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The Therapeutic Potential of T Cell Metabolism

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**Abstract**
Transplant rejection mediated by the adaptive immune system remains a major barrier to achieving long-term tolerance and graft survival. Emerging evidence indicates that lymphocytes rapidly shift their metabolic programs in response to activation, co-stimulatory, and cytokine signals to support required effector cell differentiation and function. These observations have led to the hypothesis that manipulating the metabolic programs of immune cells could serve as a powerful therapeutic strategy for attenuating deleterious immune responses and facilitating durable tolerance in the setting of allogeneic solid organ or bone marrow transplant. In this mini-review, we introduce the fundamentals of metabolism, highlight the current understanding of how adaptive immune cells utilize their metabolic programs, and discuss the potential for targeting metabolism as a therapeutic approach to induce tolerance in the transplant setting.

**Introduction**
Metabolism comprises an intricate web of molecular pathways tasked with providing a cell with requisite energy, reducing equivalents, nutrients, and macromolecules to support normal function. Cellular and organismal metabolism are necessarily highly dynamic.
systems, responding to environmental cues, nutrient availability, and functional demands. While metabolism has been canonically associated with the study of “metabolic tissues” such as liver, adipose (fat), or muscle, there is a growing appreciation that the metabolic programs of individual immune cells play a critical role in shaping both innate and adaptive immunity. In this mini-review, we introduce the fundamentals of cellular metabolism and emphasize our current understanding of the impact that cellular metabolism can have on lymphocyte fate and function. We also highlight important findings regarding the reciprocal relationship between cellular metabolism and immune function, with an eye on how this could impact transplant responses and immune tolerance in general. In this article, we specifically limit our definition of immunometabolism to the study of immune cellular metabolic programs and the impact that the metabolic states have on immune cell fate or function. While there is much research dedicated to the study of the interface of immunology and metabolism in the context of how metabolic diseases such as obesity and dyslipidemia promote inflammation and impact host defense, this area of immunometabolism is beyond the scope of this mini-review. Therefore, we direct readers to other excellent discussions of these topics (1-4).

Accumulated evidence indicates that the metabolic programs adopted by lymphocytes play a fundamental role in regulating the quality and quantity of the immune response (5, 6). Naïve T and B lymphocytes are endowed with the capacity to undergo rapid replication in response to activation or instructional signals through the antigen receptor, co-stimulatory molecules, and cytokine pathways. In combination, these signals dictate the extent to which lymphocytes proliferate during an immune response. In addition to their powerful ability to undergo rapid clonal expansion, lymphocytes are subject to differentiative programs that direct acquisition of a broad array of effector functions. For example, CD8 T cells differentiate into cytotoxic T cells tasked with defending the host from intracellular pathogens or tumors. Likewise, B lymphocytes differentiate into plasmablasts which synthesize and secrete antibodies. CD4 T cells undergo more nuanced differentiation programs resulting in
a range of effector functions which either direct specific types of pro-inflammatory responses (e.g., Th1, Th2, and Th17) or attenuate immune responses and maintain self-tolerance (e.g., Tregs) (7). Remarkably, the metabolic programs employed by each of these types of lymphocytes appear to have distinct features that are essential to supporting their proliferative capacity and effector function (8). Perhaps more surprisingly, an inability to acquire an appropriate metabolic program fundamentally perturbs the nature of inflammatory responses generated by immune cells and impacts adaptive immune responses in both sterile and infectious disease settings. These observations demonstrate that a fundamental crosstalk between metabolic and inflammatory programs exists in immune cells and indicates a potential for therapeutic manipulation of metabolism (9, 10).

A Brief Introduction to Key Cellular Metabolic Pathways

Although metabolism at the cellular and organismal level is exceedingly complex and cannot be adequately addressed in the setting of a brief review, it remains helpful to take a reductionist approach to key metabolic pathways or nodes which have been identified as critical regulators in lymphocyte biology. These pathways include glucose, amino acid, and fatty acid/cholesterol metabolism, as well as the intertwined redox metabolism of the pentose phosphate pathway.

