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COMMENTARY

T helper 17 cells: A new actor on the stage of type 2 diabetes and aging?

In the late 1980s, Mosmann and Coffman[1] proposed the T helper 1 cell (Th1) and Th2 cell theory. Th1 cells produce interferon-γ, and induce $CD8^+$ cytotoxic T cells and macrophages to fight against intracellular pathogens (cell-mediated immunity), whereas Th2 cells produce interleukin-4 (IL-4), IL-5, IL-10 and IL-13, and stimulate B cells to become plasma cells to secrete antibodies against extracellular pathogens, such as parasites (humoral immunity). In contrast, dysregulated T-cell responses trigger autoimmune and chronic inflammatory diseases. For example, uncontrolled Th2 cell responses induce asthma[2], and abnormal Th1 cells responses contribute to the pathogenesis of psoriasis[3] and inflammatory bowel disease[4].

However, many complicated immune situations cannot be simply explained by the Th1/Th2 model. The discovery of new T helper cell subsets, including T regulatory cells (Tregs) and Th17 cells resolved many previously unexplained phenomena[5]. Th17 cells are characterized by the production of IL-17, IL-21 and IL-23, and can mobilize neutrophils to defend against extracellular bacteria and some fungi[6]. Tregs are immunosuppressive, and suppress the induction and proliferation of effector T cells. Tregs produce a number of inhibitory cytokines including transforming growth factor beta, IL-10 and IL-35. Tregs also induce apoptosis of effector cells, directly interact with dendritic cells to suppress immune reaction and suppress effector T cells through interaction with cytotoxic T lymphocyte-associated protein 4[6,7].

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Obesity status is characterized by increased infiltration of M1 macrophages, neutrophils, Th1 cells, $CD8^+$ T cells, immunoglobulin G-secreting B cells and mast cells, whereas lean status is characterized by infiltration of eosinophils, Tregs, Th2 cells, M2 macrophages, immunoglobulin M-secreting B cells and type 2 innate lymphoid cells, an innate lymphoid cell mimicking Th2 cells[8,9]. In obesity status, adipose tissues composed up to 40% immune cells of the entire cell population. The recruitment of inflammatory cells in obese adipose tissue is possibly mediated by fatty acids from lipolysis and lipopolysaccharide from gut pathogens. Both fatty acids and lipopolysaccharide bind the Toll-like receptor 4 to trigger a pro-inflammatory response. In addition, hypoxia due to expansion of adipose tissue in obesity status leads to necrosis of adipocytes, which might attract macrophage infiltration ('crown-like necrosis')[10].

The 'classically activated' M1 macrophages are induced by interferon-γ, and secrete IL-6, IL-1β, and tumor necrosis factor-α. In contrast, the 'alternatively activated' M2 macrophages participate in tissue repair and inflammation resolution, and secrete anti-inflammatory cytokines, including IL-4, IL-13, IL-10 and arginase 1. Lymphocytes account for 10% of non-adipocyte cells in adipose tissue and are often present in the surrounding necrotic adipocytes. Transgenic mice models and human observational studies showed that Th1 cells, $CD8^+$ T cells, B cells and mast cells provoke a pro-inflammatory response in adipose tissue, whereas Th2 cells, Tregs, eosinophils and type 2 innate lymphoid cells suppress an inflammatory response in adipose tissue[8,9].

In steady state, Th17 cells reside nearly exclusively in the barrier of the intestine, skin and lung. Th17 cells show greater plasticity than other immune cells; that is, they can change their phenotypes more easily on stimulation. Th17 cells have been implicated in the pathogenesis of many autoimmune diseases, including multiple sclerosis, psoriasis, inflammatory bowel disease, rheumatoid arthritis and type 1 diabetes. IL-17-deficiency in non-obese diabetic mice delayed the onset of diabetes and decreased the severity of insulitis[11]. In addition, transplant of highly purified Th17 cells into non-obese diabetic/severe combined immunodeficiency mice accelerates the onset of diabetes[12].

How about the role of Th17 cells in type 2 diabetes? IL-17 knockout mice are more insulin sensitive and glucose intolerant than controls[13]. IL-17 knockout mice also have elevated serum adiponectin, and reduced serum insulin and IL-6[13]. In addition, administration of anti-IL-17 antibody in angiotensin II-induced insulin-resistant mice improved insulin resistance and glucose intolerance[14]. Anti-IL-17 antibody also increased glucose uptake in skeletal muscle and enhanced adipogenesis marker gene expression, and reduced pro-inflammatory cytokine levels[14]. These data show the blockade of IL-17 exerted an insulin-sensitizing effect, probably through the resolution of inflammation.

