DKMS Stiftung Leben Spenden

Project Summary

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Multimodal mapping of the leukemia immune microenvironment to personalize the therapy of posttransplantation relapses

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The metabolic pathways encoded by the human gut microbiome constantly interact with the host through various bioactive molecules. Primary bile acids (BAs) are synthesized by hepatocytes and released into the duodenum to facilitate absorption of lipids or fat-soluble vitamins. Some BAs (approximately 5%) reach the colon, where gut commensal bacteria convert them into intestinal (secondary) BAs that regulate host cholesterol metabolism and energy balance via several nuclear receptors and/or G-protein-coupled receptors. These receptors have pivotal roles in shaping host innate immune responses. However, the effect of this host–microorganism biliary network on the adaptive immune system remains poorly characterized. We and others showed that microbiota shifts in patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT), which is a well-established treatment for hematologic diseases that cannot be cured with conventional treatments. Graft-versus-Host disease (GVHD) is a major limitation of allo-HCT, which occurs when donor T cells recognize the recipient as foreign and attack host tissue. The microbiome shifts in allo-HCT recipients include loss of diversity and domination by single bacteria and are associated with increased transplant-related mortality. We hypothesize that gut microbiota perturbations change the BA pool and modulate GVHD through the BA-nuclear receptor signaling axis. We propose a series of studies in mouse models and allo-HCT patients that aim to clarify the mechanisms underlying host-BA crosstalk and better understand how BA modulate GVHD. Knowledge gained in these efforts can guide the development of novel therapies to abate toxicities of allo-HCT and to improve efficacy of this treatment.