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Title: Integrative understanding of immune-metabolic interaction

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ABSTRACT

Recent studies have revealed that the immune system plays a critical role in various physiological processes beyond its classical pathogen control activity. Even under a sterile condition, various cells and tissues can utilize the immune system to meet a specific demand for proper physiological functions. Particularly, a strong link between immunity and metabolism has been identified. Studies have identified the reciprocal regulation between these two systems. For example, immune signals can regulate metabolism, and metabolism (cellular or systemic) can regulate immunity. In this review, we will summarize recent findings on this reciprocal regulation between immunity and metabolism, and discuss potential biological rules behind this interaction with integrative perspectives.

INTRODUCTION

The immune system is a specialized system that can protect our body against various pathogens. It can be generally categorized into two systems: an innate immune system and an adaptive immune system. Each system expresses its own receptors to recognize various pathogens. The innate immune system utilizes various pattern recognition receptors (PRRs) including Toll-like receptors, Nod-like receptors, and C-type lectin receptors to recognize specific pathogen-associated molecular patterns (PAMPs). Adaptive immune cells such as T cells and B cells express different types of antigen receptors. Individual T cells and B cells express their unique receptors through genetic recombination, thereby increasing the diversity of their antigen receptors. Through these receptors, adaptive immune cells can recognize various pathogens. These two layers of innate and adaptive immunity can provide strong protection against a variety of pathogenic invasions.

Recent research has revealed that the immune system does more than just controlling pathogens. Even without an infection, the immune system can induce sterile inflammatory responses. This non-canonical function is currently a subject of many discussions. What is suggested through these discussions is that the classical pathogen-killing role of the immune system is just a part of the entire function of the immune system. In this line, efforts are being made to understand the immune system's role with a comprehensive perspective from the viewpoint of physiological homeostasis [1, 2].

Many properties of immunity allow the immune system to play a crucial role in homeostatic functions of our body beyond pathogen killing. For example, immune cells such as phagocytes can uptake and clean various materials. This property not only can be utilized to kill bacteria, but also can be exploited to remove dying or dead cells for homeostasis. Moreover, the same signaling for cell death in the context of infection can be used for apoptosis under other cellular stresses. Innate immunity can be activated with damage-associated molecular pattern (DAMP) besides PAMP with the same PRR signaling to maintain homeostasis [3]. Adaptive immune receptors recognizing various pathogenic molecules can also be utilized to detect mutant proteins that malignant cells make. This idea has become a foundation for cancer immunology and immunotherapy. Various cytokines that immune cells make can have a pleiotropic effect on the function of non-immune cells not only in the context of infection, but also in other stressors. These properties of immune system provide a strong basis for the discussion of immune response beyond pathogen control.

Stress and Inflammation

Cellular, tissue-level, and organismal stressors have been linked to inflammation. Various cellular stressors can elicit inflammatory responses even without an infection. For example, genotoxic stress with radiation can cause interferon responses [4]. Micronuclei formed under genotoxic stress and cell cycle progression can be sensed by pattern-recognition receptor cyclic GMP–AMP synthase (cGAS) to induce inflammatory responses [4]. Endoplasmic reticulum (ER) stress can also induce inflammatory responses. Unfolded protein response is triggered by ER stress, which involves the activation of several transmembrane receptors such as **activating transcription factor** (ATF) 6, **protein kinase RNA-like ER kinase** (PERK), and **inositol-requiring enzyme 1** (IRE1) α . IRE1 α can bind **TNF receptor associated factor** (TRAF) 2 to the ER membrane once it is activated, triggering inflammatory responses via the **nuclear factor kappa B** (NF- κ B) pathway [5]. A recent study has found that two members of the NLR family of PRRs, nucleotide-binding oligomerization domain (NOD) 1 and NOD2, are significant mediators of ER stress-induced inflammation [6]. Other studies have found that lysosomal stress can induce inflammation via NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation. Crystalline substances such as silica, alum, and cholesterol can provoke lysosomal destabilization and rupture and finally lead to NLRP3 activation [7, 8]. Other cellular stressors such as mitochondrial stress and oxidative stress can also be sensed by various cellular pathways and lead to NLRP3 inflammasome activation [9]. The fundamental biological rationale behind this phenomenon has been discussed in detail elsewhere [1, 10, 11], and it is beyond the scope of this review. However, it is obvious that inflammation induced by cellular stress is beneficial for the survival of an organism either by removing the stressors or by promoting adaptation to the stressors. These reports strongly support the notion that properties of the immune system can be utilized to regulate other body functions beyond pathogen control.

