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Chapter

Th17/IL-17, Immunometabolism and Psoriatic Disease: A Pathological Trifecta

Seema Chhabra, Smrity Sahu, Keshav Sharma, Maryada Sharma, Lekha Rani, Ranjana Minz and Sunil Dogra

Abstract

The burgeoning arena of immunometabolism provides evidence of how cellular, as well as local (tissue)/systemic metabolic pathways, are playing an important role in controlling immunity and inflammation. An intricate and elaborate network of various metabolic circuits specifically glycolysis, fatty acid oxidation and synthesis and amino acid metabolism precisely generate metabolites that rewire the immune response. Psoriasis is a chronic progressive self-perpetuated “IL-17-centric” inflammatory disease characterized by the co-existence of autoimmune and autoinflammatory pathways. Metabolic responses, governed by oxygen levels, nutrient availability, growth factors, cytokines, AMP/ATP ratios and amino acids, play a pivotal role in programming Th17 cell fate determination. Understanding the intricate interactions and complex interplay of molecular mechanisms responsible for Th17 cell metabolic rewiring, an important determinant of Th17 cell plasticity and heterogeneity, holds the potential to reshape psoriatic therapeutics in ways currently unimagined. This chapter entails with most recent updates on major cellular and systemic metabolic pathways regulating differentiation of Th17 cells as well their cross-talk with intracellular signaling mediators and also sheds light on how dysregulation of these pathways can be responsible for immune impairment and development of psoriatic disease. A better understanding of these metabolic processes could unveil an intriguing leverage point for therapeutic interventions to modulate metabolic programming and Th17 cell responses in this multi-systemic inflammatory disease.

Keywords: IL-17, Th17 cells, immune-metabolism, psoriasis, psoriatic disease

1. Introduction

Environment-driven metabolic adaptations perform important roles in regulating the immune system. Specific metabolic pathways control T-cell activation/proliferation/differentiation and regulate the switch towards either pro- or anti-inflammatory responses: it, therefore, seems rational that metabolic trepidations can alter self-immune tolerance [1]. Aberrant metabolic pathways constitute a molecular snapshot of the cellular processes that are exaggerated during disease pathogenesis [2]. This
immune-metabolic interactome can orchestrate the choreography of interleukin (IL)-17-producing T helper (Th17) cells-induced pathogenicity in psoriatic patients, manifested as a ‘psoriatic march’, ultimately resulting in the development of a variety of psoriasis-associated co-morbidities [3]. Metabolic anomalies influencing the T regulatory cells (Treg)/Th17 axis play a paramount role in the pathophysiology of psoriasis, so it is imperative to understand the close linkage between metabolic pathways and immune cell function: this may unveil specific interventional targets and suggest indirect dietary styles and repositioning of metabolic drugs that beneficially impact the abnormal T-cell metabolism [4].

2. Th17 cells

Faced with any antigenic stimulus, either an intracellular or extracellular pathogen or any tissue homeostatic alteration, naïve CD4+ T-cells respond via activation, proliferation, and finally differentiation into specialized T-effector cell subsets which are specifically programmed to deal with the offending agent/s. One such specialized T-effector cell subset is comprised of Th17 cells, best known as a host-defensive effector T-cell subset at barrier mucosal tissues (intestine, lung, skin) with a prime role in providing immunity against fungi and other extracellular pathogens and in sustaining gut barrier integrity by transdifferentiating into Th1-like or Treg-like cells [5].

Retinoic acid-related orphan receptor-gamma (RORγt), a signature ligand-dependent transcription factor for Th17 cells has been characterized as the molecular orchestrator of Th17 cell program. RORγt belongs to a subfamily of nuclear receptors, encoded by the master switch gene RORA-C (or NR1F1-3) [6]. A variety of transcriptional regulators of RORγt, as well as other transcription factors that either interact with RORγt or bind the promoter or the intergenic regions of the IL-17 gene locus, play a crucial role in the generation of Th17 cells (Figure 1) [7].

Th17 cells exhibit much superior plasticity compared to other T-cell subsets and epitomize a highly functionally diverse effector T cell population and also display stem cell-associated features [8]. Transforming growth factor (TGF)-β1 and IL-6 induced non-pathogenic/anti-inflammatory Th17 cells have been shown to play an important role in supporting cellular and organismal metabolic homeostasis as well [9]. However, Th17 cells are also recognized for their pathogenicity against the host, due to their association with several autoimmune diseases including psoriasis, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and diabetes mellitus. TGF-β3-induced, IL-23- dependent, functionally distinct pathogenic Th17 cells are characterized by different molecular, biochemical, and metabolic profiles (Table 1), conferring a proinflammatory phenotype to this effector T-cell subset [10].

Th17 cell evolution towards pro-inflammatory vs. anti-inflammatory or homeostatic phenotype is determined not only by a set of specific polarizing cytokines (TGF-β3 + IL-23 or IL-1β + IL-6 + IL-23 vs. TGF-β1 + IL-6) but also by a dynamically changing metabolic milieu comprised by a variety of metabolites viz. fatty acids, phospholipids, cholesterol intermediates, oxysterols and amino acids [11–16]. These metabolites drive Th17 plasticity by changing the latter’s epigenetic landscape by serving as substrates for chromatin-modifying enzymes [17]. This remarkable metabolic heterogeneity can hugely influence Th17 cell lineage plasticity and their effector function, thereby impacting the course of Th17-associated autoimmune inflammatory diseases, including psoriasis [18].
Figure 1. 
IL-17 induced "Psoriasogenicity": psoriatic march. (A) A constellation of regulatory factors including hypoxia-inducible factor (HIF)-1α (with recruited factor p300 having histone acetyltransferase activity), runt-related transcription factor (RUNX1), basic leucine zipper ATF-like transcription factor (BATF)-Jun B heterodimer, nuclear factor of activated T cells (NFAT), p65 NF-κB subunit, and signal transducer and activator of transcription (STAT) 3 act as co-operators of RORC gene, enhancing its expression and resulting in increased Th17-lineage-specific transcription factor RORγt. (B) RORγt binds to ROR response elements (RORE) located in CNS2 (conserved non-coding sequences) of the IL-17 gene, and globally controls its transcription. The effect of transcriptional regulator RUNX1 (binding to CNS2 region of IL-17) is also dependent on RORγt; HIF-1α (coactivator for RORγt) physically associates with RORγt promoting IL-17 expression without direct binding on IL-17 locus. Nuclear protein inhibitor of κB (IκB)ζ, is another regulator, that also binds CNS2 elements in the IL-17 locus. Various other transcription regulators that promote IL-17 gene expression by binding to its promoter include BATF, JunB, interferon regulatory factor (IRF)4, STAT3, Kruppel-like factor (KLF)4. (C) IL-17 leads to induction of various genes encoding for inflammatory mediators, chemokines, antimicrobial peptides, and the osteoclastogenic factor RANKL. This leads to the wide-spread biological effects of IL-17, affecting a variety of cell types/tissues including keratinocytes, endothelial cells, fibroblasts, epithelial cells, and bone.
Psoriasis is a progressive self-sustained and self-perpetuated inflammatory disease driven by the coexisting autoimmune and autoinflammatory pathways that, while primarily presenting with cutaneous involvement, also manifests as seronegative inflammatory arthritis with synovitis, enthesitis, dactylitis, and spondylitis [19]. It is quite heterogeneous in nature, characterized by a dynamic interplay of the individual's genetic landscape, tissue-specific immune micro-environments, metabolite/microbiome interactions, and biomechanical stressors [20, 21].

