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O-GlcNAc: a novel regulator of immunometabolism

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Abstract

The rapidly expanding field of immunometabolism focuses on how metabolism controls the function of immune cells. CD4⁺ T cells are essential for the adaptive immune response leading to the eradication of specific pathogens. However, when T cells are inappropriately over-active, they can drive autoimmunity, allergic disease, and chronic inflammation. The mechanisms by which metabolic changes influence function in CD4⁺ T cells are not fully understood. The post-translational protein modification, O-GlcNAc (O-linked β -N-acetylglucosamine), dynamically cycles on and off of intracellular proteins as cells respond to their environment and flux through metabolic pathways changes. As the rate of O-GlcNAc cycling fluctuates, protein function, stability, and/or localization can be affected. Thus, O-GlcNAc is critically poised at the nexus of cellular metabolism and function. This review highlights the intra- and extracellular metabolic factors that influence CD4⁺ T cell activation and differentiation and how O-GlcNAc regulates these processes. We also propose areas of future research that may illuminate O-GlcNAc's role in the plasticity and pathogenicity of CD4⁺ T cells and uncover new potential therapeutic targets.

Keywords

O-GlcNAc; T cells; Metabolic regulation; Inflammation

Introduction

The immune system is composed of a host of widely distributed and extremely dynamic cells capable of expanding and contracting rapidly in response to a myriad of microbial and environmental threats. Within this complex network of cells, CD4⁺ T cells orchestrate the adaptive immune response's elimination of a pathogen in a highly specific manner. Among their many functions, CD4⁺ T cells dictate which class of immunoglobulin is expressed by B cells, enhance phagocytic function of innate immune cells like macrophages, and themselves differentiate into various effector cells specialized to eliminate a class of pathogens (Geginat et al. 2013). Due to the dynamic and highly proliferative nature of CD4⁺ T cells, a fascinating question about their biology has emerged: How can metabolism, another highly dynamic cellular process, influence their function? Indeed, the burgeoning field of

immunometabolism seeks to understand how the metabolic state of immune cells alters function and may be targeted or manipulated for therapeutic purposes. This review will address the ways metabolic pathways influence CD4⁺ T cell function and how a post-translational protein modification, O-GlcNAc (O-linked β -N-acetylglucosamine), whose cycling is dependent on input from multiple metabolic pathways, is critical for CD4⁺ T cell function. We will also offer our perspective on the intriguing possibilities of how O-GlcNAc plays a role in CD4⁺ T cell function and inflammatory diseases.

Distinct metabolic programs are critical during T cell activation

In lymph nodes, naïve CD4⁺ T cells are activated by antigen presenting cells (APC), such as dendritic cells, expressing major histocompatibility complex II (MHC II) loaded with an antigenic peptide on their cell surface. Activation requires recognition of this peptide-MHC II complex by the clonally unique T cell receptor (TCR). In addition to this first signal, a second signal is required to stimulate optimal proliferation of that particular T cell receptor-bearing clone. This second signal is provided by a co-stimulatory molecule, such as CD28. With these two signals, a T cell is now activated to respond specifically to the pathogen loaded onto the MHC II complex. Activation triggers massive proliferation of the T cell and thus requires a tremendous influx of metabolites to sustain initial cell growth and subsequent multiple cellular divisions. Not surprisingly, T cell activation triggers a complete switch in metabolic programs.