Metabolism and Immunity

Recent reports have indicated a strong link between metabolic regulation and immunity. Cellular and systemic metabolism can greatly affect immune function. Immune responses can also significantly influence metabolism. However, the precise mechanism of their interaction and biological rules behind such interaction remain unclear. Here we will discuss recent findings on this subject.

Type 1 immunity and metabolism

Metabolic regulation of immune function

Traditionally, immune responses have been categorized based on CD4 T helper (Th) cell responses. For example, naïve CD4 T cells can be differentiated into various types of Th cells such as Th1, Th2, Th17, and regulatory T cells (Treg). Each Th cells express their own transcriptional factor and secrete their unique cytokines. Th1 cells express T-bet and produce interferon (IFN)- γ . Th2 cells express GATA3 and secrete IL-4 and IL-13. Th17 cells express ROR γ t and secrete IL-17. Treg cells express Foxp3 and secrete IL-10. These unique cytokines of each lineage can suppress the expression of other transcriptional factors so that differentiation toward each lineage is stably maintained. Recent discovery of innate lymphoid cells (ILC) has shown that these immune responses are not exclusive to Th cells. The use of an overarching name such as type 1, type 2, and type 3 (type 17) immunity has been suggested.

Type 1 immune responses are traditionally well studied in the context of anti-viral or intracellular pathogen control. Active cytokine players in this axis include IFNs and inflammatory cytokines such as IL-1 β and TNF- α . Previous studies have found that the metabolic state is highly

linked to proper induction of type 1 immune responses in various immune cells. For example, it is found that polarization of macrophages is accompanied by metabolic reprogramming. When macrophages are treated with lipopolysaccharide (LPS) or IFN- γ , glycolysis is dramatically up-regulated while other metabolic pathways such as tricarboxylic cycle (TCA), fatty acid oxidation (FAO), and glutaminolysis are weakened [12, 13]. Inhibition of these metabolic alterations leads to the reduction of classical macrophage M1 activation and function [12, 13]. Other cytokines such as IFN- β and IL-1 β can also increase glucose uptake and glycolysis in macrophages, which augments the inflammatory function of the macrophages [14-16]. Metabolic and immune functional changes are tightly intertwined together, so it is not easy to determine which comes first. However, it is clear that enhancement of glycolytic pathway is necessary for the downstream function such as inflammatory cytokine and nitric oxide production in macrophages (Figure 1A) [17]. In contrast to the role of glycolysis, enhancement of oxidative phosphorylation (OXPHOS) in macrophage can lead to reduced inflammatory responses (Figure 1A) [18]. Metabolic alteration in tricarboxylic acid (TCA) cycle also affects macrophage function. Citrate, a component of the TCA cycle, can be catalyzed to itaconate by the enzyme encoded by immune responsive gene 1 (IRG1) [19]. Itaconate shows an anti-inflammatory effect by inhibiting the activity of succinate dehydrogenase (SDH) [20]. This induction of itaconate and accumulation of succinate has been identified as a hallmark in M1 activation [21]. Succinate can stabilize hypoxia-inducible factor (HIF)-1 α , thereby increasing the production of IL-1 β [22]. This is in line with previous reports showing that M1 macrophage activation is dependent on HIF-1 α rather than Myc [12, 23]. Recent studies also found that itaconate performs its anti-inflammatory action via activation of nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor for anti-oxidant and anti-inflammatory function [24, 25]. Fatty acid synthesis (FAS) is also important in the differentiation

and function of macrophages [26]. In this study, primary lipid class switch from cholesterol to phosphatidylcholine is found during the differentiation of monocyte to macrophages. Inhibition of this process leads to the dysfunction of organelle development and phagocytic function of macrophage [26].