3. Psoriasis/psoriatic disease

Psoriasis has long been recognized as a chronic immune-mediated multi-systemic inflammatory disorder, associated with numerous comorbidities *viz*. Crohn's disease,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-pathogenic Th17 cells</th>
<th>Pathogenic Th17 cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polarizing cytokine</td>
<td>TGF-β1/IL-6</td>
<td>TGF-β3 + IL-6 IL-1β + IL-6 + IL-23</td>
</tr>
<tr>
<td>Master transcription factor</td>
<td>RORγt</td>
<td>RORγt</td>
</tr>
<tr>
<td>Upregulated expression of other relevant genes important for Th17 cell heterogeneity</td>
<td>IL-10, Ahr, cMaf</td>
<td>IL-23, T-bet, CSF2</td>
</tr>
<tr>
<td>CDSL expression</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Cytokines secreted</td>
<td>IL-17, IL-10, IL-9</td>
<td>IL-17, IFN-γ, GM-CSF</td>
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<tr>
<td>Metabolic profile</td>
<td>Glycolytic ↑</td>
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<td></td>
<td>Glutaminolytic ↑</td>
<td>Glutaminolytic ↑↑</td>
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<tr>
<td>Lipogenic (FAS) ↑</td>
<td>Lipogenic (FAS) ↑↑</td>
<td></td>
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<tr>
<td>Cholesterol biosynthesis ↑</td>
<td>Cholesterol biosynthesis ↑↑</td>
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Ahr, aryl hydrocarbon receptor; c-maf, c-musculoaponeurotic fibrosarcoma expression; csf2, colony stimulating factor; T-bet, T-box expressed in T cells; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; α-KG, alpha-ketoglutarate; 2-HG, 2-hydroxyglutarate.

Table 1. Differences between non-pathogenic and pathogenic Th17 cells.

3.1 Psoriasis and metabolic syndrome

Psoriasis has long been recognized as a chronic immune-mediated multi-systemic inflammatory disorder, associated with numerous comorbidities *viz*. Crohn's disease,
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depression, cardiovascular disease, and metabolic syndrome [22]. A concept of ‘psoriatic march’ was postulated by Boehncke et al. for this inflammatory cascade to highlight the series of systemic inflammatory effects and their relationship with obesity and metabolic syndrome [23]. Metabolic syndrome represents a spectrum of metabolic complications encompassing obesity, hypertension, type 2 diabetes, insulin resistance, atherogenic dyslipidemia and non-alcoholic fatty liver disease (NAFLD) [21]. A recent metaanalysis of 63 studies encompassing 15,939 psoriasis patients and 103,984 controls reported a significant association of psoriasis and metabolic syndrome (Odds ratio: 2.077; 95% confidence interval: 1.84–2.34) emphasizing regular monitoring of psoriatic patients for metabolic syndrome complications, including increased fasting plasma glucose levels, raised triglyceride levels, lowered high density cholesterol (HDL) levels, hypertension, and waist circumference [24]. Concurrent occurrence of these metabolic complications in psoriatic patients increases their risk of developing micro and macrovascular adversities contributing to significant morbidity and mortality [25, 26]. Increasing evidence demonstrates a complex interplay among immune cells with attendant aberrant immune dysfunction (such as is seen in psoriasis) and altered cellular and systemic metabolic axes across various organ systems, including adipose tissue, in triggering both local and systemic inflammation [27].

3.2 Th17/IL-17: crucial players in psoriasis

Psoriasis is considered as a “IL-17 centric” disease with a preponderance of pathogenic Th17 cells [28]. Psoriatic Th17 cells produce high levels of IL-17 (A to F), IL-26, IL-29 and IL-22 that synergistically act as transcriptional enhancers of many keratinocyte-expressed genes. IL-26 is linked with increased vascularisation while IL-29 regulates the expression of antiviral proteins [29, 30]. IL-17 induced inflammatory effects are not only limited to cutaneous plaques but also to more distant alterations in numerous different cell types that are responsible for producing systemic inflammatory effects and psoriasis-associated co-morbidities [31]. (Figure 1) IL-17 mediated psoriasogenicity is also linked in part to its synergism with other cytokines such as tumor necrosis factor (TNF)-α, IL-22, IL-23, IL-1β, IL-6, TGF-β across various organ systems [32].

4. Immunometabolism

A multifaceted, complex regulation of immune networks both depend on, and influences, cellular and local/systemic metabolic environment. This intricate, dynamic interplay between immunity and metabolism, i.e., “immunometabolism” outlines the metabolic patterning of immune cells and maintains metabolic homeostasis (local/systemic) but can also result in metabolic disorders dominated by deranged immune cells [33, 34]. In other words, immunometabolism can be defined as a molecular and biochemical intertwining of metabolism and immunology in all organisms that accounts for the physiological functioning of the immune system in different metabolic conditions in health and disease [35]. Immune response/inflammation can modulate cellular and tissue/systemic metabolism and vice-versa. Therefore, there are 2 dimensions to immunometabolism: the first is “cellular immunometabolism”, which includes the intracellular metabolism of a variety of immune cells under different states of activation, polarization, proliferation, and
differentiation and the 2nd dimension is tissue/systemic immunometabolism, which explores the influences of immune cells and their products on local and systemic metabolism across various settings/organs [36]. Thus, the immune system, which can be prompted by the metabolic status of the body can, in turn, have significant consequences on cellular and systemic metabolic homeostasis or disarray.

We will cover these two dimensions of psoriasis-associated immune-metabolism separately:

A. Cellular immunometabolism

The impact of changes in major cellular metabolic pathways on differentiation of Th17 cells, the "signature" cells in psoriasis.