Naïve CD4⁺ T cells switch from relying primarily on oxidative phosphorylation for their metabolic needs to aerobic glycolysis and glutaminolytic programs. With this switch comes an influx of metabolites capable of fueling cell growth and proliferation. For example, early studies identified a sudden influx of glucose into activated T cells (Loos and Roos 1973). This initial observation has been further expanded upon by studies showing that activation triggers the upregulation of GLUT1 on the T cell surface. This upregulation is mediated through the CD28 co-stimulatory signaling pathway that engages the PI3K-AKT signaling cascade as well as MYC-mediated transcriptional activation of glycolytic genes (Frauwallner et al. 2002; Rathmell et al. 2003; Wang et al. 2011). In addition to increased glucose, activated T cells also require more amino acids. TCR and CD28 engagement both increase expression of amino acid transporters, particularly those needed for the import of leucine and glutamine (Sinclair et al. 2013; Nakaya et al. 2014). Activated T cells have a very strong requirement for glutamine as an energy source (Griffiths and Keast 1990)—increasing uptake of this particular amino acid ten times more than any other amino acid (Jones and Thompson 2007). Besides being necessary for increased protein translation, glutamine is a versatile building block for many other cellular metabolites, including nucleotides via the de novo synthetic pathway and serving as an anaplerotic source of oxaloacetate (OAA) in the TCA cycle. By replenishing OAA, citrate can be continuously generated and transported out of the mitochondria where it is converted to acetyl CoA, the foundational building block for fatty acid and cholesterol synthesis. Essentially, conversion of glutamine to acetyl CoA provides the building block required for increased fatty acid synthesis during T cell activation. This step is critical since activated effector T cells favor de novo synthesis rather than exogenous uptake of fatty acids (Wang et al. 2011). Overall, T cell activation induces major metabolic shifts, resulting in the cell switching from oxidative phosphorylation and

fatty acid oxidation for its energetic needs to aerobic glycolysis, glutaminolysis, increased pentose phosphate pathway flux, and de novo lipid generation. This substantial change in metabolism is thought to be required to meet the cell's new, increased metabolic demands. *Importantly, these metabolic pathways all produce substrates required in the hexosamine biosynthetic pathway for UDP-GlcNAc synthesis and thus protein O-GlcNAcylation* (Fig. 1).

Intrinsic and external metabolic factors are required for specific CD4⁺ T cell differentiation and function

In addition to providing the stimuli needed for T cell activation, cytokines secreted by the antigen-presenting cell during activation will direct CD4⁺ T cell differentiation into one of at least six classes of specialized effectors. In this review, we focus on four of the “main” classes of these effectors: 1) T helper 1 (Th1), which target intracellular and viral pathogens; 2) Th2, which target helminths; 3) Th17, which target fungal and extracellular bacteria; and 4) inducible regulatory T cells (iTregs), which have an opposing function in decreasing the inflammatory immune response (Fig. 2). Th1, Th2, and Th17 are often categorized as “effectors” due to their vital function in eliminating specific classes of pathogens, while regulatory T cells serve to “soothe” inflammation and thus can be considered a special class of effector T cell. Additionally, effectors are inappropriately increased in situations of autoimmunity (Th1 and Th17) and allergies (Th2). Based on their varied functions, it is not surprising that distinct metabolic pathways are also critical for the differentiation of specific T cell subsets. Th1, Th2, Th17 primarily utilize glycolysis and glutaminolysis for their energy needs and absolutely require GLUT1, while iTregs continue to utilize oxidative phosphorylation to meet their energetic needs and are unaffected by GLUT1 deficiency (Michalek et al. 2011; Macintyre et al. 2014). Instead, inhibition of fatty acid catabolism blunts iTreg differentiation, and increased AMPK signaling (such as that induced by metformin) serves to increase iTreg differentiation (Michalek et al. 2011). A glycolytic enzyme recently found to be integral to CD4⁺ T cell differentiation is pyruvate dehydrogenase (PDH), which converts pyruvate to acetyl CoA, the major building block for fatty acid biosynthesis. Pyruvate dehydrogenase kinase 1 (PDHK1) inhibits PDH activity and enhances glycolytic flux. PDHK1 is selectively up-regulated in Th17, but not in Th1 or iTregs. Inhibition of PDHK1 decreases Th17 differentiation, demonstrating a glycolytic dependence for Th17 cells (Gerriets et al. 2015).