The function of T cells and ILCs can also be greatly affected by the regulation of their metabolic pathways during activation [27]. When these cells are in a naïve stage, they show quiescent metabolic status which produces ATP from a minimal carbon source because anabolic processes are not required [28-30]. In contrast, activated T cells or ILCs can increase their overall metabolic fluxes toward both glycolysis and OXPHOS [31-34]. For example, T cell receptor (TCR)-mediated signaling can induce the expression of enzymes involved in glycolysis and glutaminolysis and transporters for glucose and amino acids uptake [35, 36]. The increase of these metabolic pathways is required to supply metabolic building blocks for cells to proliferate, differentiate, and release cytokines [37-39]. In addition to these general effects, metabolic function can specifically influence Th1 differentiation and function. For example, when aerobic glycolysis is blocked during T cell activation, production of IFN- γ is markedly compromised (Figure 1A) [40]. The intense glycolysis is important to prevent moonlighting action of GAPDH, a key enzyme of glycolysis, which can inhibit the translation of IFN- γ under inhibition of glycolysis [40-42]. Metabolic status and Th differentiation are also well described, particularly in the context of mammalian target of rapamycin (mTOR) signaling, which is reviewed elsewhere and beyond the scope of our discussion [43]. As reviewed, it is obvious aerobic glycolysis can support Th1 function via the activation of mTOR complex (mTORC) 1 and 2 [43].

Immune regulation of metabolic function

Type 1 immune response can significantly affect metabolism. Upon M1 activation of macrophage, IFN- γ can suppress mTORC 1 and inhibit the translation of anti-inflammatory repressors such as HES1 [44]. This metabolic reprogramming can potentiate macrophage activation [44]. **Increased fatty acid uptake and lipid synthesis but decreased lipolysis has been found upon activation of macrophages with ligands of TLRs [45].** On the other hand, alternatively activated M2 macrophages show increased OXPHOS with intact TCA cycle without showing a significant induction of glycolytic activity [13, 21, 46, 47]. At the cellular level, type 1 interferon can increase fatty acid oxidation and OXPHOS in plasmacytoid dendritic cells (pDC) (Figure 1B) [48]. This metabolic change of FAO with type 1 interferon is partly dependent on **peroxisome proliferator-activated receptor (PPAR) α** [48]. *De novo* synthesis of long-chain fatty acid and cholesterol is reduced in bone marrow-derived macrophages (BMDMs) stimulated with IFN- β while lipid import is increased, resulting in an overall increase of fatty acid and cholesterol in cells [49]. A study with mouse embryonic fibroblast (MEF) has shown that type 1 interferon IFN- β can reduce AMP-activated protein kinase (AMPK) phosphorylation accompanied by an increase of intracellular ATP [14]. In that study, IFN- β induced glucose uptake by translocation of GLUT4 to the cell surface via PI3K-Akt signaling (Figure 1B) [14]. Other studies have found immune-metabolic reciprocal regulation at the level of cell-cell interaction. Monocytes infiltrating neuroblastoma can become M1 macrophages, which release IL-1 β and TNF- α . Through p38/ERK signaling, macrophage IL-1 β and TNF- α can promote tumor arginase 2 expression and alter arginine metabolism, leading to neuroblastoma cell proliferation [50].

Type 1 immune response can also regulate systemic metabolism. Studies over the past few decades have shown that inflammation is closely linked to various metabolic diseases. In addition, inflammation has been suggested to be a major source of pathology in various metabolic diseases.