B. Tissue/systemic immunometabolism

The influence of the resultant Th17 response on metabolism across various tissues or organs, especially white adipose tissue (visceral and cutaneous) culminating in metabolic syndrome and other psoriasis-associated co-morbidities.

Before delving deeper into these, we will brush up on immune-metabolic signaling pathways and discuss a basic outline of the major metabolic pathways used by immune cells.

4.1 Metabolic regulation of immune cells

Innate as well as adaptive immune cells have immense malleability to actively respond to different metabolic demands and diverse metabolic microenvironments via dynamic regulation of intracellular metabolism in health and disease [37]. Extracellular/environmental cues such as partial pressure of oxygen, oxidative stress, organ-specific pH, nutrient gradients, and disease-dependent fluctuations of the metabolic environment, can shift the metabolic homeostasis of immune cells. Body fluids such as blood and lymph, and the nervous system represent communication conduits for inter-organ coordination; distal communication is executed by the usual messenger molecules (hormones, neurotrophic peptides, cytokines, chemokines, and metabolites) while organelle communication within the cell is carried out by intracellular, spatially organized metabolic processes [38]. These communication networks at various levels orchestrate and harmonize responses to environmental cues/immunological challenges. The signals are sensed by metabolic serine/threonine kinases viz. phosphoinositide 3 kinase (PI3K)—protein kinase A, G and C (AGC) kinases (Akt), mechanistic/mammalian target of rapamycin (mTOR) C1/C2, and energy stress pathway kinases, i.e., liver kinase (LK) B1–5 AMP-activated protein kinase (AMPK) in co-ordination with metabolic transcription factors like hypoxia-inducible factor (HIF)-1α, cellular-myelocytomatosis oncogene (c-MYC) and associated nutrient signaling networks. These integrate available environmental information to synchronize cellular proliferation by metabolic revamping [39]. mTOR has been recognized as a molecular orchestrator of immune cell metabolism and catalyzes aerobic glycolysis and anabolic metabolism after stimulation by proinflammatory agents [40]. AMPK, a sensitive radar for decreased cellular nutrients and energy, stimulates catabolic pathways by impeding mTORC1 activity and primarily facilitates T cell adaptation to situations of low nutrient availability as seen during malnutrition, starvation and in hypoxic microenvironments associated with chronic inflammatory conditions [41].
AMPK signaling promotes cell survival and also triggers autophagy (as an energy-preserving mechanism) and mitochondrial biogenesis. HIF-1α, regulated by growth factor signals, oxygen levels, and reactive oxygen species (ROS), rapidly increases in an mTOR-dependent manner and binds to hypoxia response elements (HRE) located in the promoter region of various target genes, this leads to their activation by opening the chromatin structure. Thus, the mTOR/HIF-1α axis is associated with the initiation and development of a “pro-inflammatory” metabolic signature while activation of AMPK favors the generation of an anti-inflammatory/tolerogenic response.

These intertwined and reciprocal PI3K-Akt/mTORC/HIF-1α/c-MYC and LKB1-AMPK immunometabolic signaling networks crosstalk via direct reciprocal antagonisms, such as between mTORC1 and AMPK or Akt and LKB1 to regulate metabolism to meet context-specific and cell-specific functional needs [39]. These pathways are also mutually influenced by metabolites and nutrients generated as a consequence of these kinase dependent metabolic signaling, constituting ‘bidirectional metabolic signalling’ e.g. amino acid availability promoting mTORC1 signaling while low cellular glucose, low glutamine and elevated adenosine monophosphate (AMP) and adenosine diphosphate (ADP) concentrations can activate the AMPK pathway; metabolites generated from mitochondria-associated metabolism, i.e. α- ketoglutarate (α-KG), 2-hydroxyglutarate (2-HG) and acetyl-CoA, can influence transcription of a variety of genes lying in these immunometabolic signaling networks [42].

Figure 2. Signaling pathways regulating immunometabolism of immune cells. T-cell receptor ligation and CD28 costimulatory signals regulate immune-metabolic signaling pathways, i.e., mTORC1/C2 and LKB1-AMPK signaling. These signaling pathways are intertwined and crosstalk via direct reciprocal antagonism, i.e., AMPK directly inhibits mTORC1 while Akt suppresses LKB1 activity. (Left) Nutrient replete conditions activate PI3K-Akt/mTOR signaling that skew metabolic programming towards anabolism-associated processes such as glycolysis, fatty acid synthesis, and glutaminolysis supporting proliferation, differentiation, and heightened immune responses executed by effector immune cells (Th1, Th2, Th17 cells). (Right) Energy stress (increased AMP/ADP:ATP ratio), oxidative stress (increased reactive oxygen species, ROS), nutrient (glucose, glutamine) deprivation during malnutrition/starvation promotes LKB1-AMPK signaling, activating mitochondria-driven oxidative metabolism (citric acid cycle, oxidative phosphorylation, fatty acid oxidation), catabolic programs (autophagy/mitophagy), mitochondrial biogenesis, and inhibiting anabolic programs ultimately resulting in cellular quiescence.
Figure 2 explains how T-cells, under the influence of environmental signals, renew their metabolic equipment to employ metabolic pathways that regulate and propel function of these immune cells.

4.2 Synopsis of metabolic modules used by immune cells

There are 7 fundamental inter-linked and co-regulated metabolic modules employed by immune cells to meet their energy demands. These include glycolysis, pentose phosphate pathway (PPP), citric acid cycle/Krebs cycle, mitochondrial oxidative phosphorylation (OXPHOS)/electron transport chain, fatty acid synthesis (FAS), fatty acid oxidation (FAO), and amino-acid metabolic pathways.

4.2.1 Glycolysis

Once glucose enters the cells through glucose transporters (GLUT), it is rapidly catabolized to pyruvate in a sequential enzymatic process generating a variety of macromolecules needed for different biosynthetic pathways (PPP, de novo FAS and amino acid (AA) Hypoxia synthesis pathways) as well as for maintaining cellular redox equilibrium (nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide hydrogen, NAD+/NADH), thereby supporting anabolic growth. Pyruvate either gets reduced to lactate (via lactate dehydrogenase, LDH) by engaging in cytosolic aerobic glycolysis (Warburg effect) in the presence of oxygen, generating 4 molecules of adenosine triphosphate (ATP)/unit of glucose or can enter the mitochondrial matrix (through citrate-pyruvate shuttle system) where it gets oxidized and decarboxylated to acetyl-coenzyme A (CoA) (via pyruvate dehydrogenase, PDH) to enter into Kreb’s cycle and undergo mitochondrial OXPHOS generating NADH/reduced flavin adenine dinucleotide (FADH2) and a total of 36 molecules of ATP/unit of glucose. Though ATP generation via glycolysis is far less as compared to OXPHOS, activated and effector immune cells rely on glycolysis because of its 100 times faster rate of ATP production, its proficiency to generate a range of biosynthetic intermediates needed for cell growth, as well as its ability to provide both these facilities in oxygen-poor conditions [43]. The mitochondrial enzyme PDH, a key bifurcation enzyme in the choice between glycolytic and mitochondrial oxidative metabolism, in its active dephosphorylated form catalyzes the movement of pyruvate from the cytoplasm to mitochondria for Kreb’s cycle. Because of its crucial bifurcating function, PDH is under tight regulation of PDH kinases (PDHKs) that inactivate PDH via phosphorylation, and PDH phosphatases (PDHPs) that dephosphorylate and activate phosphorylated-PDH.

