Project Summary

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STAT1-driven orchestration of the intestinal stem cell response to gastrointestinal graft-versus-host disease

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Allogeneic bone marrow transplantation (BMT) is a powerful therapy for hematologic malignancies, but this potentially curative treatment can be complicated by severe tissue damage associated with graft-versus-host disease (GVHD). In particular, gastrointestinal (GI) GVHD is the predominant contributor to acute GVHD-related morbidity and mortality. In the GI tract, intestinal stem cells (ISCs) play a pivotal role in tissue maintenance and regeneration, and we have found that donor T cells kill ISCs during GI GVHD in experimental BMT models. This finding suggests that a treatment strategy to protect ISCs could reduce GI GVHD without necessarily increasing immunosuppression and post-transplant immunodeficiency. However, the function of ISCs after BMT and during GVHD is not fully understood. To perform a comprehensive evaluation of ISC function and its relationship to the other cellular components of the intestinal lining, we have analyzed gene expression of the ISCs after experimental BMT and found the transcription factor STAT1 to be a major regulator of the physiologic and pathologic responses occurring within the intestinal tissue after BMT. Notably, STAT1 signaling can be impaired by drugs, known as JAK inhibitors, whose use is currently increasing in the field for their immunosuppressive properties. In this project, we will further explore the function and gene expression of ISCs after BMT, we will validate the importance of ISC-intrinsic STAT1 for GI function and dysfunction in GVHD, and we will investigate new approaches to optimize the ISC compartment after transplant in conjunction with emerging small molecule and biologic therapies. This work will provide new fundamental insights into the impacts of cytokines on tissue stem cells, and help to develop novel approaches for treating and preventing GVHD without sacrificing beneficial immune responses in transplant patients.