Bone marrow–induced behavior?

Hoxb8 mutant mice exhibit excessive pathological grooming behaviors that are similar in nature to the human obsessive–compulsive disorder trichotillomania. Hox genes are typically involved in establishing body plans, although these genes also play a direct role in formation of the hematopoietic system. The brain is responsible for implementing grooming behavior, and Chen and colleagues recently demonstrated that the only detectable cells derived from the Hoxb8 cell lineage in the brain were microglia. Surprisingly, transplantation of wild-type bone marrow into irradiated Hoxb8 mutant mice rescued the pathological grooming behavior, despite the spinal cord defects that are present in these mutant mice. In agreement with this finding, restricted deletion of Hoxb8 in hematopoietic cells induced the excessive grooming phenotype. Taken together, these results suggest that the pathological grooming behavior observed in Hoxb8 mice results from a deficiency in bone marrow-derived microglia. (Cell 141:775–85, 2010)

Improving DC homing

Development of dendritic cell (DC)-based tumor immunotherapy has been the focus of intensive research efforts. Unfortunately, poor mobilization of adoptively transferred antigen-pulsed DCs to draining lymph nodes (DLNs) has limited the efficacy of such treatments. Previous studies have indicated that mast cell activation and mast cell–derived tumor necrosis factor (TNF)-α are important for efficient Langerhans cell migration to DLNs. Ren and colleagues found that homing of bone marrow-derived (BM)-DCs to DLNs increased following mast cell activation and degranulation. Intradermal injection of the known mast cell activator c48/80 induced BM-DC migration to the DLNs. In addition, this induced mast cell degranulation also enhanced antigen-pulsed BM-DC-mediated immune responses, such as antigen-specific lymphocyte proliferation and cytokine production. These results provide a potential mechanism for improvement of DC-based immunotherapies. (Cell Immunol 263:204–11, 2010)

Beneath the epidermis

Inhibition of tumor blood flow and neoangiogenesis has been the target for new approaches to cancer therapy. Protein kinase C (PKC) regulates keratinocyte viability and is often inactivated or downregulated in squamous cell tumors, suggesting that this kinase is a suitable target for tumor therapy. Indeed, ingenol-3-angelate (Ing3A) exhibits antitumor activity upon topical application, and this drug, which is in clinical trials for treatment of basal cell carcinoma, actinic keratosis, and squamous cell carcinoma, is a PKC agonist. Recently, Li and colleagues showed that this drug engages the epidermis, but, unlike the similar protumor factor phorbol 12-myristate 13-acetate, Ing3A penetrated through the epidermis to the dermis and subcutis where the vasculature resides. In these experiments, Ing3A bound to P-glycoprotein (P-gp), a factor that is linked to the development of multidrug resistance in cancer cells, and P-gp transported this drug through the ABC transporter ABCB1 to subepidermal compartments. Given that the skin is increasingly considered an advantageous site for drug delivery, future studies of the absorption and effects of this drug as well as of the impacts of polymorphisms in the human ABCB1 gene (MDR1) are warranted. (Cancer Res 70:4509–19, 2010)

Autonomous contribution of mTECs

Medullary thymic epithelial cells (mTECs) function in the generation of a self-tolerant T-cell repertoire. Although these cells express peripheral-tissue antigens, the function of mTECs as antigen-presenting cells is not clearly understood. After decreasing the major histocompatibility complex class II molecules on mTECs in order to maintain the functional properties of these cells, Hinterberger and colleagues found an enlarged CD4 single-positive T-cell compartment in these mice. These findings indicate that mTECs contribute to deletional CD4+ tolerance by acting as antigen-presenting cells. Furthermore, antigen recognition on mTECs enhanced the development of regulatory T cells. Together, these results demonstrate that mTECs autonomously contribute to central CD4+ T-cell tolerance. (Nat Immunol 11:512–9, 2010)

Engineering strategies for gene therapy

A tumor-reactive T-cell repertoire can be generated via introduction of genes that encode tumor-reactive T-cell receptor (TCR) αβ chains into peripheral T cells; however, these TCR chains may form TCRs that yield self-reactive T cells. Bendle and colleagues recently introduced such an antigen-specific TCR into murine T cells and found that a lethal autoimmune pathology resulted because of the formation of self-antigen-reactive mixed TCR dimers. This so-called transfer-induced graft-versus-host disease could be limited or prevented using strategies that result in reduced pairing of endogenous and exogenous TCR chains or in a limited diversity of endogenous TCR repertoire of the transduced T cells. These strategies, which included the addition of a disulfide bond between the α and β chains as well as replacement of the sequence that links these chains with the porcine teschovirus–derived P2A sequence, may be useful in preventing an otherwise fatal autoimmune attack following tumor-specific gene therapy; these engineering strategies will be examined further in the clinical setting. (Nat Med 16:565–70, 2010)