Besides metabolizing glucose differently, differential components of the amino-acid sensing mTOR signaling pathway are specifically required by different T cell subsets. Loss of the entire mTOR complex leads to loss of differentiation into all effector lineages except for iTreg, whose differentiation remains unaffected. This underscores the iTreg reliance on AMPK signaling, which normally serves to inhibit mTOR activity (Delgoffe et al. 2009). mTOR is composed of two different complexes (mTORC1 and mTORC2), each with its own distinct regulation and function (Wullschleger et al. 2006). Interestingly, mTORC1 and Rheb, the GTP-binding protein that activates mTORC1, are required for Th1 and Th17 differentiation, while mTORC2 is needed for Th2 differentiation (Delgoffe et al. 2011). T cell effectors also have a differential requirement for fatty acid metabolic pathways.

Specifically, Th17 cells require acetyl CoA carboxylase (ACC), the rate-limiting enzyme in fatty acid synthesis, while iTreg differentiation is unaffected by ACC knockout (Berod et al. 2014). Further demonstrating a necessity for fatty acid anabolism versus catabolism in iTregs, ACC is upregulated in obese mice and human memory CD4⁺ T cells. The enzyme also provides fatty acid ligands that enhance retinoic acid receptor-related orphan receptor γ isoform (ROR γ t), the lineage-defining, “master” transcription factor for Th17 cells, critical for their activity and IL-17 production (Endo et al. 2015). Increased ACC activity also increases substrates for cholesterol metabolism. Specific oxysterols derived from cholesterol metabolism are potent activating ligands for ROR γ t, increasing ROR γ t transcriptional activity, and thus Th17 differentiation (Soroosh et al. 2014; Santori et al. 2015).

In addition to intrinsic metabolic pathways, various extrinsic metabolic and environmental signals heavily influence CD4⁺ T cell differentiation, particularly along the Th17 and iTreg axis. As an example, sites of inflammation are frequently hypoxic. Accordingly, hypoxia inducible factor-1 α (HIF-1 α) has been demonstrated to be essential in upregulating glycolytic genes in Th17 cells (Shi et al. 2011). HIF-1 α also directly enhances transcription of ROR γ t, while actively targeting forkhead box P3 (Foxp3), the iTreg master transcription factor, for ubiquitin-mediated degradation (Dang et al. 2011). Hormones also exogenously regulate CD4⁺ T cell differentiation. Many autoimmune diseases exhibit sexual dimorphism with increased incidence in females. Androgens act as ligands for different peroxisome proliferator activated receptor (PPAR) types. In human CD4⁺ T cells, androgens upregulate PPAR α which suppresses Th1 and interferon- γ (IFN γ) production, while selectively enhancing IL-17 secretion (Zhang et al. 2012). Human male CD4⁺ T cells with PPAR α knockout secreted IFN γ similarly to female CD4⁺ T cells (Zhang et al. 2012). Other hormonal influences on T cell differentiation include leptin, a hormone released to indicate satiety. Leptin signals through signal transducer and activator of transcription 3 (STAT3), which is the major STAT required for enhancing ROR γ t and IL-17 transcription in Th17 cells. Fittingly, leptin receptor expression is required for Th17 differentiation (Reis et al. 2015) and is yet another signaling pathway found to upregulate glycolytic metabolism via HIF-1 α (Gerriets et al. 2016). On the stranger, yet fascinating side, disrupted circadian rhythms have been shown to increase Th17 differentiation (Yu et al. 2013). Clock proteins rhythmically inhibit NFIL3 (nuclear factor, IL-3 regulated) expression, which ordinarily represses ROR γ t transcription. However, when mice are subjected to altered light/dark cycles to mimic jet lag, increased inhibition of NFIL3 by the Rev-erba clock protein results in increased Th17 differentiation (Yu et al. 2013). Finally, modestly elevated NaCl concentrations induce activity of serum glucocorticoid kinase 1 (SGK1), which stabilizes IL-23 receptor expression, important for locking in a pathogenic Th17 phenotype (Wu et al. 2013; Kleinewietfeld et al. 2013). Knockout of SGK1 results in decreased Th1- and Th17-driven autoimmune inflammation in a mouse model of multiple sclerosis (EAE, experimental autoimmune encephalomyelitis) due to a loss of Th17 stability. This effect was completely reversed by feeding the mice a high-salt diet (Wu et al. 2013; Kleinewietfeld et al. 2013). Recently, SGK1 regulation of the Th1 vs Th2 axis was clarified (Heikamp et al. 2014). Activation of SGK1 occurs downstream of mTORC2, which is required for Th2 differentiation (Delgoffe et al. 2011). Accordingly, knockout of SGK1 ameliorated a Th2-