For example, pro-inflammatory immune cells can accumulate in adipose tissues under obesity. Various inflammatory cytokines such as IL-1 β , IL-6, and TNF- α produced from these immune cells can directly cause insulin resistance (Figure 1B) [51-59]. However, specific signaling affected by these cytokines can be context-dependent, particularly in the case of pleiotropic IL-6. Thus, further studies are required to have a definite answer. Type 1 immune response also has broad effects on other metabolic pathways beyond glucose metabolism. Type 1 interferon signaling via interferon receptor interferon alpha and beta receptor subunit 1 (Ifnar1) in adipose tissues plays a significant role in the development of metabolic diseases. Mice without type 1 interferon signaling in adipose tissues can develop obesity, glucose intolerance, and insulin resistance with high fat diet challenges (Figure 1B) [60]. Pleiotropic IL-6 can modulate fat metabolism in muscles, enhances fatty acid oxidation rates, and reduce lipogenic effects of insulin (Figure 1B) [61]. However, TNF- α shows no effect on fatty acid oxidation, although it can enhance fatty acid incorporation into diacylglyceride, which could contribute TNF-induced insulin resistance in skeletal muscles [61].

Type 2 immunity and metabolism

Metabolic regulation of immune function

Type 2 immunity generally includes responses from immune cells in anti-parasite and allergic responses. Lymphoid cells (such as Th2, ILC2, and IgE B cells) and myeloid cells (such as eosinophils, mast cells, and basophils) belong to type 2 immunity. IL-4, IL-5, IL-13, IL-25, and IL-33 are major cytokines in this axis. Studies have also found that metabolic status can greatly influence type 2 immunity. M2 polarization of macrophage is increased by activation of PPAR γ , a master regulator of lipid metabolic pathway (Figure 2A) [62]. PPAR γ activation has no effect on

M2 marker expression in resting or M1 macrophages. It only has such an effect in monocytes, implying that M2 polarization with PPAR γ activation can only be primed in naïve monocytes [62]. Another study has found that T cells and dendritic cells (DC) undergo development of type-2 immune responses when PPAR γ signaling is activated [63]. Upregulation of PPAR γ signaling by IL-4 and IL-33 in lung-resident CD11b⁺ DCs can promote the migration of these cells to draining lymph nodes and prime Th2 differentiation (Figure 2A) [63]. Nuclear receptor PPAR δ/β also plays an important role in M2 polarization of adipose tissue macrophage and liver residing Kupffer cells [64, 65]. Deficiency of PPAR δ/β signaling in macrophage can result in impairment of glucose tolerance and aggravation of insulin resistance with high-fat diet challenges (Figure 2A) [64, 65]. Lactic acid produced by tumor cells as a by-product of aerobic or anaerobic glycolysis plays a key role in signaling for M2-like polarization of tumor-associated macrophages (Figure 2A) [66]. This effect is mediated by hypoxia-inducible factor 1a (HIF1a) and arginase 1 [66]. Similarly, a recent study has found that endothelial lactate can promote M2-like macrophage polarization, which can induce muscle revascularization and regeneration under ischemia [67]. Recent studies have also found that metabolic reprogramming affects germinal center B cell responses. Metabolic reprogramming induced by IL-4 in B cells is crucial for epigenomic activation of Bcl6 expression to promote germinal center (GC) B cell differentiation [68]. Another study has found that germinal center B cells mainly rely on fatty acid oxidation (but little on glycolysis) for energy generation, which is directly linked to germinal center B cell responses (Figure 2A) [69].

Immune regulation of metabolic function

Type 2 immunity can significantly affect metabolism. As type 1 and type 2 immunities are mutually exclusive, opposing effect on metabolism has also been identified with type 2 immune

response. When type 2 immune responses are blocked with STAT6 deficiency, insulin action is reduced and PPAR α -driven oxidative metabolism program is enhanced [70]. On the other hand, activation of STAT6 by IL-4 can increase insulin action by blocking the PPAR α -regulated food catabolism program and reducing adipose tissue inflammation (Figure 2B) [70]. Moreover, IL-4 can modulate glucose and lipid metabolism by improving glucose tolerance and decreasing adipogenesis via PPAR γ down-regulation [71]. Furthermore, IL-4 can promote hormone-sensitive lipase translocation, which increases lipolysis in adipocytes (Figure 2B) [71]. Studies have also found that type 2 immunity plays a significant role in cold adaptation and beige fat biogenesis [72]. Treatment with IL-33 can increase levels of ILC2s in inguinal adipose tissues of mice, which can stimulate the biogenesis of functional beige fat by stimulating the commitment of PDGFR $^+$ adipocyte precursor cells to the beige adipocyte lineage in an IL-4/13-dependent manner (Figure 2B) [72]. Another study has also found that ILC2s induced by IL-33 can promote beiging of adipose tissues by producing methionine-enkephalin peptides [73]. Type 2 immune response can also influence muscle endurance exercise and metabolism. Endurance training can enhance a network of mitochondrial and fatty acid oxidation genes, which is dependent on IL-13 signaling (Figure 2B) [74]. IL-13 can activate Stat3 by acting directly on skeletal muscles via its receptor IL-13R1 and boosted mitochondrial respiration [74].