4.2.2 Citric acid cycle/Krebs cycle

Kreb’s cycle serves as an important node for multiple nutrient inputs as it integrates fatty acid (FA) and AA metabolism with that of glucose by generating a variety of metabolic biosynthetic intermediates required for FA and AA synthesis and by metabolizing other substrates such as glutamine via glutaminolysis or FAs via β-oxidation. Kreb’s cycle results in the generation of different epigenetic-regulating metabolites, e.g., α-KG, 2-HG and acetyl-CoA to calibrate T-cell function [42].
4.2.3 PPP

The PPP provides important precursor molecules for nucleotide synthesis thereby contributing to cell growth. It also generates reducing equivalents of NADPH needed for the maintenance of a favorable cellular redox environment.

4.2.4 Amino acid metabolism

AAs have a significant impact on immune cell metabolism. They contribute to glycolysis by increasing translocation of GLUT1/GLUT4 (by leucine and isoleucine) to the cell surface and also by activating a glycolytic enzyme pyruvate kinase muscle enzyme 2, PKM2 (by serine). Glutaminolysis, i.e., conversion of glutamine into glutamate, is a basic and widespread metabolic process linking OXPHOS, redox regulation, and biosynthetic pathways (protein, nucleotides and branched chain FAs [44]. Glutamate, the first product of glutamine decomposition, can either aid in de novo synthesis of glutathione (GSH) to balance oxidative stress, or get converted into α-KG and enter the Kreb’s cycle to generate ATP, mitochondrial ROS, and biosynthetic precursors. Hence, the varied end-products of glutamate, by generating counteracting metabolites, i.e., GSH and ROS, enable meticulous synchronization of metabolic flux. AA-derived metabolic products like α-KG and 2-HG assist in chromatin remodeling by affecting histone and DNA modifications [42].

4.2.5 Lipid metabolism

FAs and cholesterol, important building materials for cell membranes, are energy-dense substrates, and are required for post-translational modifications, thereby modulating T-cell proliferation and differentiation. This ability to guide post-translational modifications (by serving as ligands for several transcription factors) varies with the length of their carbon atom chains (short-chain FAs with less than 6 carbon atoms vs. long-chain FAs with more than 12 carbon atoms) and their degree of saturation (polyunsaturated fatty acids, PUFA vs. saturated fatty acids, SFA/monounsaturated fatty acids, MUFA).

4.2.5.1 Fatty acid synthesis

FAS is chiefly mediated by the enzyme acetyl-CoA carboxylase 1 (ACC1), catalyzing the rate-limiting step in FA biosynthesis, i.e., the carboxylation reaction of acetyl-CoA to malonyl-CoA in the cellular cytoplasm. Acetyl-CoA needed for de novo FAS is made available in the cytoplasm through the citrate-pyruvate shuttle that first transfers pyruvate (final glycolytic product) from the cytoplasm into mitochondria to form acetyl-CoA and then transfers a substantial portion of citrate (one of the intermediates generated in the Kreb’s cycle by the combination of acetyl-CoA with oxaloacetate) from the mitochondria into the cytosol. In the cytoplasm, citrate lyase generates cytosolic acetyl-CoA from citrate that subsequently powers downstream FA, cholesterol, and lipid biosynthesis [45, 46]. Another important enzyme participating in the initial steps of SFA/MUFA/PUFA generation is fatty acid synthase (FASN), a multienzyme complex that operates downstream of ACC1 and mediates the conversion of acetyl-CoA and malonyl-CoA to saturated long-chain FAs [47].
CD5 antigen-like (CD5L) protein, a member of the scavenger receptor cysteine-rich superfamily inhibits the de novo synthesis of SFA through direct binding to FASN, thus helping maintain the intracellular lipidome saturation by modulating PUFA versus SFA levels. CD5L is more than a general inhibitor as it regulates the quantity as well as the quality of fatty acids being generated inside the cell, fine-tuning the FA composition in T cells, causing elevation of PUFA and alterations in specific lipid species, including cholesterol metabolites, guiding post-translational modifications [13].

Acetyl-CoA is a central intermediate in lipid metabolism. In addition to FAS, cytosolic acetyl-CoA can be catalyzed in the mevalonate-cholesterol synthetic pathway, generating cholesterol and its derivatives (desmosterol, 4α-carboxy, 4β-methylzymosterol, oxysterols viz. 7β, 27-dihydroxy-cholesterol <7β, 27-OHC > and 7α, 27-OHC, 20α-OHC, 22R-OHC, 25-OHC) [15, 48]. All these lipid biosynthetic processes are delicately regulated by coordinated actions of sterol response element binding proteins (SREBPs), the transcription factors which activate all genes necessary for lipogenesis whereas SREBP2 activating genes necessary for cholesterol synthesis and uptake [49].

4.2.5.2 Fatty acid oxidation

Long-chain free FAs enter the metabolizing cells via specific transport proteins (SLC27) where they are acted upon by long-chain fatty acid-CoA ligase resulting in a fatty acyl-adenylate, which then reacts with free coenzyme A (CoA) in the presence of acyl-CoA synthetase (ACS) to give an acyl-CoA molecule. Acyl-CoA enters the mitochondria through carnitine transporter, which itself is directed by 3 enzymes including carnitine palmitoyl transferase I (CPT I) located on the cytosolic faces of the outer and inner mitochondrial membranes, and carnitine-acylcarnitine translocase (CAT) and carnitine palmitoyl transferase II (CPT II) located on the interior face of the inner mitochondrial membrane. In the mitochondrial matrix, beta-oxidation cuts the long-chain FAs (now in the form of acyl-CoA molecules) into a series of two-carbon acetate units, which, combined with CoA, form acetyl CoA. This is how acetyl-CoA is added to the cycle, which will be dissipated as carbon dioxide and water, releasing a substantial quantity of energy - captured in the form of ATP—with each beta oxidative cut of the acyl-CoA molecule yielding 5 ATP molecules. It has been calculated that complete β-oxidation of a single palmitate molecule can potentially yield over 100 ATP molecules.