mediated allergic lung inflammation, suggesting importance in Th2 rather than Th1 differentiation (Heikamp et al. 2014).

Finally, bacterial metabolic by-products unique to the gut can regulate CD4⁺ T cell differentiation. The gut is considered a distinct immunological site due to the constant presence of commensal and potentially pathogenic bacteria, which the immune system must carefully discriminate between to appropriately balance inflammation and tolerance. Proper balance of the Th17 versus iTreg axis is of particular importance in the gut, and thus much research has gone into exploring mechanisms regulating this balance. Specific strains of bacteria, the segmented filamentous bacteria, are required to induce gut resident Th17 cells (Ivanov et al. 2009). Fatty acids derived from the microbiota critically regulate the balance of iTreg and Th17 in the gut. Short chain fatty acids, such as butyrate, induce iTregs, while long chain fatty acids induce Th1 and/or Th17 differentiation sufficient to enhance autoimmune EAE (Haghikia et al. 2015). Additionally, tryptophan derivatives derived from gut bacteria promote iTreg differentiation and quell EAE autoimmune inflammation (Yan et al. 2010).

O-GlcNAcylation is required for T cell activation

A less well known, yet critical metabolic pathway is the hexosamine biosynthetic pathway (HBP). Incorporating metabolites from carbohydrate, amino acid, fatty acid, and nucleic acid pathways, the HBP results in the synthesis of UDP-GlcNAc, the substrate used by O-GlcNAc transferase (OGT) to O-GlcNAcylate proteins. As the concentration of UDP-GlcNAc rises, more substrate is available and O-GlcNAcylation increases (Kreppel and Hart 1999). Glutamine is a substrate required by GFAT (glucose:fructose-6-phosphate amidotransferase), the rate-limiting enzyme in the HBP. Thus, when glucose and glutamine influx rapidly increase during T cell activation, UDP-GlcNAc levels and subsequent O-GlcNAcylation can also increase (Swamy et al. 2016). This effect was first observed during the initial identification of intracellular glycosylation with O-GlcNAc in activated Jurkat T cells (Kearse 1991). T cell activation rapidly induced distinct changes in the population of O-GlcNAcylated nuclear and cytoplasmic proteins. O-GlcNAcylation is essential during T cell activation, since siRNA knock-down of OGT significantly hinders T cell activation (Golks et al. 2007). This effect is due in part because O-GlcNAcylation of NF- κ B and NFAT, transcription factors essential for IL-2 gene transcription which drives the proliferative response, is required for their translocation from the cytoplasm to the nucleus (Golks et al. 2007; Ramakrishnan et al. 2013). Interestingly, O-GlcNAcylation of NF- κ B was induced under specific conditions such as hyper-glycemia, suggesting a link between increased O-GlcNAcylation and exaggerated production of inflammatory cytokines such as IFN γ under its transcriptional control (Ramakrishnan et al. 2013). O-GlcNAcylation is required during activation in primary human T cells as well (Lund et al. 2016). A specific requirement for OGT but not OGA function was identified, which was linked to OGT localization to a cluster of kinases immediately downstream of TCR signaling (Lund et al. 2016). This study also identified several new O-GlcNAcylated proteins among these proximal kinases, such as LCK and ZAP-70, which are key players in transmitting the TCR signal (Lund et al. 2016). Identification of OGT-mediated modification of proteins at the beginning of the TCR signaling pathway provides a possible explanation for why O-

GlcNAcylation levels rise so rapidly after activation before nutrient transporters have had a chance to demonstrably increase nutrient flux. Taken together, the data strongly support O-GlcNAc as a critical regulator of activation signals needed for T cell proliferation.