Type 17 regulatory immunity and metabolism

Metabolic regulation of immune function

Despite the fact that Th17 and Treg have completely distinct functions, they are known to share molecular pathways in differentiation. For a long time, the unique relationship between Th17 and Treg has been discussed and many molecular mechanisms that control Th17 and Treg balance

have been discovered. Interconversion between these two cell types is even possible after differentiation [75, 76]. Metabolic context has a significant effect on the differentiation of Th17 and Treg and their cognate functions. In general, inflammatory T cells have a high glycolytic gene expression. They rely on glycolysis to proliferate and survive, whereas Tregs rely on mitochondrial oxidative metabolism to survive and function [77, 78]. The HIF1 α -dependent transcriptional pathway is critical for modulating glycolytic activity and influencing Th17 and Treg cell lineage decisions [79]. HIF1 α is only expressed in Th17 cells. Its activation is required for mTOR signaling. When the glycolytic pathway is inhibited, Th17 differentiation is inhibited, while Treg generation is promoted (Figure 3A) [79]. Another study has found that the fate decision of Treg and Th17 cells is controlled by *de novo* fatty acid synthesis [80]. In that study, inhibition of acetyl-CoA carboxylase 1 (ACC1) decreased the production of Th17 cells but enhanced the development of Treg in humans and mice (Figure 3A) [80]. For their development, Th17 cells rely on *de novo* fatty acid synthesis driven by ACC1 and the underlying glycolytic-lipogenic metabolic pathway [80]. Metabolic alteration can also regulate the balance of Th17 and Treg cells by epigenetic modification. In developing Th17 cells, enhanced transamination primarily catalyzed by glutamate oxaloacetate transaminase 1 (GOT1) can result in higher amounts of 2-hydroxyglutarate [81]. This 2-hydroxyglutarate can lead to hypermethylation of the Foxp3 gene locus and suppression of Foxp3 transcription, which promotes fate determination toward Th17 cells (Figure 3A) [81].

Immune regulation of metabolic function

Studies on metabolic alteration by Th17 and Treg immune signaling are also accumulating. These cells and their cognate cytokine signaling have significant effects on the function of various metabolic tissues. In the liver, IL-17 signaling regulates hepatic steatosis (Figure 3B). Increased

IL-17 can promote sterol regulatory element-binding protein 1c (SREBP-1c) and carbohydrate-responsive element-binding protein (ChREBP) transcription while suppressing enoyl-CoA hydratase short chain 1 (ECHS1) and PPAR α for the alteration of fatty acid metabolism [82]. Mice lacking IL-17 gained more fat mass as they aged, indicating that IL-17 could regulate glucose homeostasis and inhibit adipogenesis (Figure 3B) [83, 84]. This effect is partly dependent on the suppression of adipogenic PPAR γ and CCAAT/enhancer binding proteins (C/EBP) α by IL-17 [84]. Recent studies have highlighted the role of $\gamma\delta$ T cells in metabolic homeostasis and cold adaptation. Visceral adipose tissue resident population of $\gamma\delta$ T cells in adipose tissues can regulate age-dependent Treg expansion and control core body temperature (Figure 3B) [85]. Moreover, $\gamma\delta$ T cells in thermogenic adipose tissue play an important role in sympathetic innervation by increasing TGF- β 1 production in parenchymal cells, at least in part, through the IL-17 receptor C (IL-17RC) [86]. Treg cells residing in adipose tissues are depleted in obesity. They can inhibit inflammation and insulin resistance by producing anti-inflammatory IL-10 (Figure 3B) [87]. A recent study has further identified that plasmacytoid dendritic cells that produce IFN- α can provoke the loss of adipose tissue Treg (Figure 3B) [88]. Moreover, a pro-inflammatory state is developed when local Treg cells are removed from brown adipose tissues, which can decrease thermogenic activity [89]. Treg is also induced by cold exposure and beta3-adrenergic receptor (ADRB3) stimulation. It can enhance adipose tissue beiging, thermogenesis, and lipolysis, which is mediated by T cell specific Stat6 and Pten signaling [90, 91].

