Nomograms Identify Risk in Patients with Thin Melanomas

The prognosis for patients with thin (T1) melanomas, defined as <1 mm in Breslow thickness, is very good. However, recurrent disease leads to death in a high absolute number of individuals because as many as 81% of patients with primary cutaneous melanomas have T1 melanomas. Prediction of recurrent disease is an important goal, and only T-stage and sentinel node (SN) status are currently used to predict survival. Sharouni et al. (2021) developed and validated nomograms to predict local, regional, and distant recurrences in patients with T1 melanomas from clinical data from nearly 29,000 patients. An online tool that is freely available to clinicians will facilitate the integration of these nomograms into clinical practice and may guide the management of care for patients with T1 melanomas. (J Clin Oncol 39:1243–52, 2021; https://doi.org/10.1200/JCO.20.02446) Selected by I. Brownell

Reduced Activation and Survival of Immune Cells Impair Wound Healing

Diabetic foot ulcers (DFUs) are characterized by epidermal hyperproliferation, dysregulated inflammatory responses, impaired epithelialization, and infection, often leading to delayed healing and wound chronicity. Not only does prolonged inflammation prevent healing, but the transition of M1 to M2 macrophages in these wounds also impairs the healing process. In a comparison of patient biopsies from acute wounds in oral mucosa and from healthy skin with those from DFUs, Sawaya et al. (2020) uncovered the transcriptional networks implicated in the activation, proliferation, and survival of immune cells in wounds. These networks were dysregulated in DFUs, resulting in delayed wound healing and suppression of the recruitment of neutrophils and macrophages to the wounds. Downregulation of the forkhead transcription factor FOXM1 mediated the effects on the immune cells, contributing to the inability of DFUs to heal. The deficiency in immune cell recruitment in DFUs suggests targeted approaches for therapies aimed at reprogramming DFUs to healthy wound-healing pathways. (Nat Commun 11:4678, 2020; https://doi.org/10.1038/s41467-020-18276-0) Selected by M.C. Udey

SARS-CoV-2 Activates Plasmacytoid Dendritic Cells and IFN Production

Late-stage disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is characterized by viral persistence, excess production of proinflammatory cytokines, and a defect in IFN-I production. Early-stage antiviral immune responses have yet to be fully characterized. Onodi et al. (2021) reported that SARS-CoV-2 activates plasmacytoid dendritic cells (pDCs), resulting in the diversification of P1, P2, and P3 pDC subsets, although these pDCs were not infected by SARS-CoV-2. In addition, SARS-CoV-2–activated pDCs efficiently induced IFN-I and IFN-III responses, which are essential viral responses and are lacking in critically ill late-stage SARS-CoV-2–infected patients. Molecularly, this response is dependent on the toll-like receptor downstream factors IRAK4 and UNC93B1. Treatment of cultured virus and pDCs with hydroxychloroquine, a drug that has been investigated for the treatment of SARS-CoV-2 disease, inhibited pDC activation and diversification and cytokine production. These results delineate some of the immune effector pathways that are activated during early infection by SARS-CoV-2 and may inform the development of effective treatment strategies aimed at viral infection stages. (J Exp Med 218:e20201387, 2021; https://doi.org/10.1084/jem.20201387) Selected by M. Bagot

Fecal Transplant Beneficial for Patients with Melanoma Resistant to PD-1 Therapy

mAbs that target PD-1 are efficacious in a subset of patients with melanoma. Resistance to this therapy is thought to stem from both tumor-intrinsic and tumor-extrinsic mechanisms, such as the gut microbiome. Davar et al. (2021) treated 16 patients with anti–PD-1 therapy–refractory melanoma with a fecal microbiota transplant from donors who had exhibited either complete or partial responses to PD-1 therapy. After additional PD-1 therapy, three of the recipients exhibited objective responses, and three exhibited stable disease. The transplant shifted the composition of the microbiome toward taxa that were favorable to clinical response. In addition, responders exhibited proteomic and metabolomic signatures that were regulated by the altered gut microbiome. Fecal microbiota transplantation together with anti–PD-1 therapy overcame resistance in some patients with PD-1–refractory melanoma with immunological ability to respond to treatment, supporting further clinical trials to establish the desirable characteristics of the patient. (Science 371:595–602, 2021; https://doi.org/10.1126/science.abf3363) Selected by I. Brownell and M. Tomic-Canic

Mature Adipocytes Inhibit Antimicrobial Function in Obesity

Obesity is associated with comorbidities that stem from chronic inflammation. However, infections, which are more frequent in immunosuppressed patients, are also common in individuals with obesity. Zhang et al. (2021) showed that in diet-induced obesity, adipocytes are lost from the dermis in mice as well as in humans. This decrease in adipocytes was mirrored by lower levels of antimicrobial peptides and increased susceptibility to infection with Staphylococcus aureus. Although early adipocytes, which provide a critical source of antimicrobial peptides, are active in the innate immune response, diet-induced obesity results in the accumulation of mature adipocytes. Mature adipocytes inhibit antimicrobial function through the production of TGFβ, which in turn inhibits adipocyte progenitors and halts the production of cathelicidin. In additional studies in obese mice, treatment with a TGFβ receptor inhibitor or rosiglitazone, an agonist of the peroxisome proliferator–activated receptor–γ (PPARγ) that is suppressed by TGFβ expression, restored antimicrobial functions and improved resistance to S. aureus. These findings shed light on the seemingly contradictory increase in infections during chronic inflammation in obesity and also highlight the potential of TGFβ inhibition or PPARγ activation as a therapeutic approach for preventing infections in individuals with obesity. (Sci Transl Med 13:eabb5280, 2021; https://doi.org/10.1126/scitranslmed.abb5280) Selected by M. Tomic-Canic