Glucose Metabolism

Glucose is a key metabolite that contributes to the energetics, redox status, and macromolecular synthetic processes of lymphocytes. Activation of T and B lymphocytes results in the rapid upregulation of glucose transporters (such as GLUT1 and GLUT2) and correspondingly robust uptake of glucose into the cell (11, 12). Upon glucose entry,
hexokinase converts glucose to glucose-6-phosphate (G6P), trapping G6P inside the cell and committing glucose to cellular metabolic processes. The majority of G6P flows through the downstream enzymes of the glycolysis pathway into the cytosolic pyruvate pool. Pyruvate can then be converted by lactate dehydrogenase (LDH) to lactate (i.e. fermentation of glycolysis) and subsequently exported from the cell through the monocarboxylic transporters. Some of the pyruvate pool is also shuttled into the mitochondria to replenish intermediates of the tricarboxylic (TCA) or citric acid cycle, in a process termed anaplerosis. This provides carbons for anabolic metabolism and electrons for the electron transport chain (often termed oxidative phosphorylation or OXPHOS). Alternatively, G6P can be diverted into the oxidative branch of the pentose-phosphate pathway (PPP) to provide ribose for nucleic acid synthesis, and reducing equivalents (such as NADPH) for use in lipid biosynthesis. Another important role of NADPH production by the PPP is to maintain the redox status of cells by contributing to the pool of reducing equivalents used by proteins such as glutathione dehydrogenase. These reducing equivalents are needed to counterbalance the reactive oxygen species (ROS) generated by mitochondria and other cellular processes.

**OXPHOS Metabolism**

To varying degrees, cells catabolize carbohydrates, amino acids (primarily glutamine through glutaminolysis), and fatty acids (through β-oxidation) to provide requisite carbons to fill the acetyl-CoA pool. Acetyl-CoA is a building block of isoprenoids, cholesterol, flavonoids, and fatty acids. It is also used to acetylate histones and proteins. In the mitochondria, acetyl-CoA enters the TCA cycle where it is oxidized to generate CO₂ and NADH. NADH fuels the electron transport chain of OXPHOS in complex I. Succinate, an intermediate in the TCA cycle, also helps generate the mitochondrial proton gradient and ATP synthesis in complex II. Overall, oxidation of glucose in the TCA cycle yields 30–36 ATPs by the electron transport
chain of OXPHOS. Therefore, under aerobic conditions, oxidative metabolism is greatly advantageous in terms of generating ATP (11).

As delineated above, pyruvate flows through two distinct metabolic pathways. It can either 1) be fermented by LDH into lactic acid to support anaerobic production of ATP and NADH, or 2) be transported into the mitochondria to support mitochondrial metabolism. While these two fates of pyruvate are often described as occurring in a mutually exclusive fashion, it is important to recognize both lactate production and glucose-dependent OXPHOS metabolism can, and often do, occur to varying levels in the same cell at the same time under normal physiologic conditions. This is particularly evident in newly activated lymphocytes, where there is significant upregulation of both glycolysis and glucose-dependent OXPHOS metabolism. Specifically how a cell utilizes pyruvate depends on multiple factors, including the expression levels of enzymes that regulate glycolytic flux and the availability of oxygen.

Nevertheless, the concomitant increase in glucose flux through both the glycolytic and OXPHOS metabolic pathways during T cell blastogenesis indicates that the upregulation of these metabolic pathways are programmed as part of a physiologic response to activation signals. Moreover, these observations suggest that targeting one or both of these pathways may serve as a potential therapeutic approach in controlling pathologic lymphocyte proliferation and effector function (13). In support of this concept, recently published studies in pre-clinical models of rheumatic disease and transplantation have demonstrated reduced pathology when key proteins of the glycolysis and OXPHOS pathways are pharmacologically targeted (14). As to why activation of effector lymphocytes would concomitantly upregulate both OXPHOS and glycolysis has remained poorly understood. However, recent studies suggest that ensuring high levels of flux though the glycolysis pathway is important for maximizing effector cytokine production, whereas OXPHOS metabolism more specifically supports anabolism and proliferation (15-18).
Amino Acid Metabolism