Conclusion

Recent reports strongly suggest that the immune system's traditional pathogen-killing role is only a small part of its overall functions. Studies on sterile inflammation have shown that cellular stress

can elicit inflammation which is beneficial for the organism's survival either by eliminating or promoting adaptability to stressors. There is also a clear link between metabolic regulation and immunity. We have reviewed how type 1, type 2, type 17, and regulatory immunity are significantly controlled by metabolism and how metabolism is altered by different types of immune responses. Although studies on immunity in systemic metabolic and physiological homeostasis are being accumulated, the discussion on this subject is still stagnant partly due to the lack of a framework that can encompass classical and novel roles of immune responses with homeostatic and evolutionary points of view. Thus, an experiment to test a big idea on this subject is highly needed. Emergence of a new perspective may be facilitated by accumulated public OMICS data and systems biology approaches.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FIGURE LEGENDS

Figure 1. Type 1 immunity and metabolism. (A) Metabolic regulation of type 1 immune function. **Glycolysis promotes and OXPHOS inhibits M1 macrophage polarization. Both**

glycolysis and OXPHOS metabolic pathway (aerobic glycolysis) support Th1 differentiation and function. (B) Type 1 immune regulation of metabolic function. Inflammatory cytokines such as IL-1 β , TNF- α , and IL-6 provoke systemic insulin resistance. IL-6 induce lipid oxidation in muscles. Type 1 interferon inhibits insulin resistance and obesity. Type 1 interferon promotes glucose uptake in embryonic fibroblast and fatty acid oxidation in plasmacytoid DC.

Figure 2. Type 2 immunity and metabolism. (A) Metabolic regulation of type 2 immune function. Transcription regulation by PPAR γ promotes monocyte M2 polarization and lung CD11b⁺ DC for Th2 priming. Transcription regulation by PPAR δ increases tissue macrophage M2 polarization. Lactic acid also induces tissue macrophage M2 polarization. Fatty acid oxidation promotes germinal B cell reaction. (B) Type 2 immune regulation of metabolic function. IL-4 and its downstream activation of STAT6 inhibit systemic insulin resistance. Type 2 immune activation via IL-33/ILC2 and IL-4/IL-13 responses leads to beige adipose tissue differentiation and lipolysis. IL-13 promotes mitochondrial respiration in muscles.

Figure 3. Type 17 and regulatory immunity and metabolism. (A) Metabolic control of type 17 and regulatory immune function. HIF- α activation and/or glycolysis promotes Th17 and suppresses Treg differentiation. *De novo* fatty acid synthesis by ACC1 promotes Th17 and suppresses Treg differentiation. 2-hydroxyglutarate by GOT1 also promotes Th17 and suppresses Treg differentiation. (B) Type 17 and regulatory immune control of metabolic function. IL-17 promotes fatty acid synthesis in livers while suppressing adipogenesis. $\gamma\delta$ T cells promotes adipose tissue thermogenesis. Treg also supports thermogenesis. Treg inhibits systemic insulin resistance and type 1 interferon can negate this function by depleting Treg.