Effector and regulatory/tolerogenic immune cells employ different metabolic modules to fulfill their energy requirements. Activated immune cells and effector immune cell subsets including Th1, Th2, Th17 cells and M1 macrophages upregulate glucose and AA transporters to increase their uptake and rely on aerobic glycolysis, glutaminolysis, PPP and FAS to support pro-inflammatory cytokine secretion while regulatory cells including T regs, memory T cells and M2 macrophages predominantly utilize FAO and OXPHOS to meet their ATP requirements [43].

5. Cellular immunometabolism of Th17 cells, their development and pathogenicity: how intracellular metabolism plays a fundamental role in determining plasticity of Th17 cells

Within Th17 cell subset, depending on the presence of further local stimulatory cues (metabolites), there exists substantial functional and molecular heterogeneity
determining the generation of pathogenic or non-pathogenic Th17 cells [18]. Due to the shared developmental requirement of TGF-β and due to functional and physical interaction of master transcriptional factors, i.e. RORγt and Foxp3 regulating Th17 and Treg respectively, these cells are capable of transdifferentiating into each other. The reciprocal metabolic cues are fundamental in shaping the relative proportions of Th17 vs. Treg cells and non-pathogenic vs. pathogenic Th17 cells, affecting Th17 cell plasticity and pathogenicity. Essentially, the active Th17 cells utilize the faster ATP-producing, oxygen-independent pathways, while the Treg cells utilize the more efficient, if slower, oxidative pathways. Metabolically, Th17 cells are characterized by “glycolytic-lipogenic-glutaminolytic” anabolic phenotype with highly active PPP, ensuring the availability of biosynthetic precursors [50].

5.1 Glycolysis

T cell receptor (TCR) ligation and CD28 co-stimulatory signals induce PI3K dependent phosphorylation of Akt that activates key metabolic regulator mTOR (selective role of mTORC1 but not mTORC2 in Th17 differentiation) leading to increased glycolysis (Figure 3). Under Th17-polarizing conditions, the PI3K-Akt/mTORC1/HIF-1α/c-MYC axis activates a series of reactions shifting the Th17/Treg cell balance in favor of Th17 cells. HIF-1α drives Th17 differentiation while simultaneously suppressing Treg induction via its differential interaction with transcription factors RORγt and Foxp3 causing transactivation of the former and proteasomal degradation of the latter [51]. HIF-1α doubly enhances this response: firstly, it binds to hypoxia response element (HRE) located in the proximal region of the RORC gene promoter (Figure 1) and secondly, it might physically associate with RORγt transcription factor, serving as a coactivator for RORγt, thereby increasing IL-17 gene expression without direct DNA binding on the IL-17 gene locus [7]. HIF-1α is an essential facilitator of the acquisition of Th17 glycolytic metabolism as shown in Figure 3 as it enhances expression of a series of glycolytic enzymes including GLUT1 (central glucose transporter on T cells) leading to robust glucose uptake, hexokinase 2 (HK), pyruvate kinase muscle enzyme (PKM2) and lactate dehydrogenase (LDH) causing a shift to aerobic glycolysis. The enzyme PDHK1 that inactivates the PDH enzyme, has been identified as an important player in selective regulation of Th17 cell differentiation and inflammation as evidenced by higher levels of PDHK1 expression on Th17 cells [52]. The transcription factor, inducible cAMP early repressor (ICER, an endogenous repressor of cAMP-responsive element (CRE)-mediated gene transcription, plays a vital role in deciphering Th17 cell biology. It has been shown to be overexpressed in Th17 cells, binds to and suppresses PDHs, reducing PDH activity thereby enhancing glycolysis, and subsequently increasing Th17 differentiation [53]. Therefore, activation of glycolytic pathways contributes to the differentiation of pro-inflammatory Th17 cells that exhibit enhanced pathogenicity in the context of autoimmune responses.

5.2 Amino acid metabolism

Rapid AA import mediated by the amino acid transporters propels Th17 cell lineage specification by enhancing mTORC1 activity leading to enhanced protein biosynthesis and glycolysis. ICER binds to the IL-17 gene promoter, enhancing its transcription. It enhances glutaminolysis through glutaminase induction and finally
generates glutathione that supports Th17 cell steadiness by enhancing ROS-associated detoxification pathways, polarizing them towards a pathogenic phenotype [54]. Transamination of glutamate (catalyzed by the glutamate oxaloacetate transaminases (GOT)1/2), can epigenetically redirect Th17/T reg equilibrium towards Th17 cell destiny by generating epigenetic-regulating metabolites (α-KG and 2-HG). 2-HG, an inhibitor of α-KG-dependent histone/DNA demethylases, directly increases DNA methylation at CpG islands at the Foxp3 gene locus leading to its transcriptional repression (Figure 4). This is how increased levels of 2-HG in Th17 cells lead to blockade of Treg cell lineage commitment. Th17 cells are characterized by an abundance of α-KG and 2-HG. This highlights the importance of the glutamate-GOT1/2-α-KG-2-HG axis in guiding Th17 cell destiny. GOT1 also contributes to increased mTORC1 signaling by suppressing AMPK activation [55].

Methionine-derived S-adenosyl methionine (SAM) plays a crucial role in chromatin remodeling by serving as a co-factor for epigenome-modifying enzymes, maintaining permissive H3K4me3 marks on IL-17a, IFNG, and CSF2 genes promoting their transcription leading to increased pathogenic Th17 generation [56].

In this way, amino acids regulate energy metabolism, redox balance, and impact the epigenetic landscape, modulating Th17 lineage heterogeneity and plasticity [42].
5.3 Lipogenesis

Rather than utilizing already-available exogenous FA for their lipid requirements, Th17 cells primarily engage in the ATP-costly process of de novo FA$\textsuperscript{$\text{S}$} for their proliferation and differentiation [45]. De novo FA and cholesterol synthesis promote activation-induced proliferation and differentiation of Th17 cells (Figure 5). Cholesterol precursors, as well as its derivatives, are essential for Th17 cell lineage commitment [57]. They enhance the transcriptional activity of ROR$\gamma$t by increasing co-activator recruitment leading to enhanced IL-17 and IL-23 gene transcription (Figure 5 Inset). CYP51 and CYP27A1, key mediators of the cholesterol biosynthesis pathway are the most highly upregulated genes in Th17 cells [15]. An upregulation of cholesterol biosynthesis and simultaneous downregulation of cholesterol metabolism and efflux during Th17 differentiation leads to the accumulation of the cholesterol precursors desmosterol and its sulphate conjugates. Th17-polarizing milieu upregulates expression of SREBP1 and SREBP2, FASN, 3- hydroxy-3-methylglutaryl-CoA reductase (HMGC$\text{R}$, the rate-limiting enzyme in the mevalonate–cholesterol pathway) as well as expression of enzymes involved in citrate-pyruvate shuttle system leading to enhanced cholesterol synthesis and rapid de novo FA$\textsuperscript{$\text{S}$} from glucose. This metabolic alteration is again under
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5.3.1 Type of fatty acids governing pathogenicity of T cells

