Steroid Modulators of Treg Lymphocytes and Pro-Inflammatory T Helper Cells For Autoimmune Disease

Innovative methods to modulate host T regulatory (Treg) and Th17 cells in autoimmune disease treatment.

Technology

This invention from the Littman Lab (NYU Langone Health) and colleagues describes novel steroid compounds that could be used to reduce symptoms associated with autoimmune or inflammatory disorders. As described in Hang et al Nature 2019, a screen was preformed to identify bile acids and bile acid derivatives (bacteria transformed “secondary bile acids”) in the human gut that modulate T cell differentiation and function. Two derivatives of lithocholic acid (LCA), isoalloLCA and 3-oxoLCA, were identified that substantially affected the differentiation of Tregs and Th17 cells, respectively. Proof-of-concept (PoC) studies showed isoalloLCA to enhance Treg differentiation in vitro (demonstrated by increased FOXP3 expression) and 3-oxoLCA to inhibit Th17 differentiation in vitro (demonstrated by reduced IL-17a expression). In in vivo mouse studies, administration of isoalloLCA and 3-oxoLCA increased Treg differentiation and reduced Th17 cell differentiation, respectively, in the intestinal lamina propria. In summary, theses described secondary bile acid metabolites represent promising scaffolds for development of more potent and selective T cell modulating agents for the treatment of autoimmune diseases.

Background

Autoimmune diseases are a family of more than 80 chronic diseases broadly characterized by aberrant immune response against one’s own organs, tissues, and cells. Autoimmune diseases affect an estimated 23.5 million Americans and are increasing in prevalence. Treg lymphocytes are long-lived cells in the host immune system that suppress excessive or uncontrolled immune responses. Past research has demonstrated that Tregs can be used to treat many autoimmune diseases (Type 1 Diabetes, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis). Moreover, Treg cell therapy has been shown to be efficacious in controlling alloimmune responses in organ/cell transplantation and Graft Vs Host Disease. Therefore, innovative strategies that potentiate Treg differentiation and function would serve as valuable therapeutics for chronic autoimmune diseases, many of which lack curative treatments. Similarly, alternative therapeutic approaches that act to suppress pro-inflammatory Th17 cells, a subset of T helper cells implicated in autoimmune diseases, may also provide therapeutic benefit in combating chronic autoimmune disorders.

Applications

Technology ID

LIT01-13

Category

Life Sciences/Biologics
Life Sciences/Therapeutics/Autoimmu
Disease
Life Sciences/Therapeutics/Immunolo
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- Treatment of autoimmune diseases
  - Type 1 Diabetes
  - Inflammatory bowel disease
  - Systemic lupus erythematosus
  - Multiple sclerosis
  - Rheumatoid arthritis
- Treatment of autoimmune diseases arising from organ/cell transplantation and GVHD
- Use in ex vivo expanded T cell therapies

Advantages

- Known mechanism of action (MoA):
  - IsoalloLCA increases the differentiation of Tregs through the production of mitochondrial reactive oxygen species (mitoROS) which leads to increased FOXP3 expression.
  - 3-OxoLCA inhibits the differentiation of TH17 cells by directly binding to the key transcription factor retinoid related orphan receptor-γt (RORγt).
- Broad potential therapeutic applicability Small molecule modulation of host T cells may confer broad therapeutic benefit across multiple automimmune indications
- Orally-administered small molecule therapy Given the role of secondary bile acids in the human gut, these derivatives could be administered orally to modulate T cell function.
- Innovative alternative administration method Bacteria (to be identified) harboring the specific bile-acid-metabolizing enzymes that produce the immuno-modulating secondary bile acids could be administered in the form of a probiotic.

Intellectual Property

US9505798B2

References

1. Hang, S., Paik, D., Yao, L. et al. , Bile acid metabolites control TH17 and Treg cell differentiation