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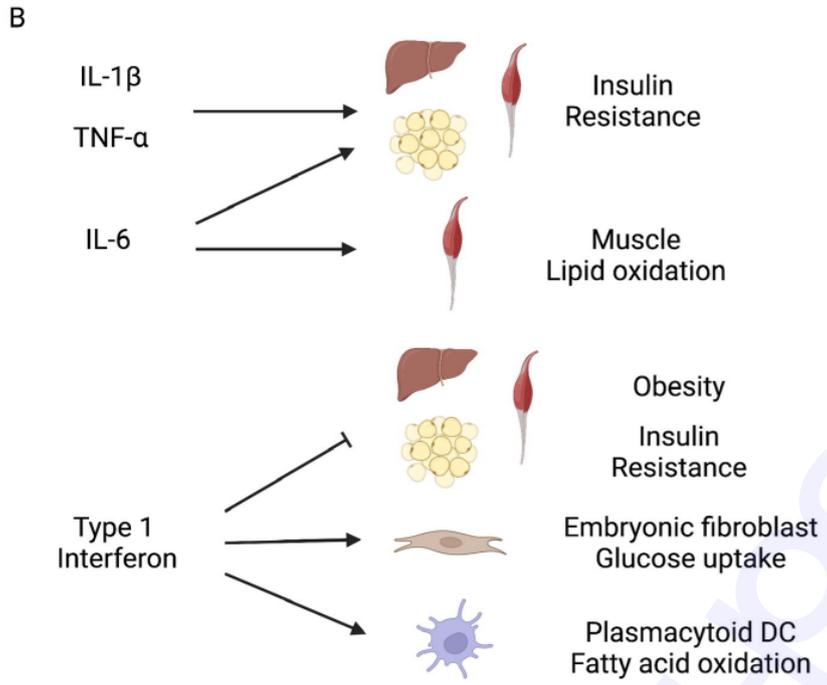
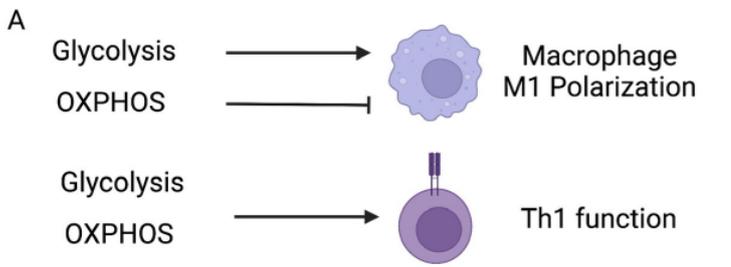


Fig. 1.