O-GlcNAc in T cell mediated diseases

The role of O-GlcNAc in CD4⁺ T cell differentiation is poorly understood, but several studies hint at a role for this modification in regulating T cell effectors in autoimmune diseases. The X-linked OGT gene is hypomethylated in T cells from female patients with systemic lupus erythematosus, an auto-immune disease with a high prevalence especially in females mediated in part by Th1 and Th17 cells (Hewagama et al. 2013). Additionally, miRNA15-b targeting of OGT transcripts was recently found to be down-regulated in T cells from multiple sclerosis patients, resulting in increased Th17 differentiation (Liu et al. 2017). ELF-1, a transcription factor for the TCR ζ chain gene, requires O-GlcNAcylation and phosphorylation to translocate from the cytoplasm to the nucleus. Decreased O-GlcNAcylation was found on ELF-1 in SLE patients and led to a decrease in TCR ζ chain levels on their T cells (Juang et al. 2002; Tsokos et al. 2003). Interestingly, restoring appropriate levels of TCR ζ chain was sufficient to ameliorate T effector cell dysfunction (Nambiar et al. 2003). These observations suggest dysregulated O-GlcNAcylation results in aberrant CD4⁺ T cell effector function. Particularly, dysregulated cycling of O-GlcNAc due to changes in OGT levels may have a role in enhancing pro-inflammatory T effector function in the context of autoimmunity. Finally, O-GlcNAcylation is essential for T cell malignancy, since T cell specific OGT knockout prevented malignant transformation of PTEN-knockout thymocytes (Swamy et al. 2016). However, this is likely due more to O-GlcNAc's essential role in organizing the mitotic spindle and regulating cellular division than in regulating T cell cancers specifically (Tan et al. 2013; Slawson et al. 2005; Lanza et al. 2016). Many unanswered questions remain in our understanding of how O-GlcNAc regulates CD4⁺ T cell differentiation and how aberrant O-GlcNAcylation may promote inflammatory diseases.

Future perspectives

As a post-translational protein modification exquisitely sensitive to changes in metabolic state and environmental factors, O-GlcNAc seems poised as a major regulator of T cell function. Besides a clear role in activation, what other functions might O-GlcNAc have in CD4⁺ T cell biology and how might aberrant O-GlcNAcylation contribute to T cell mediated disease? We propose three areas in which the dynamic nature of T cells and their surrounding environment might intersect with the dynamic nature of O-GlcNAc.

First, a fascinating feature of CD4⁺ T cell subsets is their substantial plasticity. For example, Th17 cells have two distinct functional states—a non-pathogenic state in which cells secrete both IL-17 and IL-10, an anti-inflammatory cytokine typical of iTregs, and a pathogenic state, in which cells secrete both IL-17 and IFN γ , the classical Th1 cytokine (Boniface et al. 2010; Lee et al. 2009). This dual Th17/Th1-like phenotype is linked to the pathogenesis of many autoimmune diseases, including multiple sclerosis, inflammatory bowel disease, and type 1 diabetes (Lee et al. 2009; Ghoreschi et al. 2010; Martin-Orozco et al. 2009). Non-

pathogenic Th17 convert to a pathogenic state when injected into a non-obese diabetic mouse model of type 1 diabetes, suggesting that abnormal metabolism may be involved in this conversion (Martin-Orozco et al. 2009). Further supporting a role for metabolic factors, the saturated to unsaturated fatty acid ratio in Th17 cells is critical for pathogenicity. Increased saturated fatty acids due to a decreased expression of CD5L, a protein whose only previously known function was in macrophages, drove pathogenicity by creating ligands that specifically enhanced ROR γ t transcriptional activity at the IL-17 locus, while decreasing IL-10 transcriptional activity (Wang et al. 2015). In future studies, it would be interesting to examine how O-GlcNAc might regulate critical nodes that shift plasticity, such as CD5L, and ways this could be altered therapeutically as a molecular switch of cellular states.