Amino acids are the building blocks of proteins. Amino acids are broadly categorized as essential and non-essential based on the ability of the body to synthesize a particular amino acid or whether it must be absorbed as part of the nutrients derived from food. Examples of essential amino acids include histidine, lysine, and phenylalanine (19). However, it is important to note that many non-essential amino acids are not synthesized in appreciable amounts in quiescent lymphocytes and must be imported to meet the anabolic demands of blastogenesis. As such, nearly all amino acids become de facto essential for proper growth and effector function. In addition to their important role in protein biosynthesis, some amino acids, such as glutamine or branched chain amino acids, also have the ability to influence the signaling capacity of important growth regulators like mTOR signaling (20). This ensures that anabolic pathways driven by upstream signaling (e.g., TCR or CD28) are coordinated with the nutrient supply chain and metabolic capacity. Finally, amino acids can be catabolized to refill metabolic intermediates of the TCA cycle in anaplerosis. This is a metabolic process whereby nutrients, in particular glutamine, can be directed to the TCA cycle to provide carbons for metabolites that flow out of the mitochondria (e.g., citrate) and subsequently flow into the acetyl-CoA pool for macromolecular synthesis (e.g., fatty acids and cholesterol). Perhaps not surprisingly, controlling the influx of amino acids, in particular the branched chain amino acids and glutamine, has emerged as a potential pharmacologic target in controlling aberrant lymphocyte proliferation (14).

Lipid Metabolism

Lipids are a chemically diverse class of molecules that play essential roles in biophysical and biochemical cellular processes through their ability to regulate membrane properties, bioenergetics, and signaling (21). For the purposes of simplicity and clarity, we will not
discuss lipids that intrinsically act as signaling molecules (e.g., eicosanoids, diacyl-glycerol, oxysterols) and restrict our discussion to the roles that lipids can play in maintaining proper membrane architecture and energetics. These include lipids containing one or more fatty acids such as glycerophospholipids (e.g., phospholipids), sphingolipids (e.g., sphingomyelin), glycerolipids (e.g., triglycerides), as well as free and esterified sterols (in particular cholesterol). Depending on the cell type, upwards of 40% of the biomass of a cell is composed of these lipids. During clonal expansion, lymphocytes must efficiently double their lipid content over the course of each cell cycle in order to ensure that the lipidome is broadly maintained with every division. To meet this anabolic demand, lymphocytes rely on a combination of lipid import from the serum or lymph and de novo synthesis. Genetic and pharmacologic studies indicate that flux through the de novo biosynthetic pathway of cholesterol and fatty acids is required for proper lymphocyte growth in response to activation (22, 23). Conversely, import pathways appear to have redundancy or can be dispensable to meet the biosynthetic demands of lymphocytes (24). Finally, lipids, especially long chain fatty acids, can be utilized to generate energy through the process of β-oxidation (21). In general, anabolic lipid metabolism (i.e. movement of carbons through the de novo fatty acid biosynthetic machinery) antagonizes flux into the catabolic pathways (i.e. β-oxidation). However, there appear to be examples in lymphocyte biology, in particular memory T cells, where flux through the anabolic fatty acid machinery may be required to maintain β-oxidation and cellular energetics (25).

**Lymphocyte Metabolism Rapidly Shifts With Activation State and Functional Capacity**

Naïve T cells migrate though the lymphatic system, sampling antigens presented by dendritic cells, and in the naïve state, their metabolic requirements are largely met by oxidation of glucose and fatty acids. Lymphocytes require extrinsic signals to maintain their metabolism and survival through IL-7 and T cell receptor signals, resulting in the
maintenance of cell surface glucose transporter 1 (GLUT1), which in turn allows cells to maintain mitochondrial potential and ATP homeostasis (26, 27). Without these extrinsic signals, there is a decrease in GLUT1 expression, glucose uptake and ATP synthesis, leading to cell death, even in the presence of sufficient glucose and oxygen (28).

Naïve lymphocytes undergo rapid clonal proliferation and differentiation in response to activation signals. To meet the replicative demand of this event, activated lymphocytes rapidly reprogram their metabolism to facilitate nutrient uptake and increase synthesis of nucleic acids, proteins, and lipids. This is best demonstrated by the upregulation of glucose transporters and enzymes of the glycolysis pathway resulting in heightened glycolytic flux in response to TCR signaling and CD28 co-stimulatory signals (27). Likewise, activation of B lymphocytes through the antigen receptor, TLR4, or CD40 signaling axis can drive a similar induction in glycolysis. The heightened utilization of glycolysis occurs irrespective of ambient oxygen tension and has been likened to the Warburg effect commonly observed in tumor cells (29). In both B and T cells, the AKT and mTOR signaling proteins are essential for the early induction of glycolysis and for sustaining flux through the glycolytic pathway. Perhaps not surprisingly, one of the key pharmacologic effects of small molecules that inhibit the mTOR signaling pathway for the purpose of immunosuppression is significant reduction in glucose uptake and flux into anabolic pathways. Inhibition of T cell activation through PD-1 or CTLA-4 also prevents the increase of glycolytic metabolism, demonstrating an intrinsic relationship between inhibitory signals and metabolic programming (30, 31).

