Genetic predisposition to precursor B-cell acute lymphoblastic leukemia (pB-ALL) is present in up to 5% of children, but only 1% of predisposed children develop pB-ALL. The reasons for this are unclear, but infections have been suggested to play a role. Accordingly, Dueñas and colleagues tested whether gut microbiota may be involved in leukemogenesis in pB-ALL using genetically predisposed (Pax5+/-) and wild-type (WT) mice raised in a specific pathogen free (SPF) environment for the first six weeks after birth. Regardless of predisposition status, no mice that continued to be housed in SPF developed leukemia; however, among mice transferred to conventional housing facilities, no WT mice developed leukemia, whereas half of predisposed mice developed pB-ALL. There were marked changes over time in the gut microbiomes of all mice housed in conventional facilities, but not in those of mice housed in SPF, perhaps because of immune challenge with common infections in conventional facilities. In both SPF and conventional facilities, predisposed mice had different microbiomes from WT mice; specifically, many types of microbes were absent in the predisposed mice, a finding validated in another mouse model of pB-ALL. Bone marrow–transplantation experiments showed that hematopoietic stem cells with or without genetic predisposition were sufficient to modulate the gut microbiota within six weeks of transplantation. Importantly, half of genetically predisposed mice housed in SPF and treated with antibiotics developed pB-ALL, whereas none of the untreated predisposed mice in SPF developed leukemia. This implies that normal microbiota is essential for preventing pB-ALL in genetically predisposed mice. Comparing the gut microbiomes of healthy and leukemic predisposed mice revealed that no single microbe was linked to pB-ALL; rather, it was a general lack of microbial species that was associated with leukemia development. Together, these results demonstrate that the gut microbiota is a key factor determining whether genetically predisposed mice develop pB-ALL, a finding that may be worth investigating in patients.


Autophagy is a catabolic process that involves recycling intracellular material, and host autophagy can promote tumor growth by, for example, supplying circulating arginine. Poillet-Perez and colleagues found that conditional deletion of Atg7 in mice to abolish autophagy caused buildup of proinflammatory cytokines in serum. Atg7−/− mice implanted with high–tumor mutational burden (TMB) tumors exhibited greater tumor growth than single-knockout mice. Additionally, tumors in Atg7−/− mice had greater T-cell infiltration than WT mice. Depletion of T cells via injection of CD4 and CD8 antibodies increased tumor growth more substantially in Atg7−/− mice than in Atg7+/WT mice. Together, these results suggest that host autophagy loss hinders growth of high-TMB tumors by increasing T cell–mediated immunity. In Atg7−/− and Atg7+/− mice, T-cell depletion increased growth of high-TMB tumors, and this increase was greater in Atg7−/− mice. Also in high-TMB tumors, autophagy loss decreased expression of T-regulatory (Treg) cell–related genes; notably, Treg cells mediated cytotoxic T-cell exhaustion in the tumor microenvironment. In Atg7−/− mice, CD4+ T cells had decreased expression of the exhaustion markers TIM3, PD-1, and LAG3, and CD8+ T cells also had decreased expression of TIM3. Atg7−/− mice exhibited upregulation of genes involved in the IFNα/β pathway and genes that increase IFNα/β production, including Sting and Sting−/−Atg7−/− mice had greater tumor growth than single-knockout mice. Additionally, tumors in Atg7−/− mice had upregulation of genes involved in the IFNγ pathway and genes that increase IFNγ production, and the IFNγ pathway was upregulated in tumor-infiltrating T cells in these mice. Loss of Ifng in Atg7−/− mice increased tumor growth relative to Ifng single knockout. Importantly, all the effects of host autophagy seen in this work were specifically attributable to autophagy by hepatocytes. Collectively, these results demonstrate that host autophagy enhances the growth of high-TMB tumors in vivo by inhibiting T-cell-mediated immunity.