Cellular lipid composition influences both generation as well as pathogenicity of Th17 cells. CD5L gene, encoding CD5L protein, a “negative” regulator of Th17
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Pathogenicity; has been recognized as a critical molecular switch of Th17 cell’s function (pathogenic versus non-pathogenic phenotype) though it does not affect Th17 differentiation [59]. Loss of CD5L transforms non-pathogenic Th17 cells into disease-inducing pathogenic ones by modulating intracellular lipidome saturation (PUFA versus SFA lipid balance) and by elevating intracellular free cholesterol, thereby regulating the quality and/or quantity of available ligands for RORγt [13]. PUFA regulates the ligand-dependent function of RORγt: in the absence of CD5L/PUFA (Figure 5), RORγt binding to the IL-17 and IL-23 loci is increased leading to transactivation of both these genes, while binding to IL-10 locus is decreased leading to its downregulation. Thus, the balance of lipid saturation contributes to CD5L-dependent regulation of Th17 cells by regulating the RORγt genomic binding and Th17-cell transcriptome.

Dietary LCFAs enhance Th1 and Th17 cell differentiation and also alter the composition of the gut microbiome whereas SCFAs (derived from diet/intestine/microbiota) promote Treg cell formation, demonstrating unique phenotypes driven by different fatty acids [60].

The same glycolytic-lipogenic-glutaminolytic metabolic axis co-ordinated by mTORC1/HIF-1α, plays an equally important role in controlling the generation as well as the “pathogenicity” of Th17 cells. These findings highlight how the generation of Tregs/non-pathogenic Th17/pathogenic Th17 cells is tightly linked to their metabolic state, offering potential new targets for the regulation of these two reciprocally regulated T cell subsets (Table 2). Thus, it is quite clear that the generation of Th17 cells is entwined with complex and intricate intracellular metabolic adaptations.

<table>
<thead>
<tr>
<th>Metabolic adjustments favoring Th17 differentiation</th>
<th>Metabolic adjustments impairing Th17 differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation of PI3K/AKT-mTORC1 pathway</td>
<td>Activation of AMPK with 5-aminimidazole-4-carboxamide riboside, AICAR (a direct activator) and metformin</td>
</tr>
<tr>
<td>Induction of transcription factors HIF-1α and c-MYC (c-MYC initiates the metabolic reprogramming while HIF-1α sustains it)</td>
<td>Inhibition of glycolysis with 2-deoxyglucose (an inhibitor of all hexokinases)</td>
</tr>
<tr>
<td>Activation of glycolysis, pentose-phosphate pathway and glutaminolytic pathway</td>
<td>Inhibition of hexokinase-2 with specific inhibitor 3-bromopyruvate</td>
</tr>
<tr>
<td>Selective expression of PDHK1 (inhibited PDH activity) directing pyruvate flow through LDH-mediated reactions to produce lactate (aerobic glycolysis)</td>
<td>Inhibition of acetyl CoA carboxylase 1 with a pharmacological inhibitor soraphen A, inhibiting de novo fatty acid synthesis</td>
</tr>
<tr>
<td>Overexpression of inducible cAMP early repressor (ICER) that suppresses expression of PDHPs leading to reduced PDH activity and enhanced glycolysis</td>
<td>Inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) with statins</td>
</tr>
<tr>
<td>A diet low in cholesterol and high in fibers can skew Th17 cells towards non-pathogenic anti-inflammatory phenotype</td>
<td>Inhibition of glutamine oxaloacetate transaminase (GOT1/2) by aminooxyacetic acid that leads to decreased production of α-ketoglutarate and 2-hydroxyglutarate skewing Th17 differentiation to the inducible T regulatory cells (iTregs) lineage</td>
</tr>
<tr>
<td>A diet high in glucose/salt/methionine can induce the generation of pathogenic pro-inflammatory Th17 cells</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Comprehensive list of metabolic changes determining Th17 cell fate.
5.4 Crosstalk between IL-17 and cellular immunometabolism in psoriasis

IL-17 has the potential to temper the cellular metabolism in a variety of ways. IL-17 has already been shown to regulate metabolism in psoriatic keratinocytes by reprogramming the urea cycle resulting in excessive polyamine generation that facilitates self-RNA sensing by immune cells independent of RNA-binding proteins LL37 and HNRNPA1 (the proven autoantigens) ultimately leading to amplification of inflammatory circuits [61, 62].

IL-17 also induces intracellular cholesterol accumulation that facilitates NF-κB mediated up-regulation of CCL20, IL-8 and S100A7 expression in keratinocytes thereby further intensifying IL-17A induced psoriatic inflammation [63]. This highlights that how IL-17-induced metabolic alterations can actively participate in eliciting infiltration and activation of innate and adaptive immune cells and keratinocyte hyperproliferation leading to sustained inflammatory dermatoses.

5.4.1 Therapeutics in psoriasis

Depending upon disease severity (based on PASI scores), topical therapy (vitamin analogues, tars, corticosteroids, dithranol, and retinoids), phototherapy (UV-B or PUV-A), and systemic therapy are considered for treatment of psoriasis. Systemic therapeutic agents used in psoriasis include methotrexate, cyclosporine, retinoids and biologics including etanercept, adalimumab, efalizumab, and alefacept. Other approved biologics for psoriasis include anti-IL-23 antibodies (ustekinumab, guselkumab, tildrakizumab, mirikizumab, risankizumab) targeting only IL-23/IL-17 axis and anti-IL-17 antibodies including anti-IL-17A agents (ixekizumab and secukinumab), anti-IL-17 receptor molecules (brodalumab); or drugs targeting both IL-17A and IL-17F (bimekizumab) [64]. These antibodies have shown promising results in the treatment of psoriasis with IL-17 blockers showing much quicker clinical efficacy resulting in a 50% decline in PASI scores as early as 1.8 weeks as compared to IL-23 blockers [65, 66].

