected) macrophages is not only associated with mitochondrial functions but also with improved cellular metabolism [371]. For instance, MTB reduces glycolysis and the use of the TCA cycle along with oxidative phosphorylation in macrophages—with gradual differences between MTB and BCG. MTB reprograms macrophages to use exogenous fatty acids as compared to endogenous. MTB infection leads to reduced mitochondrial dependence on glucose and to increased use of fatty acids. Thus, acetate and HDAC inhibitors, which have been shown to “reprogram” mitochondria (in TIL and Trm), impact on MTB-associated effects on the mitochondrial competence in macrophages to produce reactive oxygen radicals and oxidizing fatty acids, glutamine, and glucose. The MTB-imprinted microenvironment is reminiscent of the tumor microenvironment that is characterized by “functional starvation,” defined by increased potassium, altered mitochondrial metabolism, depletion of acetyl-coenzyme A (CoA) and methionine intermediates, thereby limiting histone acetylation and the possibility of epigenetic programming and inducing effector molecules and T-cell differentiation [340]. Increased potassium in the (extracellular) space, most likely derived from necrotic cells [341], resulted in a “starvation” program of immune cells associated with increased TCF-1 expression, increased autophagy, and decreased nucleocytoplasmic acetyl-coenzyme A (AcCoA). That provides stronger persistence of (potentially anti-target-directed) T-cells in TIL or granuloma-associated lymphocytes (GAL) [372] which are associated with stemness, reminiscent of the recent observation that MTB granuloma lesions obtained from a non-human primate model of TB did not exhibit strong expression of immune exhaustion [373]. Thus, there may be similarities between the TME and MTB granuloma lesions, i.e., that hypoxia, necrosis, subsequent high potassium, and a particularly nutrient pattern impose a starvation program facilitating immune cell stemness. A better understanding of
these intricate pathway may help to individually map the patients’ “immune situation” and guide therapeutic options to eradicate or to contain the pathogen (or transformed cells), while preserving long-term memory and avoid overt tissue damage by non-productive inflammation.

Conclusions

Modulating the immune system using nutrient supply may benefit future treatment regimens for patients with cancer or infections at healthcare centers. In addition, ongoing clinical trials evaluating vaccine and drug efficacy may also consider including molecularly defined nutrients and the microbiome as part of their monitoring schemes. The same applies to studies on the microbiome and host directed therapies. Clinical responses in patients with cancer or infections may be improved if ‘holistic’ treatment modalities, include immunonutrition and consider the patients unique genetic and immunological background.

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Author contributions

All authors conceptualized and reviewed all available data and clinical trials. RR and MM wrote the first draft. All authors finalized the review.

Compliance with ethical standards

Conflict of interest

All authors are members of THE GLOBAL ALLIANCE BETWEEN CLINICAL CANCER AND INFECTIOUS DISEASE RESEARCH with a particular focus on the COVID-19 pandemic, to better understand the nature of COVID-19 pathophysiology and to take forward host-directed therapies. (Website: https://champalimaud.org/covid19/acvi).

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