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| Titolo | MODULAZIONE DEL SIGNALING DI STAT PER PREVENIRE IL RIGETTO DEL TRAPIANTO DI MIDOLLO OSSEO ALLOGENICO [Tesi di dottorato] |
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Sommario

Janus Kinase (JAK)/ Signal Transducer of Activated Transcription (STAT) signaling represents the main molecular pathway dictating T cell differentiation both in humans and in mice. Allogeneic hematopoietic stem cell transplantation (HSCT) is a potential curative strategy for patients with hematologic malignancies and its outcome depends on the interplay between host and donor immune system resulting in graft rejection (GR) or graft versus host disease (GVHD), respectively. We therefore proposed to investigate the role of JAK/STAT signaling in these two phenomena that are biologically considered as mirror images. First, we found that host-mediated graft rejection requires JAK3 expression and that a broad inhibitor of STAT3 signaling prevents GR in a mouse model of rejection. Second, we moved to assess the role of STAT3 signaling in acute GVHD that represents the major cause of mortality in allogeneic HSCT, for which administration of FoxP3+ Treg cells has been proposed as a therapy. However, the phenotypic stability of Treg cells is controversial and cytokines that signal through STAT3 can inhibit FoxP3 expression. In a mouse model of acute GVHD, we assessed whether the elimination of STAT3 in T cells could limit the severity of GVHD, and if so, what mechanisms were involved. We found STAT3 limited the numbers of FoxP3+ Tregs following allogeneic bone marrow transplant by two pathways: instability of natural Tregs and inhibition of inducible Treg polarization from naïve CD4+ T cells. Third, we found that the

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| | infusion in vivo of a potent inhibitor of STAT3 could prevent the onset of acute GVHD, both by reducing Th1 alloreactivity and maintaining the Treg subset in vivo. These data strongly support the potential use of JAK/STAT inhibitors in vivo in order to prevent GR and GVHD in patients receiving allogeneic HSCT. |
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