To decrease toxicity and enhance efficacy, a few anti-metabolites are currently being repurposed and investigated as potential therapeutic agents for the management of psoriasis [67]. Metformin, an anti-diabetic drug, has the potential to exert an antipsoriatic effect via. AMPK activation [68]. Simvastatin, an HMG-CoA reductase inhibitor, in combination with steroids, has demonstrated positive clinical outcomes in psoriatic patients in terms of improved PASI and dermatological life quality index [69]. These examples provide insight to clinicians for investigating the safety and efficacy of existing anti-metabolite drugs to reposition them as effective psoriasis therapeutic agents.

6. Adipose tissue and systemic immunometabolism

One tissue that has recently become an area of intense metabolic research is adipose tissue. The adipose tissue is an important metabolic organ that regulates the balance of energy intake and consumption and is actively involved in the regulation of many systemic metabolic pathways including glucose and lipids. Adipose tissue also serves as an endocrine organ (secreting bioactive adipocytokines) and an important immune cell niche (secreting chemokines and cytokines, exerting beneficial or detrimental effects on immunometabolism) with visceral white adipose tissue as the major immune-metabolic communication hub. Adipose tissue also
communications with other organs including the liver and muscle and contributes to systemic metabolism via secretion of a variety of bioactive molecules as mentioned above [70]. Adipose tissue (visceral as well as cutaneous) has recently emerged as an important node linking immunity/inflammation, obesity and a cluster of metabolic diseases including psoriasis. Adipose tissue is a highly dynamic tissue showing the extreme degree of plasticity and remodeling potential (by expansion or contraction of adipocytes in response to energy surplus or famine) that makes it a suitable centre for maintaining immune-metabolic homeostasis [71].

6.1 Adipose tissue and immune-metabolism: an interesting interlink

Besides metabolically active parenchymal adipocytes and preadipocytes, adipose tissue is also comprised of a diverse and malleable immune-landscape comprising both innate and adaptive immunocytes residing in special adipose niches [72]. This diversity of T cell pools in adipose tissue is the result of intracellular metabolic alterations that in turn influence systemic metabolism in innumerable ways. Adipose tissue-resident immune cells include T cells, B cells, macrophages, and dendritic cell subsets and other unconventional lymphocyte subtypes viz. invariant natural killer T (iNKT) cells, mucosal-associated invariant T (MAIT) cells, γδ T cells and innate lymphoid cells 2 (ILCs) with either stimulating or regulatory roles under different physiological or pathological conditions [73]. All these immunocytes work in close co-operation with preadipocytes, adipocytes, endothelial cells and stromal cells (fibroblasts) to maintain the immune and metabolic homeostasis of adipose tissue, providing a steady environment to maintain the normal systemic metabolism of an organism [74]. Extremely heterogeneous mesenchymal stromal cells (five subtypes numbered 1–5, defined by single-cell transcriptomics analysis and cytofluorimetric assessment of marker expression) in visceral white adipose tissue have been characterized as key orchestrators of metabolic-immunologic cross-talk by their ability to balance 'immunocyte' numbers through secretion of IL-33 (subtypes 1–3) and 'adipocyte' numbers/activities through regulation of adipocyte precursors (subtypes 4 and 5) [75]. The stromal cell-derived IL-33, a mechanosensitive chemokine, dampens aberrant inflammation by increasing Treg numbers. IL-33 has been recently shown to induce mitochondrial rewiring, thereby promoting differentiation of alternatively activated macrophages finally leading to resolution of inflammation [76]. Taken together, tight and well-balanced cooperation and coordination exist between parenchymal-stromal-immune cell populations that ultimately regulate adipose tissue homeostasis.

Intradermal adipocytes residing in “superficial subcutaneous adipose tissue” or “dermal white adipose tissue” of psoriatic skin secrete monocyte chemoattractant protein-1 (MCP-1) favoring macrophage recruitment via the C-C chemokine receptor 2 (CCR2) pathway and also release high levels of antimicrobial peptides, cathelicidin, contributing to the pathophysiology of psoriasis [77].

6.1.1 Adipocytokines and cytokines released by adipocytes

Adipocytes participate in the regulation of the immune system via secretion of various cytokines – including IL-6 – and adipocytokines such as adiponectin and leptin. IL-6, an obligatory pro-inflammatory cytokine, drives naïve CD4+ T cells differentiation into Th17 lineage, and in association with IL-17A, regulates the differentiation of adipocytes and their capacity to secrete adipocytokines (especially leptin) and chemokines [78].
Adiponectin is an insulin-sensitizing anti-inflammatory adipocytokine that corrects insulin resistance and obesity-induced NAFLD (21). Leptin is a critical hormonal regulator of metabolism and an important signaling transducer that activates JAK2 kinase causing tyrosine phosphorylation of various downstream signaling proteins, e.g., STAT3, SHP2, IRS2, and PI3K, thereby regulating transcription of genes essential for energy intake and lipid metabolism [79, 80]. Leptin also affects various immune cells including dendritic cells (DCs), neutrophils, NK cells, T and B cells, through surface leptin receptors and regulates a variety of cellular biological processes involving chemokinesis, chemotactic responsiveness, cell migration, proliferation, cell survival (delayed apoptosis) and pro-inflammatory cytokine production [81, 82]. Resistin, another cytokine is also known as an adipose tissue-specific secretory factor (ADSF) also has the pro-inflammatory potential [83].

A disturbed balance of pro-inflammatory and anti-inflammatory cytokines and adipocytokines (hormones) can cause chronic adipose tissue inflammation resulting in obesity and associated metabolic complications.

6.2 Obesity, systemic immunometabolism and psoriasis

Obesity (fat and weight gain/body mass index (BMI) ≥ 35 kg/m²/increased abdominal fat mass) resulting from adipose tissue expansion and adipocyte hypertrophy, is a state of chronic systemic low-grade inflammation that accelerates obesity-related insulin resistance (IR), leading to the development of the metabolic syndrome, including diabetes mellitus (DM). Obesity increases the body’s vulnerability to a variety of immune diseases, such as psoriasis, by abnormally altering the whole biology of adipose tissue including stromal-driven regulation of immunocyte and adipocyte numbers. Obesity evokes extensive remodeling of adipose tissue morphology and function with alterations of both immune as well as stromal cell landscapes resulting in metabolic and/or immunologic aberrancies [84]. The number of pro-inflammatory immunocytes viz. CD8⁺ T cells, M1 macrophages, neutrophils, mast cells, and γδ T cells increases while the proportions of tolerogenic/immunosuppressive cells viz. Tregs, regulatory B cells (B regs), eosinophils, iNKT cells, alternatively activated macrophages and type 2 ILCs (copiously producing anti-inflammatory cytokines IL-10, IL-15, IL-2, IL-5, and IL-25) are either decreased or have impaired functional capacity. Various studies have already shown a strong “dose-dependent” relationship between PASI scores and obesity with improvement in disease severity as a result of weight loss in psoriatic patients [85, 86].

