EUROPEAN HEMATOLOGY ASSOCIATION

Stem cell transplantation – GvHD - Section 1

Pathophysiology of GvHD

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There is considerable redundancy in the mechanisms leading to GvHD and a lack of whole system approaches that address the complexity of this disorder, especially in humans where immunogenetic variation leads to diverse clinical outcome.[1] Many of the important elements that promote T cell immunity against infection, including molecular sensors of microbial patterns,[2] dendritic cells[3] and organized lymphoid tissue[4] are redundant in models of GvHD. Furthermore, it remains unexplained why only certain tissues are prone to injury despite widespread antigen expression. Recent studies have increased our understanding of the role of the innate immune system in GvHD development, particularly the involvement of monocytes,[5] neutrophils[6] and innate lymphoid cells.[7] Changes to host-microbiome interactions[8,9] and inadequacy of epithelial regeneration[7,10] are also implicated in driving tissue damage. Thymic GvHD may perpetuate inflammation by blocking Treg generation11 or permitting peripheral release of autoreactive T cells.[12] Our recent work has evaluated the concept that GvHD-target tissues are the major participants in shaping tissue injury. We postulate that T-cell receptor repertoire-independent mechanisms may be most important in instructing GvVHD development and reflect extrinsic regulation by tissue-specific factors. We have previously demonstrated that the presence of inflammation within the skin is required for maximal recruitment of activated donor T cells[13] and that host Langerhans cells are critical for switching incoming activated T cells into fully competent effectors capable of inducing GvHD.[14,15] We are currently examining whether this tissue-mediated 'licensing' is specific to the skin or is generally applicable to other GvHD sites.

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