Concomitantly, newly activated lymphocytes also upregulate mitochondrial metabolism. This is mediated in part by intrinsically increasing mitochondrial metabolic activity (i.e. heightened flux through TCA cycle and heightened electron transport chain activity) and by significantly increasing mitochondrial mass during clonal expansion. Mechanistic studies indicate that the increase in mitochondrial function and mass are regulated through the Estrogen Related Receptor alpha (ERRα) signaling axis. ERRα promotes the TCA cycle and mitochondrial
electron transport (32) and is upregulated in T cell activation (33). Isotopic tracer studies indicate that both glucose and glutamine are the dominant metabolic contributors to mitochondrial anaplerosis of activated T cells. Accordingly, attenuation of the flux of these metabolites into the TCA cycle significantly inhibits mitochondrial metabolism and T cell function.

The reason for the simultaneous increase in OXPHOS and glycolytic metabolism in effector lymphocytes upon activation remains an important question in the field of immunometabolism. Perhaps the most parsimonious explanation is that having both of these pathways “ramped up” is required to meet the energetic, redox, and anabolic demands of blastogenesis and the subsequent rapid cell cycle progression of lymphocytes. Additionally, having both OXPHOS and glycolysis pathways engaged likely provides significant metabolic plasticity for T cells. Naïve T cells usually encounter their cognate ligands for the first time in locations remote from the infection (e.g., LN or spleen) and must be prepared to function in an unknowable metabolic environment. Indeed, this metabolic plasticity appears to be critical for effector T cells to function (34). Other studies suggest that flux through the glycolysis pathway is necessary for controlling cytokine production in effector T cells, (15, 18) whereas mitochondrial function plays an important role in controlling the ability of T cells, and likely B cells, to enter into the effector or memory pools.

**Overlapping but distinct metabolic programs are associated with functional subtypes**

The model of metabolic reprogramming delineated above is largely germane to newly activated naïve T and B lymphocytes undergoing initial blastogenesis and clonal expansion. Overlaid upon clonal expansion are robust differentiative programs that drive the acquisition of unique effector functions. CD8 T cells acquire cytotoxic function or enter the long-lived memory pool. Analogously, B cells go through affinity maturation and class switching as part

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of a plasmablast to plasma cell differentiative program. CD4 T helper cells are capable of adopting a broad array of T effector programs.

Analysis of the metabolic programs employed by these different functional fates indicates that many of the cells have overlapping but distinct metabolic elements (Figure 1). For example, Th1 and Th2 cells are highly glycolytic and glutaminolytic to support energetic and anabolic programs (17, 35). In contrast, examination of naturally occurring and inducible differentiated FOXP3+ regulatory T cells (Tregs) reveal a dependence on fatty acid import and β-oxidation to provide requisite carbons, energetics, and reducing equivalents for expansion and regulatory function (36). Th17 cells appear to be far more plastic in their preferred metabolic state, relying on elements of glycolysis, OXPHOS, and β-oxidation to maintain their effector functions. The balance of Th17 and Tregs is determined by HIF1α, which enhances Th17 development through RORγt and p300 while attenuating Treg development by targeting FOXP3 for proteasomal degradation (37). Tightly regulated by oxygen levels, HIF1α upregulates glycolytic genes and promotes anaerobic metabolism (38). It is also highly expressed in Th17 cells but not the other CD4 subsets. Inhibition of HIF1α, which regulates the expression of a number of glycolytic genes to facilitate the transition to glycolysis, results in inhibition of glycolysis and thus impairment of Th17 differentiation (39).