Obesity has been postulated to worsen psoriasis via. Its effect on the Treg/Th17 axis through various metabolites, adipocytokines like leptin and pro-inflammatory cytokines like IL-6, released by inflamed adipocytes [72, 87, 88] for example, higher leptin and resistin concentrations have been observed in obese, psoriatic patients [89, 90].

Adiponectin plays a crucial role in controlling psoriasiform dermatosis by reducing Th17 cell differentiation, restraining glycolysis in an AMPK dependent fashion, thus tightly regulating their nutritional demands and metabolic function [91–93]. Psoriasis patients with or without metabolic abnormalities exhibit significant hypo-adiponectinemia (negatively correlated with psoriasis area severity index, PASI) and hyperleptinemia with leptin resistance (positively correlated with PASI), that contribute to the development of the metabolic syndrome.

The pro-inflammatory cytokine IL-17, a potential linker between metabolic syndrome and psoriasis, causes adipose tissue inflammation by mediating important interactions between adipose tissue and the immune system, leading to IR (the key
component of metabolic syndrome) finally manifesting as obesity, DM, hypertension, NAFLD, and hyperlipidemia [21].

Thus, it can be inferred that obesity-driven immune and stromal landscape alterations in adipose tissue, in turn leading to disturbances in systemic metabolism might enhance Th17 differentiation and effector function, consequently leading to increased severity of psoriasis.

6.3 Nutritional metabolism and psoriasis

Beyond the adipose tissue, the diet or nutritional status, a.k.a. nutritional metabolism, also has a profound impact on the immune system by influencing the immune cell metabolic parameters; malnutrition is clearly associated with diminished immune function whereas a “Western” lifestyle/nutritional pattern rich in calories, fat, and salt, leads to a low-grade systemic inflammation thereby predisposing individuals to a variety of autoimmune diseases associated with metabolic complications, including psoriasis. Diet-associated obesity by increasing availability of extracellular lipids revamps cellular metabolism of innate as well as adaptive immune cells [94]. It is quite tantalizing to consider dietary interventions like fasting-mimicking diets and diets low in salt and calories re-stabilizing the immune-metabolism in psoriasis patients, potentially serving as viable substitutes or adjuvants to drugs directly targeting cellular metabolism.

Understanding the relationship between nutrition and metabolism and its impact on cellular/systemic immunometabolism in psoriasis is important to develop novel therapeutic strategies.

7. Metabolomics in psoriasis

Metabolites/biochemical intermediates/end-products, unique chemical fingerprints of proteomic or cellular metabolic pathways, are viewed as keystones of life as they provide vital communication signals that are necessary to sustain life. Metabolomics, a systematic study of the global metabolite profile in a biological system, i.e., cell, tissue, organ, or organism, provides an “instantaneous snapshot”/direct “functional readout of the physiological state”, capturing the metabolic perturbations driving physiological and disease states. The metabolome, highly dynamic like transcriptome and proteome, and a rapid indicator of biological status, refer to the complete set of diverse small-molecules (<1500 Da) such as sugars, nucleotides, amino acids and lipids in any biological system.

A large number of psoriatic disease-related metabolomic studies have been carried out in the recent past to identify metabolomic biomarkers associated with psoriatic disease [95]. The majority of studies have focused on identifying a metabolic profile that can be used for diagnosis of psoriasis and/or psoriatic arthritis while others have explored correlating the metabolome with different dimensions of psoriatic disease activity to improve clinical management. A variety of biological samples including peripheral blood (whole blood, plasma, serum, peripheral blood mononuclear cells), urine, and skin tissue (uninvolved skin, psoriatic skin, and corticosteroid treated psoriatic skin) have been researched in these metabolomic studies, revealing alterations predominantly in pathways associated with lipid and amino acid metabolism. To get more meaningful information, a few study-groups have compared metabolite concentrations in different biological milieu by examining metabolomes across multiple
sample matrices. A variety of metabolites in the eicosapentaenoic, docosahexaenoic and arachidonic acid pathways are elevated in both the skin and the peripheral blood of psoriatic patients [96, 97]. Plasma and psoriatic skin choline levels correlated positively while citrulline levels across both sample matrices correlated negatively with disease activity scores [98].

A step further, Tarentini et al. integrated results of metabolomic profiling and cytokine/chemokines profiling from lesional skin and serum of psoriatic patients and identified immuno-metabolic clusters indicating biochemical pathways associated with the initial phases of psoriasis development, thus hinting at putative biomarkers of new-onset psoriasis [99].

8. Future perspectives and summary

It is intriguing to explore and validate metabolomic biomarkers that can accurately and reliably predict which psoriatic patients will develop psoriatic arthritis. Identifying metabolites that could differentiate psoriatic arthritis patients from patients with other inflammatory arthritides would be a great added advantage. The synovial fluid, being in direct contact with articular cartilage, bone and synoviocytes, is a very promising candidate for deciphering metabolomic information which can serve as a promising source of biomarkers for psoriatic arthritis.

Metabolic health and gut microbiome dysbiosis are emerging areas of intense investigation as the gut microbiome influences host immunity and metabolism by producing numerous compounds [100]. The connection between the microbiome and the metabolome of patients with heterogenous psoriatic disease holds the potential to highlight aberrant signaling pathways likely driving “psoriatic march”. This could pave the path for the development of clinically useful biomarkers for early recognition and management of comorbidities for this patient population [101].

Thus, immuno-metabolic reprogramming may be worth further exploration for the comprehension of its therapeutic potential in psoriasis. In future studies, it will be quite intriguing to define the interplay between IL-17–driven metabolic reprogramming and epigenetics/chromatin remodeling that are responsible for chronic, sustained transcriptional responses seen in psoriasis, which in turn modulate the activity of IL-17-related proinflammatory cytokine programs.

Integrating metabolomics with other high-throughput-omic technologies such as genomics, epigenomics, transcriptomics, and proteomics can unravel molecular, cellular, and functional signatures associated with psoriasis pathogenesis [102, 103]. The “omics” datasets, thus generated, can help construct predictive or diagnostic classifiers, grouping psoriatic patients based on their probability of developing systemic comorbidities or their likelihood to respond to a specific therapy [104]. This cutting-edge, systemic, and holistic approach will allow the clinicians to institute tailored, targeted, precision medicine, based on individual patient characteristics thereby maximizing efficacy and minimizing toxicity and at the same time overcoming the biggest challenge we face in achieving long-term, stable remission in psoriatic patients.

Conflict of interest

None.
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