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TGF-beta signalling contributes to thymic epithelial cell damage and regeneration following myeloablative conditioning and stem-cell transplantation

MM Hauri-Hohl* and GA Hollander

Address: Pediatric Immunology, Center for Biomedicine, Basel, Switzerland
* Corresponding author

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Hematopoietic stem cell transplantation (HSCT) is considered a potentially curative therapy for a number of severe autoimmune diseases. The rationale consists of deleting auto-reactive T and/or B cell clones and re-constructing a functional immune system tolerant to auto-antigens. The re-emergence of T cell immunity following myeloablation largely depends on thymic de novo production of naïve T cells. The thymic stroma – mainly consisting of thymic epithelium (TE) – is responsible for the attraction of thymocyte precursor cells, support of developing T cells and appropriate positive and negative selection of a broad T cell receptor repertoire. Several reports including ours have demonstrated a negative impact of conditioning on TE numbers and function, which results in delayed T cell reconstitution. We have recently described the contribution of TGF-β signalling to thymic epithelial cell damage after irradiation, yet the underlying molecular mechanisms remain elusive.

In this report we analyse the involvement of TGF-β family members and downstream molecules in TE injury and regeneration following irradiation using different mouse models and *in vitro* assays. We demonstrate the detrimental effects of active TGF-β protein released by thymocytes early after irradiation on proliferation and phenotype of TE with a direct consequence on the dynamics of T cell reconstitution. The particular importance of TE in the process of efficient T cell development necessitates the development of strategies to protect the TE compartment and enhance its restoration in the context of pre-HSCT conditioning.