Furthermore, IL-17 knockout mice showed lower blood pressure, preserved endothelial function and decreased pro-inflammatory cytokines in an angiotensin II-induced hypertension model[15]. IL-17 signaling also activates Kupffer cells and hepatic stellate cells to exacerbate liver fibrosis[16]. Neutralization of IL-17 rescues amyloid-β-induced neuroinflammation, memory decline and inflammatory cytokines[17]. The IL-17 level is also upregulated in osteoarthritis, and

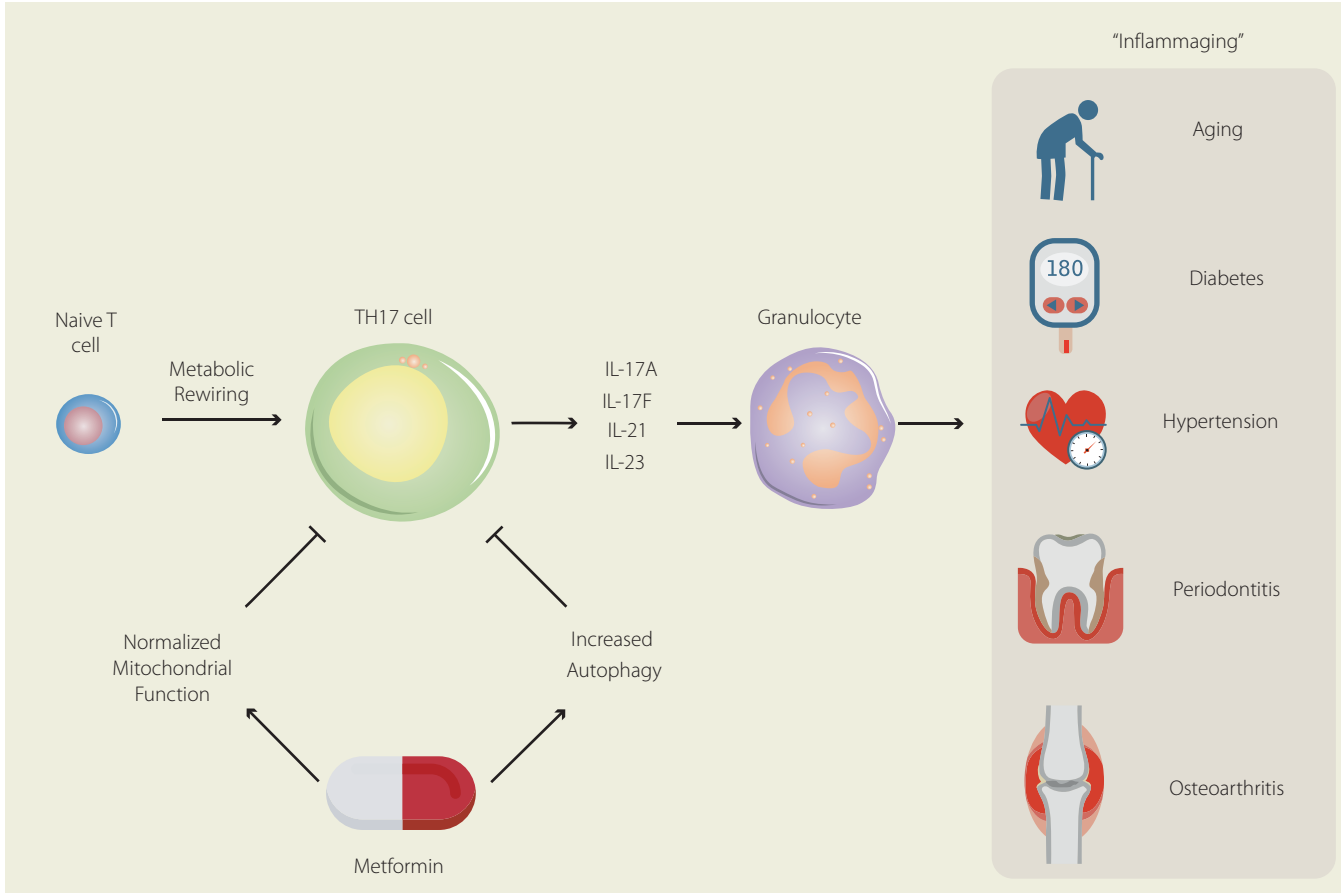

Figure 1 | Naïve T cells evolved into T helper 17 (Th17) cells on specific signals from the innate immune system and undergo extensive metabolic rewiring. The Th17 cells secrete pro-inflammatory cytokines including interleukin (IL)-17A, IL-17F, IL-21 and IL-23, and mobilize granulocytes. Dysregulated Th17 cells lead to a range of chronic inflammatory disorders related to 'inflammaging', including type 2 diabetes, hypertension, periodontitis and osteoarthritis. Metformin improves mitochondrial function and enhances autophagy of Th17 cells from older individuals, which might reverse its pro-inflammatory phenotypes.

