Dynamic communication between DCs and MCs during inflammation

As part of the innate immune system, dendritic cells (DCs) and mast cells (MCs) function at the host-environment interface to protect from invading pathogens. Previously, interactions between DCs and MCs have been observed to enhance DC maturation and T cell stimulation. Using real-time intravital multiphoton microscopy in mice, Dudeck and colleagues demonstrated that migratory DCs interact with stationary MCs in the skin following skin inflammation, establishing extensive and persistent MC/DC synapse-like contacts. These interactions facilitate transfer of proteins, including MHCII molecules, from dermal DCs to MCs, resulting in MCs that can prime allogeneic T cells. These observations suggest that dynamic communications between DCs and MCs may promote lasting effector responses at sites of initial insults. (J Exp Med. 214:3791-3811, 2017) Selected by D. Kaplan

Skin organoids from homogeneous cell source

Pure populations of fibroblasts or keratinocytes can be generated from mouse and human pluripotent stem cells (PSCs), and these cells can be combined to generate full-thickness skin. However, skin appendage development is not supported in these models. Lee and colleagues used homogeneous murine PSCs that had been cultured in defined media to generate self-assembled skin organoids that developed stratified epidermal and dermal layers on a time scale that resembles that of normal embryonic development. Moreover, these organoids featured hair follicles, sebaceous glands, and adipocytes. The hair follicles in organoids were similar to those in late embryonic or early postnatal development and contained all major components, including matrix, inner root, outer root, and dermal sheath layers, indicating that organoid hair follicle induction mimics normal hair folliculogenesis. These skin organoids may be useful in studies of requirements for hair follicle induction or to evaluate hair growth potentiating or inhibitory drugs. (Cell Reports 22:242-252, 2018) Selected by C. Niessen

Pre-transplantation myeloablation proves successful for scleroderma

While randomized trials of nonmyeloablative transplantation for the treatment of diffuse cutaneous systemic sclerosis or scleroderma appeared beneficial, this treatment has not been adopted due to questions regarding durability of responses and safety. Scleroderma remains a devastating and often fatal autoimmune disorder, although cyclophosphamide is currently approved for treatment with short-term benefit. To examine the effects of treatment on long-term outcomes, Sullivan and colleagues compared myeloablation via total-body irradiation followed by reconstitution with CD34+ selected autologous hematopoietic stem-cell transplants with 12-month cyclophosphamide therapy after 54 months. Myeloablative transplantation led to superior clinical outcomes, including longer overall and event-free survival, decreased disease severity, and decreased requirements for other autoimmune-disease modifying drugs. Despite the occurrence of adverse events in the transplantation patients, this randomized clinical trial indicated that myeloablation followed by stem-cell transplantation leads to more durable and superior clinical responses than standard cyclophosphamide therapy. (New Engl J Med. 378:35-47, 2018) Selected by I. Brownell

Macrophages implicated in neuropathy in leprosy

Mycobacterium leprae, the causative agent of human leprosy, is the only mycobacterial infection that causes demyelinating neuropathy. Technical difficulties have limited our understanding of this process. Using a new model system, in which zebrafish larvae are infected with M. leprae to study the early events leading to neuropathy, Madigan and colleagues discovered that infected macrophages that scan nerve axons initiate the nerve demyelination and axonal damage that are characteristic of this disease. Specifically, excessive production of nitric oxide by macrophages in response to the M. leprae-specific phenolic glycolipid (PGL-1) leads to damage to axonal mitochondria, resulting in demyelination. These studies revealed that both myelinated and demyelinated axons are damaged via this mechanism, supporting the relevance of this model to human disease, which exhibits damaged axons of both types. In addition to identifying the cellular culprit in leprosy demyelination, this model may be useful for understanding other neurodegenerative diseases, such as multiple sclerosis, that involve myeloid cell contribution to neuropathy. (Cell 170:973-998, 2017) Selected by M.C. Udey

Understanding methylation in squamous cell carcinoma

DNA methylation at Cpg dinucleotides by DNA methyltransferases (Dnmt) regulates gene expression involved in cellular processes such as development and differentiation. Interestingly, Dnmt3a is frequently mutated in human tumors early during tumorigenesis, suggesting that dysregulation of this enzyme promotes tumorigenesis. As deletion of Dnmt3a and Dnmt3b results in embryonic lethality, Rinaldi and colleagues generated mice with epidermal-specific deletion of Dnmt3a or Dnmt3b or both to investigate the roles of these enzymes in adult epidermal function and malignant transformation. Importantly, deletion of Dnmt3a increased the number of carcinogen-induced tumors but had no effect on tumor progression. However, deletion of both Dnmt3a and Dnmt3b promoted squamous cell carcinoma tumor progression and metastasis. Molecular studies revealed that Dnmt3a inhibits expression of lipid metabolism genes, including PPAR, and in agreement with these findings, inhibition of PPAR partially abrogated the increase in carcinogen-induced tumors following Dnmt3 deletion. Together, these results indicate that Dnmt3a plays an important role in tumor suppression in the epidermis and highlight PPAR as a novel potential therapeutic target for squamous cell carcinoma. (eLife 10.7554/eLife.21697.001, 2017) Selected by T. Oro


© 2018 The Society for Investigative Dermatology. www.jidonline.org 717