CD8 T cell differentiation is less complex than its CD4 T cell counterparts, with functional outcomes largely restricted to becoming cytotoxic lymphocytes (CTL) or memory CD8 T cells. Nevertheless, interrogating the metabolism of these two functional fates has revealed that CTLs and memory T cells adopt distinct metabolic programs (Figure 2). mTORC1 activation acts through HIF1α, and independently of PI3K and AKT, to link metabolism with CD8 T cell differentiation (40). Effector CTLs become highly glycolytic and correspondingly anabolic. Effector CD8 T cells that are unable to synthesize lipids are defective in clonal expansion (22). In contrast, memory CD8 T cells are reliant on FAO. Importantly,
pharmacologic and genetic studies indicate that restricting a CD8 T cell's ability to adopt a specific metabolic program can be used to preferentially enrich other functional fates, for example effector versus memory (16, 41).

Potential for Targeting Metabolism for Immunomodulation and Therapy in Transplantation

The observation that metabolic reprogramming is an integral component of T cell activation, differentiation, and effector function leads to the hypothesis that modulating these metabolic pathways can be targeted to achieve therapeutic goals. A number of studies have focused on this approach, ranging from glucose and amino acid uptake to OXPHOS and flux through lipid biosynthesis and utilization pathways. There is evidence that a certain level of specificity can be achieved using this approach. For example, specific deletion of the glucose transporter GLUT1 blocks the growth, proliferation, and activity of effector CD4 T cells, without affecting regulatory T cells (42). Similar results have been seen with 2-deoxy-D-glucose (2-DG, a non-metabolizable glucose analogue) and dichloroacetate (DCA, a pyruvate dehydrogenase kinase inhibitor) (39, 43).

One transplant disease model that has been successfully used to demonstrate the efficacy of manipulating T cell bioenergetics for therapeutic purposes has been graft versus host disease (GVHD). In one study, targeting mitochondrial ATP synthase with Bz-423 was able to inhibit mitochondrial ATP production and induced apoptosis in alloreactive T cells without affecting hematopoietic engraftment or lymphocyte reconstitution in a bone marrow transplant model (13). Similarly, the anti-diabetic drug metformin has been used to target alloreactive T cells in GVHD (44). Metformin is best understood to modulate mitochondria function and cellular energy homeostasis, resulting in the activation of adenosine monophosphate-activated protein kinase (AMPK), although the complete mechanism of
action for metformin remains incompletely understood. Interestingly, the administration of metformin was found to expand the population of FOXP3+ Treg cells and inhibit Th17 cell differentiation, further supporting the notion that targeting specific metabolic nodes could be an effective method to skew the balance of T helper cell subsets (Figure 3).

Analogously, inhibition of mitochondrial β-oxidation by etomoxir, an inhibitor of carnitine palmitoyl transferase (CPT)-1a, greatly decreased alloreactive T cells in a GVHD model without affecting other T cell populations (25, 45). Interestingly, the modulatory effect of etomoxir was not seen in effector T cells in acute rejection. These data support the concept that β-oxidation is not a metabolic pathway used in newly activated effector cells. In contrast, chronically activated cells appear to be reliant on β-oxidation. As such, targeting mitochondrial β-oxidation may be a way to selectively modulate pathogenic T cells in chronic inflammatory diseases while sparing acute effector function. Combinatorial targeting of these metabolic pathways has also been shown to achieve durable immunosuppression. Using a regimen consisting of inhibitors of glycolysis (2-DG) and glutamine metabolism (6-diazo-5-oxo-L-norleucine, DON) and an activator of AMPK (metformin –detailed below) was able to prevent or delay graft rejection in a skin and heart allograft transplantation model (14).

Modulation of autoimmune disease through metabolic manipulation is also being explored as a novel therapeutic approach. In mouse models of lupus, combined inhibition of glycolysis and mitochondrial metabolism using 2-DG and metformin were shown to reverse the disease (46), while blockade of either pathway alone prevented the autoimmune CD4+ T cell activation (47). AICAR (5-aminoimidazole-4-carboxamide ribonucleoside) has also been shown to decrease levels of Th1 and Th17 type cytokines in mouse models of multiple sclerosis and inflammatory bowel (48, 49). AICAR is an AMP analogue that activates AMPK activity, and consequently reprograms glucose utilization and anabolic metabolism through downstream targets (50), though AMPK-independent pathways have been implicated (51).

