Single-cell epigenomic characterization of T cells

Sequencing of the T cell receptor (TCR) of single cells can be useful for lineage tracing in either the normal immune response or in the context of malignancy. Satpathy and colleagues recently reported the robust and reproducible application of the combination of sequencing of TCRs with an assay for transposase-accessible chromatin with sequencing (T-ATAC-seq) to primary and immortalized T cells. This analysis paired epigenomic identification of cis and trans determinants of cell identity with RNA sequences of TCR genes, allowing mapping of single-cell chromatin states and immune cell phenotypes. This technique proved useful in delineating subtle phenotypes and heterogeneity in T cell populations that appear homogenous via cell surface marker analysis. Additionally, this method was used to identify clonal epigenomic signatures in primary leukemic T cells from patients, and these results may have clinical applications for determining cutaneous T cell lymphoma epigenomic classifications that have been described in association with differential responses to epigenome-targeting therapies, such as histone deacetylase inhibitors. (Nat Med. 24:580-590, 2018) Selected by I. Brownell

PD-1 is a haploinsufficient tumor suppressor

Activating mutations in signaling proteins that regulate TCR pathways have been identified in T cell non-Hodgkin lymphomas (NHL), which are heterogeneous and highly aggressive malignancies that exhibit poor outcomes. Wartewig and colleagues found that enforced oncogenic TCR signaling in lymphocytes in a mouse model yielded a highly proliferative phenotype, which was downregulated after several days, indicating the presence of T cell-inherent tumor suppressor mechanisms. Using a transposon-based screen, these investigators identified the inhibitor receptor programmed death-1 (PD-1) as a haploinsufficient tumor suppressor that often has mono- or bi-allelic deletions in human T cell lymphomas. Deletion or pharmacological inhibition of PD-1 in a mouse model led to development of aggressive lymphomas, supporting the role of this factor as a tumor suppressor. These findings support therapies using downstream signaling (PI3K) inhibitors for these T cell NHLs and suggest caution be used for currently pursued therapies aimed at PD-1 checkpoint blockade or CRISPR-Cas9-mediated gene editing of the PD-1 gene in cancer patients, due to the oncogenic potential of alteration of this locus. (Nature 552:121-125, 2017) Selected by M. Bagot

Conversion of myeloid cells to fibroblasts at wound sites

Injury is known to be a physiological trigger for cell plasticity. Blood-borne myeloid cells home to sites of injury, infiltrate the wound, acquire plasticity, and transdifferentiate into other cell types, such as endothelial cells that support angiogenesis. Sinha and colleagues recently discovered that wound-infiltrating myeloid cells convert directly into fibroblasts at the site of injury. In fact, the vast majority of fibroblasts at the wound site originate from myeloid cells. These infiltrating macrophages respond to extracellular vesicle-delivered cues, including miR-21, which enable the conversion of myeloid cells to fibroblasts necessary for wound healing. Importantly, this conversion was impaired in an experimental mouse model of type 2 diabetes. This novel finding describes myeloid cells as a previously unrecognized source of fibroblast-like cells in granulation tissue following wounding. (Nat Commun. 9:936, 2018) Selected by M. Tomic-Canic

Dynamic Hair Follicle Stem Cell Cultures

Hair follicles (HF) are maintained by a distinct stem cell (SC) population that represents a useful paradigm to study somatic adult SC lineage commitment. However, the inability to maintain HFSCs ex vivo in the absence of other cell types coupled with the inability to precisely manipulate such a system have hampered elucidation of the signaling circuitry governing HFSC homeostasis and the contribution of the niche, which instructs committed progenitors to be reprogrammed to a SC state. To overcome this challenge, Chacon-Martinez and colleagues developed an in vitro culture system that incorporates a 3D extracellular matrix and known soluble factors to allow expansion and long-term maintenance of murine multipotent HFSCs. HFSCs and their immediate progeny were generated de novo by a bidirectional interconversion process in this system, evolving into a dynamic equilibrium between the HFSCs and the non-HFSC progeny. Mechanistically, Sonic hedgehog (Shh) and bone morphogenetic protein (BMP)-mediated signaling are crucial for this equilibrium, suggesting the potential of this system for elucidating physiologically relevant processes involved in SC fate. (EMBO J. 36:151-164, 2017) Selected by M. Detmar

Classification of 10,000 Tumors

Different cancers are characterized by diverse genomic aberrations and alterations in signaling pathways and processes. To further elucidate the molecular factors that distinguish tumors from each other, Hoadley and colleagues performed a comprehensive integrative analysis of ~10,000 samples representing 33 different human cancers from the PanCancer Atlas. Aneuploidy, DNA methylation, mRNA, miRNA, and reverse-phase protein array datasets were used to identify 28 distinct molecular subtypes with cross-platform cluster relationships established via COCA and iCluster analyses. While some types of tumors clustered together, several clusters contained multiple cancer types, most often defined by immune features and copy-number alterations. The existence of these multi-cancer clusters suggests that application of cancer treatments based on molecular alterations in combination with anatomic cancer classification may result in clinical benefit. (Cell 173:291-304, 2018) Selected by I. Brownell