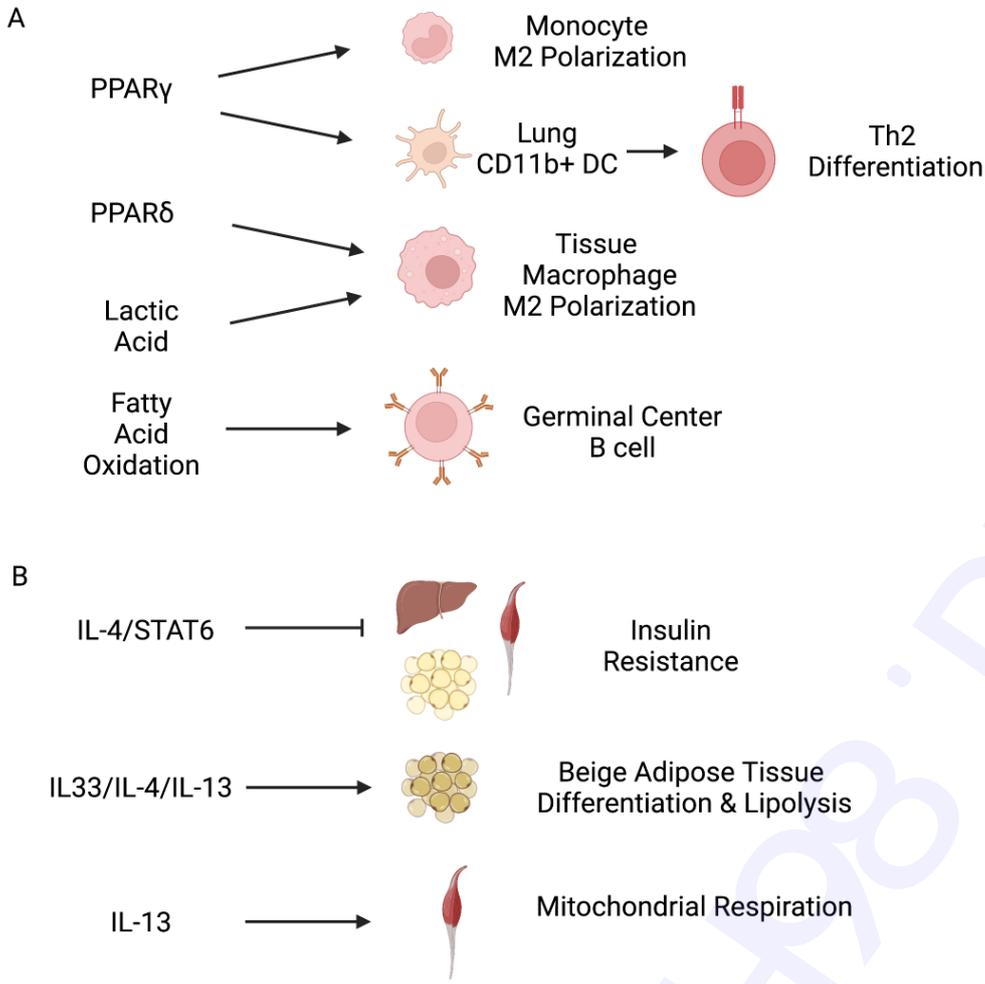


Fig. 2.

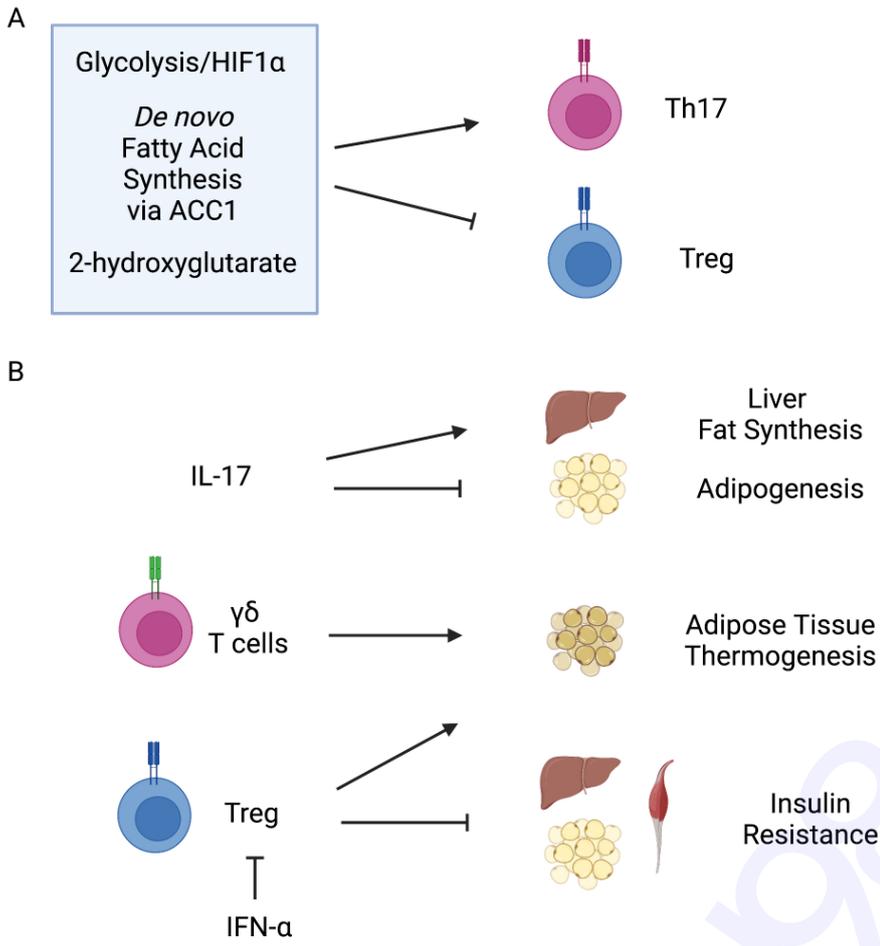


Fig. 3.