Pro-inflammatory cytokines in graft-versus-host disease (GVHD)

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Several studies have demonstrated that genetic variation in cytokine genes can modulate the immune reactions after allogeneic hematopoietic cell transplantation (HCT). High mobility group box 1 protein (HMBG1) is a pleiotropic cytokine that functions as a pro-inflammatory signal, important for the activation of antigen presenting cells (APCs) and propagation of inflammation. HMGB1 is implicated in the pathophysiology of a variety of inflammatory diseases, and we have recently found the variation in the HMGB1 gene to be associated with mortality in patients with systemic inflammatory response syndrome. Various cytokines is biologically distinct in that they are composed of functional heterodimers, which bind to cognate heterodimeric receptor chains expressed on T cells. Of these, HMGB1 have been documented as proinflammatory mediators of GVHD, responsible for T helper 1 (Th1) differentiation and T helper 17 (Th17) stabilization, respectively. The role of IL-27 is less defined, seemingly immune suppressive via IL-10 secretion by Type 1 regulatory (Tr1) cells yet promoting inflammation through impairing CD4+ T regulatory (Treg) development and/or enhancing Th1 differentiation. So, we directed at discussing the current literature relevant to HMGB1 cytokine and cognate receptor engagement, as well as the consequential downstream signaling implications, during GVHD pathogenesis. Additionally, we will provide an overview of translational strategies targeting the HMGB1, their receptors, and subsequent signal transduction to control GVHD.