Dietary Methionine in T Cell Biology and Autoimmune Disease

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Dietary methionine and its subsequent metabolism have profound effects on metabolic disease, cancer, and healthspan. In this issue of Cell Metabolism, Roy et al. (2020) report methionine as a nutritional factor for activated T cells that maintains H3K4 methylation and mediates functions that affect autoimmune disease.

Histone modifications are driven by metabolic changes to influence patterns of gene expression (Katada et al., 2012). Histone methylation, for instance, is affected by one-carbon metabolism to dynamically regulate gene expression in response to the availability of methionine (Mentch et al., 2015), an essential amino acid required for methionine adenosyltransferases (Mat)-mediated generation of S-adenosyl-methionine (SAM), a universal methyl donor for DNA and histone methylation. This Mat-mediated SAM production modulates a subset of methylation modifications on histones particularly H3K4me3, whose shape around a gene encodes cell-type-specific transcription-factor (TF) binding and predicts differential gene expression (Dai et al., 2018). Methionine metabolism is therefore important for the maintenance of transcriptional programs (Mentch et al., 2015; Tang et al., 2017).

Targeting methionine metabolism is known to have considerable effects on health. Dietary methionine restriction (MR) extends lifespan in multiple organisms and also delays aging and prevents metabolic diseases in mice (Sanderson et al., 2019). Targeting methionine metabolism is also a promising strategy for controlling cancer, and pharmacological inhibition of the methionine cycle has been shown to disrupt the capability of tumor-initiating cells (Wang et al., 2019). MR also sensitizes several cancer cells to chemotherapy and radiation (Gao et al., 2019). Notably, MR can be achieved in humans (Gao et al., 2019).

In the field of immunity, it has been shown that T cell activation and differentiation demand a sustained supply of extracellular methionine (Sinclair et al., 2019). However, how methionine metabolism regulates T cell functions and whether this regulation eventually affects autoimmune diseases in vivo remains largely unknown. In this issue of Cell Metabolism, Roy et al. (2020) provide convincing evidence that methionine is also a key nutrient affecting epigenetic reprogramming in CD4+ T helper (Th) cells, and MR reduces the expansion of pathogenic Th17 cells in vivo, suppressing T cell-mediated autoimmune encephalomyelitis (Figure 1).

By using metabolomics, Roy et al. (2020) found increased methionine-cycle activity and a significantly elevated capacity for methylation reactions (as measured by the ratio of SAM to methionine) in activated T cells, including CD8+ T effector cells and CD4+ Th1 and Th17 cells, compared with their naive status. Further experiments using stable isotope-tracing revealed that the intracellular methionine pool in activated T cells is almost entirely from extracellular methionine and is highly sensitive to changes of extracellular methionine concentrations. Exogenous methionine thus served as the main source of SAM that maintains the methylation status in activated T cells.

Roy et al. (2020) then assessed the impact of methionine-dependent SAM biosynthesis on histone methylation and further analyzed the importance of this effect on lineage-specific gene expression and Th cell function. They showed that either acute MR (3 μM) as fast as 2 h or silencing of Mat2a dramatically reduced H3K4me3 levels in T cells. Their ultralow-input (ULI-)ChIP-seq analysis further revealed that in line with previous findings in cancer cells (Dai et al., 2018; Mentch et al., 2015), in Th17 cells, the magnitude of H3K4me3 enrichment is reduced under MR conditions in identified gene-promoter clusters, whereas the distribution of H3K4me3 marks around the transcription start site (TSS) is retained. Moreover, H3K4me3 promoter methylation in Th17 cells was sensitive to methionine availability, controlling expression of genes involved in cytokine production and cell-cycle progression. As a result, under MR conditions, Th17 cells displayed reduced IL-17 production, and Th1 cells showed reduced capacity for IFN-γ production (Figure 1).

T cell dysfunction and immune imbalance are associated with autoimmune diseases. The observation that MR limits expansion and differentiation of Th17 and Th1 cells in vivo suggested a possible beneficial effect of dietary MR on progression of autoimmune diseases in vivo. Roy et al. (2020) went one-step further and provided the first piece of in vivo evidence that dietary MR is indeed protective against experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis. They showed that mice maintained on the low-methionine diet prior to induction of EAE are less susceptible to developing immune-mediated neurological deficits, with MR significantly delaying onset and reducing the overall number of symptomatic mice. Consistent with these findings, mice transferred with
Mat2a-silent Th17 cells exhibited a delayed EAE onset in comparison with control recipients. Collectively, this study provides compelling evidence that methionine metabolism links epigenetic reprogramming to CD4+ Th cell effector responses and suggests that dietary methionine intervention could be an approach to control autoimmune T cell function (Figure 1). Understanding cellular methionine metabolism in T cells therefore holds immense potential for developing new therapeutic strategies that target metabolic pathways for immunological diseases.

This work greatly expands our knowledge on how methionine affects immune cell function and autoimmune diseases, which could be linked to the interesting effects MR has on healthspan and aging. However, many questions remain. Although this work focused on the impact of methionine on histone methylation in Th cells, the effects of methionine restriction on other immune cells and other mechanisms involved remain largely unknown. Because the pathogenesis of autoimmune diseases is a complicated process involving interplay between different non-immune and immune cell types, such as T-lymphocytes, B lymphocytes, neutrophils, and macrophages, it would be very interesting to systematically investigate the role of methionine metabolism on systemic immunity. Importantly, although inappropriate activation of the immune system leads to autoimmunity, immune suppression is a critical driver for cancer development and progression. It is intriguing to note that despite similar epigenetic influences, dietary MR can achieve beneficial effects for both autoimmune diseases (Roy et al., 2020) and cancer (Gao et al., 2019; Wang et al., 2019). Further studies are required to elucidate how methionine metabolism and histone methylation regulate the interaction between immune cells and cancer cells, how dietary MR impacts cancer progression in immunocompetent animals, and how dietary methionine intervention might impact cancer immunotherapy. Finally, because T cells are emerging as having important roles in neurological aspects of aging (Dulken et al., 2019), it will be of interest to look at what effects dietary MR might have on this interplay.

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