Finally, pharmacologic inhibition of acetyl-CoA carboxylase (ACC) activity using soraphen A,
has also been used to modify the Treg to Th17 cell balance in autoimmune conditions (52). ACC is the rate limiting enzyme in \textit{de novo} fatty acid synthesis pathway, and presumably controls the TH17/Treg fate by inhibiting the flux of carbons into the fatty acid synthesis and elongation pathways. Cumulatively, these results reinforce the notion that activity of these metabolic pathways are essential for controlling the balance of these two intertwined T helper subsets.

**Future Directions**

New insights into how their metabolic programs support immune cell fate and function are beginning to highlight novel ways of exploiting metabolism to achieve therapeutic goals. The fact that metabolic programs play such important roles in supporting specific innate and adaptive immune responses suggests that metabolic manipulation could serve as an effective therapeutic approach. One significant concern regarding metabolic manipulators, however, is the possibility of “on-target” effects in bystander tissues. Because the metabolic pathways described above are not unique to lymphocytes, the therapeutic window for small molecule inhibitors of metabolic pathways could have deleterious effects. This would be particularly true in the context of combination therapy targeting multiple metabolic pathways at one time. Despite this concern, it appears that these drugs alone, or in combination, are well tolerated in pre-clinical disease models (14, 46, 47), holding the promise that targeting these metabolic pathways may be effective in human diseases. Thus, we conclude that immunomodulation by targeting metabolic programs of immune cells shows great promise as a new treatment strategy and remains an exciting field for future research.

**Disclosure**

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.
Figure Legends

Figure 1. Overlapping but distinct metabolic programs are associated with functional subtypes of CD4 T helper cells. Naïve CD4 T cells (Tn) are long lived and metabolically quiescent. They are small and reliant on catabolic metabolism to meet their energy and macromolecular requirements. Upon activation, CD4 T cells upregulate glycolysis and OXPHOS metabolic pathways. As CD4 T helper cells differentiate into functional subsets, they acquire metabolic programs that facilitate their specific functions. Th1 and Th2 cells upregulate both glycolytic flux and oxidation of glucose and glutamine (OXPHOS). Inducible Treg and thymically derived Tregs engage fatty acid oxidation (β-oxidation). Th17 cells are glycolytic but appear to maintain plasticity and can engage other metabolic programs to meet their energetic and macromolecular requirements.

Figure 2. Reprogramming of metabolism in response to lymphocyte activation. In response to TCR and CD28 costimulatory signals, CD8 T cells rapidly increase flux of glucose through the glycolysis pathway into lactate and mitochondria. Likewise, glutamine uptake is significantly increased to replenish carbons lost in the TCA cycle to macromolecule synthesis. Memory CD8 T cells acquire a metabolic program that is distinct from naïve T cells where they significantly increase their mitochondrial mass and are reliant on fatty acid oxidation to provide energy. Importantly, manipulation of the metabolic programs of effector and memory T cells appears to influence fate and function suggesting that targeting the metabolism of responding CD8 T cells may represent a viable approach to facilitating the development of protective immunity or controlling pathogenic processes.

Figure 3. Metabolic reprogramming of effector T cells to attenuate disease. Many immune diseases are driven by an imbalance between pathogenic CD4 effector T cells and CD4 regulatory T cells. Treatment of individuals with small molecules that manipulate the
metabolism of immune cells, such as the combinations of DON and 2-DG and/or metformin (or Bz-423), facilitates restoring the balance of effector and regulatory T cells and attenuates disease in pre-clinical models. These observations hold the promise that metabolic manipulation may serve as a therapeutic approach to control diseases mediated by aberrant T cell proliferation.

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Figure 2. 

**Effector CD8 T Cell**

- Glucose
- G6P
- Pyruvate
- Lactate
- TCA

**Memory CD8 T cell**

- Glucose
- G6P
- Pyruvate
- TCA

**Naïve CD8 T cell**

- Glucose
- G6P
- Pyruvate
- TCA

**Metabolic Activation**
- T Akt
- T p38 MAPK

**Transition**
- T Naïve
- T Tem

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Figure 3.

A. Pathologic condition: Imbalance of TH1/TH17 and Treg

B. Metabolic reprogramming: Restoration of Balance

- DON (D Glucuronolactone)
- Metformin (ν; ORR is)
- 2-DG (Glucose analog)