Predicting response of tumors to immune checkpoint therapy

Monoclonal antibodies targeting the immune checkpoint proteins programmed cell death protein 1 (PD-1), its ligand PDL-1, and cytotoxic T lymphocyte-associated antigen 4 have been successfully used to extend survival of patients with some solid tumor types. However, it is not yet possible to predict an individual’s response to an immune checkpoint inhibitor. Previous studies showed that a high tumor mutation burden increases generation of neoantigens, increases tumor immunogenicity and may increase the likelihood of benefit from these inhibitors. As not all studies have found a strong relationship between mutational burdens and responses, Miao and colleagues assessed clinically annotated samples and pre-treatment whole-exome sequencing data from 249 cancer patients treated with immune checkpoint inhibitors, revealing that, in addition to mutational burden, genetic driver events, intratumor heterogeneity, mutational signatures, and generation of HLA-restricted neoantigens all affect responses of tumors to immune checkpoint inhibitors. These data support further and larger studies of patient samples to delineate reliable, specific, and clinically relevant predictors of responses to these increasingly utilized immune checkpoint therapies. (Nat Genet. 9:1271-1281, 2018) Selected by I. Brownell

Effects of psoriasis treatment on cardiovascular risk

Psoriasis and other chronic inflammatory diseases are associated with impaired lipoprotein metabolism, insulin resistance, diabetes mellitus, and increased risk of cardiovascular events. Inflammatory markers which predict future cardiovascular events in individuals without chronic inflammatory disease and vascular inflammation are also increased in psoriasis patients. Psoriasis can be treated with the anti-tumor necrosis factor inhibitor adalimumab, and it has been suggested that this may be associated with reduction in cardiovascular events. Phototherapy is also efficacious in psoriasis, and its systemic immunomodulating effects may be limited. In a randomized controlled trial of moderate-to-severe psoriasis patients receiving one of these two therapies, Mehta and colleagues demonstrated that tumor necrosis factor blockade improved skin disease but it did not affect vascular inflammation. However, adalimumab improved markers of inflammation and exerted a detrimental effect on high-density lipoprotein. These findings suggest that other anti-inflammatory drugs may be more useful for treatment of psoriasis and concomitant reduction in cardiovascular morbidity and mortality. (Circ Cardiovasc Imaging 6:e007394, 2018) Selected by M. Udey

Altered endogenous mutation processes underlie SCC in RDEB

Recessive dystrophic epidermolysis bullosa (RDEB) is characterized by skin fragility, trauma-induced blisters, poor healing, and development of early-onset highly malignant cutaneous squamous cell carcinoma (SCC). While mutations in collagen VII cause the disease, the genetic landscapes in the SCC tumors in these patients have not been characterized. Cho and colleagues performed exome sequencing of 27 independent SCC tumors and determined that alterations in the apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) processes dominate the mutation signatures in these tumors, resulting in acquisition of a significant mutation burden in RDEB tumors in childhood despite apparently normal DNA repair. These mutational signatures differed from those observed in UV damage-induced tumors, suggesting that in addition to acquisition of APOBEC-driven mutations, the microenvironment in RDEB patients may favor selection of SCCs. Strong expression of APOBEC3A and associated mutations suggests that inhibition of this factor may offer a tumor prevention strategy in RDEB, an intervention that is much needed. (Sci Transl Med 10.1126/scitranslmed.aas9668, 2018) Selected by L. Bruckner-Tuderman

Reprogrammed mesenchymal cells promote wound healing

In response to injury, keratinocytes migrate into wounds from adjacent epidermis and promote re-epithelialization, a process that is less than efficient in large cutaneous ulcers. Kurita and colleagues reprogramed wound-resident adipose-derived stromal cells via transduction of deltaNp63alpha (DNP63A), CRHL2, MYC, and TFAP2A. Transduced cells formed epithelial-like colonies with features similar to primary keratinocytes in vitro, and epithelial tissues on the surfaces of cutaneous ulcers in mice. Importantly, the reprogrammed cell-generated epithelia displayed appropriate histological features and normal barrier function. Wound healing promoted by reprogrammed stromal cells was enhanced by collagen gel delivery. Reprogramming of wound-resident cells that enables re-epithelialization, relieves spatial constraints of healing, and promote acquisition of functional attributes in regenerated endogenous skin may represent an important non-surgical wound-healing advance. (Nature 561:243-247, 2018) Selected by M. Tonic-Camic and C. Niessen

miRNA classifier for mycosis fungoides

Early mycosis fungoides (MF) has a favorable prognosis, while more advanced disease is associated with associated decreased mortality. At the time of diagnosis, it is difficult to predict which patients with early MF will experience disease progression. Lindahl and colleagues performed a nationwide study of 154 Danish patients with early-stage MF to develop and validate a prognostic classifier comprising 3 miRNAs to discriminate patients with high and low risk of disease progression, based on previous reports of improved prognostic value of clinically based markers by miRNAs for other malignancies. This classifier outperformed clinical prognostic factors, including the cutaneous lymphoma international prognostic index (CLIPi), for prediction of progression-free survival. Patients with a predicted high risk of MF progression exhibited reduced overall survival, supporting use of a more aggressive treatments earlier during the disease course for patients classified as “high risk”. (Blood 10.1182/blood-2017-06-788950, 2017) Selected by I. Brownell