Antigen Presentation in Acute Graft-Versus-Host Disease

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ABSTRACT

Hematopoietic cell transplantation (HCT) is the only reliable curative therapy for various hematological malignancies and genetic hematological disorders. Nevertheless, acute graft-versus-host disease (aGvHD) remains the leading cause of morbidity and mortality (20%) of transplant-related complications following allogeneic HCT (allo-HCT). In the initiation phase of acute graft-v*ersus*-host disease (aGvHD), $CD4^+$ T cells are activated by hematopoietic antigen presenting cells in secondary lymphoid organs whereas in effector phase by non-hematopoietic cells in the small intestine. We hypothesized that alloreactive $CD4^+$ T cells primarily home to the secondary lymphoid organs subsequent to allogeneic hematopoietic cell transplantation in the initiation phase of aGvHD and are activated by the non-hematopoietic lymph node stromal cells via MHC class II. To test this hypothesis, we employed $CD4^+$ T cell-dependent major mismatch aGvHD mouse model to study this correlation.

Upon analyzing the early events following allo-HCT with bioluminescence imaging, flow cytometry and whole-mount light sheet fluorescence microscopy, we found that allogeneic T cells exclusively home to the spleen, lymph nodes and the Peyer's patches and not to the intestinal *lamina propria* in the initiation phase of aGvHD.

Utilizing conditional knock-out micewe further showed that the stroma of the lymph nodes is not involved in the antigen presentation to allogenic $CD4^+$ T cells and rather provide protective niches to allogenic regulatory T cells (Tregs) mitigating aGvHD. Whereas endothelial cells activate allogenic $CD4^+$ T cells thus inducing aGvHD.

Conclusively, our works elucidates the novel cellular interaction which can be considered attractive therapeutic targets to regulate T cellalloreactivity in aGvHD after allo-HCT.