Gutsy call on Th17 cells

By Kai-Jye Lou, Staff Writer

Researchers at the **Yale School of Medicine** have shown that the small intestine regulates proinflammatory T helper type 17 cells via two mechanisms, including one that leads to an immunosuppressive, regulatory phenotype.¹ The findings could give companies and researchers new therapeutic options in T helper type 17 cell-associated autoimmune diseases like multiple sclerosis.

Originally identified in a pair of 2005 studies,^{2,3} the IL-17 (IL-17A)-producing subset of CD4⁺ T cells known as T helper type 17 (Th17) cells has been implicated as a driver of proinflammatory processes and tissue damage in many autoimmune diseases, including MS.^{4,5} Indeed, several preclinical-stage biotechs working in autoimmune diseases, such as **Lycera Corp.** and **Tempero Pharmaceuticals Inc.**, have built their platforms around strategies to dampen the pathogenic Th17 cell response.⁶

In its ongoing effort to understand how the body restrains an aberrant, pathogenic Th17 cell response while also inducing tolerance, the Yale group evaluated T cell receptor (TCR) activators. Some of these compounds, such as CD3-specific antibodies, are known to promote immune tolerance.

In a mouse model of tolerance induction, TCR activation with CD3-specific antibodies or a *Staphylococcus aureus*-derived enterotoxin led to clearance of T cells from circulation in conjunction with an increase in Th17 cells in the small intestine, most of which localized to the duodenum. The researchers tested multiple CD3-specific antibodies, including **MacroGenics Inc.**'s teplizumab.

Next, the group elucidated the origins of these gut Th17 cells. In the mouse gut, the researchers found that IL-17 produced by Th17 cells induced upregulation of chemokine CC motif ligand 20 (Ccl20; Mip3a) in intestinal epithelial cells. This chemoattractant drew a subset of Th17 cells that expressed CC chemokine receptor 6 (Ccr6; Cd196) into the gut (see **Figure 1, "Model for gut-mediated regulation of Th17 cells"**).

In addition, a subset of proinflammatory Th17 cells in the gut took on an immunosuppressive, regulatory phenotype and began to produce anti-inflammatory cytokines like IL-10. Another subset of Th17 cells were shed into the lumen of the small intestine, where they were eliminated from the body.

In an MS mouse model, CD3 antibody-induced accumulation of Th17 cells in the small intestine or i.v. transfer of the newly identified regulatory Th17 cells suppressed disease pathology compared with what was seen using saline.

Results were published in *Nature*.

"Th17 cells have traditionally been thought to be proinflammatory, but what we found is that when these cells enter the duodenum they can take on regulatory activity," said Richard Flavell, who is cocorresponding author on the *Nature* paper and chair of the Department of Immunobiology at Yale.

"The paper is a very significant contribution and one that may help to better understand the activity of Th17 cells," said Gary Glick, founder and CSO of Lycera. "The most fascinating aspect of this study is the formation of these immunosuppressive, regulatory Th17 cells."

He said the findings could open new avenues for controlling the Th17 cell response and suggest that general gut health could be an important factor for achieving maximal therapeutic efficacy of autoimmune disease treatments.

In March, Lycera and **Merck & Co. Inc.** partnered to discover and co-develop small molecule RAR-related orphan receptor C (RORC; ROR γ ; ROR γ T) inhibitors for autoimmune diseases. ROR γ T is required for Th17 cell differentiation.⁷

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Tolerance in the gut

According to the Yale group, the newly identified mechanisms reveal multiple points of intervention that could be exploited for the design of more efficacious therapies against Th17 cell-driven autoimmune diseases.

"We believe that to find better treatments for chronic autoimmune and inflammatory diseases, there is a need to develop strategies

that both eliminate pathogenic proinflammatory T cells and induce regulatory T cells," said Samuel Huber, a lead author on the paper and an associate research scientist in the department of immunobiology at Yale. "Our current work describes a new mechanism that does both."

Huber added that the gut is well suited for dealing with the influx of proinflammatory Th17 cells.

