Systemic administration of MSCs alters immune cells to enhance wound healing

Intravenous (i.v.) injection of MSCs has provided lasting therapeutic effects for inflammatory and immune-mediated disorders. However, the persistence of these cells is short lived, and wide dissemination has not been documented. Although MSCs are thought to modulate immune cells, the mechanisms underlying their therapeutic effects remain unclear. Kosaric et al. (2020) recently demonstrated that i.v. infusion of human bone marrow–derived MSCs accelerate wound healing in a murine excisional wound healing model despite sequestration in the lungs and clearance within 48 hours. Infusion of MSCs led to the appearance of a novel set of macrophages that may be involved in vasculature development and to depletion of inflammatory macrophages in wounds. Induction of these proangiogenic CD93 macrophages was mediated by COL6A1, PRG4, and TGFβ3 that were secreted by MSCs. (Mol Ther 2020;S1525-0016(20)30286-0; https://doi.org/10.1016/j.ymtne.2020.05.022) Selected by M. Tomic-Canic

A deep learning system assists skin disease diagnoses

Skin abnormalities are common complaints in primary care interactions. Because dermatologist access is constrained, primary care providers are often tasked with triage, diagnosis, and treatment. Whereas many nonspecialists rely on store-and-forward teledermatology, strides have been made in the development of deep learning system (DLS) algorithms to improve diagnostics. Liu et al. (2020) developed and validated a DLS for 26 common skin conditions using input of multiple images and metadata, including demographic and medical history information. The resulting DLS resulted in greater diagnostic accuracy than that of nonspecialists, and this system also yielded results that were noninferior to dermatologist consultations. DLS algorithm generated top-three results and full differential diagnoses may assist clinicians in triaging cases and improve diagnostic accuracy, resulting in improved treatment decisions, shortened time to treatment, and reduced morbidity from skin diseases. (Nat Med 26:900–8, 2020; https://doi.org/10.1038/s41591-020-0842-3) Selected by T. Oro

Polygenic risk scores predict survival after immune checkpoint inhibitor therapy

Inhibitors of PD-1 and its ligand PD-L1, which have provided effective treatments for some cancers, often induce immune-related adverse events (irAEs) that are autoimmune in origin and are associated with longer overall survival. These therapies induce antitumor immunity through the inhibition of an immune checkpoint that restricts T-cell responses and regulates immune self-tolerance, supporting the autoimmune nature of the AEs. Using germline whole-genome sequencing data, Khan et al. (2020) computed polygenic risk scores based on genetic risk variants for psoriasis, vitiligo, and atopic dermatitis (AD) to determine whether these were associated with dermatological irAEs and survival in patients with metastatic urothelial carcinoma. High vitiligo, high psoriasis, and low AD polygenic risk scores were associated with increased risk for dermatological irAEs and also longer survival in patients receiving atezolizumab, an anti–PD-L1 monotherapy, but not in those receiving chemotherapy. These findings demonstrate that genetic variants that mitigate risk for dermatological autoimmunity contribute to patients’ responses to immune checkpoint blockade. (PNAS 2020:117:12288–94, 2020; https://doi.org/10.1073/pnas.1922867117) Selected by I. Brownell

The skinny on anaplastic lymphoma kinase

While several genes have been implicated in body weight regulation and obesity, few studies have examined the genetic components of resistance to weight gain. Utilizing the Estonian biobank as a data source for GWASs, Orthofer et al. (2020) identified variants in the gene encoding ALK that were associated with human thinness. Knockout of this gene in mice resulted in a thin phenotype, elevated adiponectin levels, and improved glucose homeostasis concomitant with unaltered consumption of a standard chow diet and activity. Deletion of ALK increased energy expenditure and protected the mice from developing obesity following high-fat diet or genetic manipulation. Furthermore, ALK acted in the CNS to regulate white adipose tissue lipolysis and sympathetic tonic control energy homeostasis and determine body weight and weight gain. Together, these studies define ALK as a regulator of energy expenditure, positioning the ALK gene as a central factor in thinness and suggesting that the inhibition of the ALK pathway via targeted therapeutics may promote thinness even under conditions of leptin resistance and obesity. (Cell 181:1246–1262.e22, 2020; https://doi.org/10.1016/j.cell.2020.04.034) Selected by I. Brownell

Myeloid-derived suppressor cells induce T-cell paralysis through methylglyoxal transfer

Myeloid-derived suppressor cells (MDSCs) are induced during chronic inflammation and block normal immune cell effector function, although their mechanisms of action have remained elusive due to a lack of discriminating molecular markers for MDSCs. In a recent paper, Baumann et al. (2020) described a mechanism by which MDSCs prevent T-cell activation by cell contact–dependent inhibition of signaling activity. Transfer of cytosolic contents, and of dicarbonyl methylglyoxal in particular, from MDSCs to CD8+ T cells inhibits signaling processes, depletes L-arginine accumulation, prevents upregulation of metabolic activity, and diminishes induction of effector function, effectively paralyzing the T cells. Suppression of T-cell activity was strongest after incubation of T cells with MDSCs isolated from liver cancer tissues compared to MDSCs isolated from peritumoral tissue or blood from the same patient with liver cancer. Thus, methylglyoxal is a metabolic marker of MDSCs and causally contributes to the MDSC-mediated paralysis of T cells that is observed in cancer. As methylglyoxal neutralization was able to rescue the antitumor immunity in synergy with checkpoint inhibition, exploration of combinations of these therapies to enhance cancer immune therapies is warranted. (Nat Immunol 21:555–566, 2020; https://doi.org/10.1038/s41590-020-0666-9) Selected by I. Brownell

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