Second, pro-inflammatory Th1 and Th17 cells critically drive many autoimmune diseases. As mentioned previously, dysregulated OGT levels have been implicated in promoting inflammatory T cells in multiple sclerosis and systemic lupus erythematosus (SLE) (Hewagama et al. 2013; Liu et al. 2017). Additionally, disruptions in metabolic pathways of T cells have been implicated in autoimmune inflammation, which could lead to increased shunting of metabolites into the hexosamine biosynthetic pathway, fueling O-GlcNAcylation. For example, inappropriate, chronic stimulation of the PI3K-AKT-mTOR signaling pathway leads to the accumulation of inflammatory Th17 cells in SLE (Koga et al. 2014). Synovial infiltrating inflammatory T cells in rheumatoid arthritis have decreased glycolytic flux at the rate-limiting step, shunting substrates towards the pentose phosphate pathway (PPP) (Shen et al. 2017). Increased PPP flux increases production of NADPH, an essential reductant for fatty acid synthesis, thought to drive abnormal fatty acid metabolism and formation of intracellular lipid droplets. In addition to increased shunting to the PPP, it seems likely that impaired glycolysis might also increase flux through the HBP and abnormally elevate O-GlcNAcylation. Thus, determining the exact role of O-GlcNAc regulation in autoimmune T cells could lead to fruitful insight into pathogenic mechanisms driving autoimmune CD4⁺ T cell inflammation.

Finally, patients with diseases of over-nutrition, such as obesity and type 2 diabetes, have a well-defined chronic, low-grade inflammation. This inflammation has been implicated in much of the downstream pathology associated with increased adiposity, such as atherosclerosis, insulin resistance, and increased risk of autoimmunity and cancer (Ridker et al. 2017; Chehimi et al. 2017). CD4⁺ T cell effectors, particularly Th1 and Th17 cells, are critical players in the development of atherosclerotic plaques and infiltrate adipose tissue to mediate insulin resistance (Chehimi et al. 2017; Winer et al. 2009). Fatty acid metabolism is abnormally stimulated in memory CD4⁺ T cells in obese mice and humans, which drives Th17 differentiation (Endo et al. 2015). Additionally, elevated blood glucose, free fatty acid levels, and various metabolites generated from gut dysbiosis create an environment supportive of increased O-GlcNAcylation. Thus, O-GlcNAc presents as an intriguing target in ameliorating chronic inflammation in obesity.

Initial studies implicate a bittersweet role for this sugar modification in pro-inflammatory autoimmune diseases, but the specific underlying mechanisms that lead to this enhancement in inflammatory function remain to be clearly elucidated. Future studies are needed to

understand how the nutrient-responsive O-GlcNAc modification might play a role in the rapidly expanding field of CD4⁺ T cell immunometabolism.

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Fig. 1.

T cell activation induces cell surface expression of GLUT1 and amino acid transporters, facilitating uptake of glucose and glutamine. This enhanced nutrient state provides substrates that directly feed into the hexosamine biosynthetic pathway (HBP), driving increased UDP-GlcNAc synthesis and protein O-GlcNAcylation by O-GlcNAc transferase (OGT).

Fig. 2.

Cytokines secreted by antigen presenting cells (APC) induce signaling through STAT proteins, which upregulate a lineage-defining transcription factor. This “master” transcription factor then induces transcription of cytokines that carry out the specialized function of the T cell. Th1, Th2, and Th17 have effector functions in eliminating specific classes of pathogens, but over-activity can lead to disease. Inducible Tregs serve an opposing function in diminishing effector T cell responses.