"While these proinflammatory Th17 cells initially cause pathology in the small intestine, the effect is self-limiting, as the cells are converted into the regulatory phenotype or eliminated from the body," he told *SciBX*. "Because the gut actively renews its cells, it is a well-suited site for reprogramming these proinflammatory Th17 cells."

Enric Esplugues, the other lead author and an associate research scientist in the same department at Yale, said the findings suggest combining an autoantigen such as myelin oligodendrocyte glycoprotein (MOG) or insulin with a compound that promotes the migration of Th17 cells into the duodenum could help promote tolerance against the antigen.

MOG is an MS-associated autoantigen, and insulin is an autoantigen in type 1 diabetes.^{8,9}

Figure 1. Model for gut-mediated regulation of Th17 cells. As reported by Esplugues *et al.*, the small intestine regulates the activity of T helper type 17 (Th17) cells.

Strong antigen-mediated T cell receptor (TCR) activation on naïve T cells (gray cells) is known to trigger activation-induced cell death [a]. Antigen-presenting cells (APCs; green cells) engulf these apoptotic cells and begin to secrete cytokines such as IL-6 and transforming growth factor- β (TGFB; TGF β), which convert naïve CD4⁺ T cells (blue cells) into proinflammatory Th17 cells (purple cells) [b].

In the new model, proinflammatory Th17 cells in the periphery secrete IL-17 (IL-17A), which leads to upregulation of chemokine CC motif ligand 20 (CCL20; MIP3A) in the small intestine [c].

CCL20—a chemoattractant—draws and traps CC chemokine receptor 6 (CCR6; CD196)-positive Th17 cells into the small intestine, where they are either reprogrammed into an immunosuppressive, regulatory phenotype (orange cell) [d(1)] or eliminated through the lumen [d(2)].

Anti-CD3 antibodies and small molecules that stimulate CCL20 production in the gut are two examples of compounds that might promote Th17 cell migration into the small intestine, Esplugues added.

Glick noted that mining the CCR6 signaling axis could provide additional clues on how to control immune cell migration and tolerance induction.

Flavell, who also is an investigator at the **Howard Hughes Medical Institute**, said the findings could provide new insights for the development of anti-CD3 therapies for autoimmune diseases, which have recently encountered a string of setbacks in clinical trials in type 1 diabetes.¹⁰

In 2010, teplizumab, which was then partnered with **Eli Lilly and Co.**, failed in the pivotal Phase II/III Protégé trial in children and adults with recent-onset type 1 diabetes. In March, the anti-CD3 mAb oteplizumab from **Tolerx Inc.** and partner **GlaxoSmithKline plc** failed in the Phase III DEFEND-1 trial in patients with new-onset type 1 diabetes. Tolerx received rights to oteplizumab from **BTG plc** in 2001.

“Knowing more about how the body regulates T cell activity will be important for getting a better understanding on how to deliver anti-CD3 compounds for the treatment of autoimmune diseases,” Flavell told *SciBX*.

For example, said Huber, “we found that the repetitive administration of CD3 antibody is more effective than the administration of a single dose, and this is interestingly already the standard procedure in these clinical trials. But more importantly, our results suggest that an initial activation of Th17 cells and induction of IL-17A production is crucial to induce the migration of Th17 cells to the small intestine. The key will therefore be to avoid a combination with immune-suppressive drugs that inhibit this Th17 cell activation.”

“Clearly, trying to better understand how the intestinal Th17 cells

become the regulatory Th17 cells could help identify new therapeutic targets,” Glick told *SciBX*.

Going forward, Esplugues said the group will elucidate how the gut converts pathogenic Th17 cells into immunosuppressive regulatory Th17 cells and see whether this phenomenon also occurs in other parts of the body.

The findings are unpatented.

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COMPANIES AND INSTITUTIONS MENTIONED

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GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Howard Hughes Medical Institute, New Haven, Conn.
Lycera Corp., Plymouth, Mich.
MacroGenics Inc., Rockville, Md.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
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