IL-17 induced senescence of fibroblasts, which was required for tissue repair[18]. Intra-articular injection of IL-17 neutralizing antibody reduced joint degeneration in an osteoarthritis model. In addition, Th17 cells promote periodontal disease[19], the most prevalent inflammatory disease in the world. These data suggest that IL-17 is associated with aging-related chronic inflammatory diseases in addition to autoimmune diseases.

Many studies showed that the induction of Th17 cells or IL-17 levels or IL-17 tissue expression was significantly increased in patients or mice that were older[20–24] or had diabetes[25–33] compared with young or non-diabetic patients or mice. Bharath *et al.*[34] carried out cytokine profiling and bioinformatic analyses, and found that Th17 cytokine production differentiates $CD4^+$ T cells from lean, normoglycemic older and younger individuals, mimicking diabetes-associated Th17 profile. Serum IL-17A, IL-17F, IL-21 and IL-6 levels were higher in older individuals than younger individuals, which were reversed by metformin. $CD4^+$ cells from older individuals had a higher mitochondrial respiration rate (oxidative phosphorylation [OXPHOS]), proton leakage and increased reactive oxygen species (ROS) production, but lower mitochondrial membrane potential. Metformin shifted the mitochondrial energetics to glycolysis, and increased mitochondrial membrane potential. $CD4^+$ cells from older individuals had more mitochondrial mass and matrix protein accumulation, and less autophagy as compared with younger individuals, leading to phosphorylation of the signal transducer and activator of transcription 3, a transcriptional regulator of Th1 differentiation. Metformin increased autophagy, increased mitochondrial fission and mitochondrial membrane potential, ameliorated ROS production, and reduced the phosphorylation of signal transducer and activator of transcription 3[34]. Genetic inhibition of autophagy reverses the effect of metformin on cytokine profile, mitochondrial energetics and ROS production. Collectively, Bharath *et al.*[34] showed that Th17 cells activation is associated with 'inflammaging', which could be reversed by metformin through enhanced autophagy and improved

mitochondrial function. Indeed, many studies showed that metformin triggers autophagy[35–40]. These results are also consistent with previous studies showing that metformin suppresses the function of Th17 cells, and shifts the balance between Tregs and Th17 cells[41–45].

Each human has approximately 100 million T cells with different subsets that respond to a range of exogenous and endogenous insults. Naïve T cells comprised 20–50% of the total T-cell population and reside in lymph nodes for decades. The differentiation of naïve T cells to effector T helper cells is initiated by the binding of their T-cell receptor with costimulatory molecules in the presence of specific cytokines produced by the innate immune system on different pathogen invasion. However, naïve T cells are small and quiescent with modest energy demands, and typically utilize glucose oxidation through OXPHOS and fatty acid oxidation with low levels of glycolysis[46–48]. On activation, the increase in cell size and rapid cell proliferation dramatically increased energetic and biosynthetic demands. To meet these demands, T cells rewire their metabolic machinery toward glycolysis, because the rate of adenosine triphosphate production of glycolysis is 100-fold faster than OXOPHOS, and glycolysis provides building blocks for the synthesis of lipids, proteins and nucleic acids for cell proliferation[46–48]. Later, it becomes apparent that activated T cells also upregulate OXPHOS, and cooperate with both glycolysis and OXPHOS to meet the energetic and biosynthesis demands[49]. Furthermore, OXPHOS-derived ROS is required for optimal T-cell activation[50,51]. This metabolic rewiring requires the activation of the mammalian target of rapamycin complex 1 pathway and lipogenic pathway. Most previous studies demonstrate that metformin suppresses Th17 cell through activation of 5' adenosine monophosphate-activated protein kinase (AMPK) pathway and subsequent inhibition of mammalian target of rapamycin complex 1, leading to suppressed biosynthesis and cell proliferation of Th17. This is partially inconsistent with those reports by Bharath *et al.*[34] showing that metformin increases OXOPHOS and suppresses glycolysis in Th17 cells. The discrepancy remains to be clarified.

In conclusion, the elegant work by Bharath *et al.*[34] provides a new link between IL-17 and aging, and highlighted the immunosuppressive effects of metformin through promoting autophagy in Th17 cells. These data add a new piece of evidence to the role of Th17 cells in 'inflammaging'-associated chronic diseases, including type 2 diabetes, hypertension, dementia and periodontal diseases, in addition to previously well-known autoimmune diseases (Figure 1).

DISCLOSURE

The authors declare no conflict of interest.

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