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The Nlrp3 inflammasome regulates acute graft-versus-host disease.

Abstract:
The success of allogeneic hematopoietic cell transplantation is limited by acute graft-versus-host disease (GvHD), a severe complication accompanied by high mortality rates. Yet, the molecular mechanisms initiating this disease remain poorly defined. In this study, we show that, after conditioning therapy, intestinal commensal bacteria and the damage-associated molecular pattern uric acid contribute to Nlrp3 inflammasome-mediated IL-1β production and that gastrointestinal decontamination and uric acid depletion reduced GvHD severity. Early blockade of IL-1β or genetic deficiency of the IL-1 receptor in dendritic cells (DCs) and T cells improved survival. The Nlrp3 inflammasome components Nlrp3 and Asc, which are required for pro-IL-1β cleavage, were critical for the full manifestation of GvHD. In transplanted mice, IL-1β originated from multiple intestinal cell compartments and exerted its effects on DCs and T cells, the latter being preferentially skewed toward Th17.
Compatible with these mouse data, increased levels of active caspase-1 and IL-1? were found in circulating leukocytes and intestinal GvHD lesions of patients. Thus, the identification of a crucial role for the Nlrp3 inflammasome sheds new light on the pathogenesis of GvHD and opens a potential new avenue for the targeted therapy of this severe complication.

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