METABOLISM

Seeking protective mitochondria

Cell Metabolism **33**, 1853–1868 (2021)

Adipose tissue expansion in obesity is associated with cardiovascular disease (CVD). Yet obese humans can have better prognosis than lean individuals with CVD—a clinical observation termed ‘the obesity paradox’. Scherer and colleagues find that dysfunctional adipocytes in obese mice produce mitochondria-rich small extracellular vesicles (sEVs) that induce a protective response in cardiomyocytes, which may contribute to the obesity paradox.

The researchers modelled obesity-associated mitochondria dysfunction in mice and in vitro. Adipocytes released more sEVs and cardiomyocytes produced more reactive oxygen species (ROS); both responses were abolished after systemic inhibition of extracellular vesicle production. Analyses of purified adipocyte sEVs showed enrichment of respiration-competent, albeit oxidatively damaged, mitochondrial components. sEV mitochondrial content probably originated from mitochondria-derived vesicles and could be integrated into the cardiac mitochondrial network. Adipocyte sEVs protected mice during acute myocardial infarction, potentially linked to known cardioprotective effects of low ROS. As metabolically unhealthy obese patients showed higher sEV plasma levels than control individuals, with

sEVs containing mitochondrial material, the authors propose that mitochondrially stressed adipocytes may produce sEV-associated mitochondrial particles in humans to protect cardiac health. *MC*

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COVID-19

Force boosts SARS-CoV-2 invasion

Cell Res. <https://doi.org/10.1038/s41422-021-00558-x> (2021)

SARS-CoV-2 invades host cells by using its spike protein to recognize host receptors such as ACE2. A recent study suggests that the mechanical force generated host plasma membrane bending enhances ACE2-dependent SARS-CoV-2 invasion.

The spike protein has S1 and S2 subunits. The S1 subunit contains the receptor-binding domain (RBD) for initial ACE2 recognition; the S2 subunit forms the fusion machinery after S1 and S2 dissociation. Using single-molecule biophysical assays and molecular dynamics simulation, Hu and colleagues found that increasing mechanical force by up to 10 pN prolonged the SARS-CoV-2-RBD association with ACE2 and accelerated S1 and S2 dissociation. Force strengthened SARS binding to ACE2 to a weaker extent, which might explain its reduced contagiousness compared with SARS-CoV-2. A more infectious

SARS-CoV-2 spike variant, D614G, showed stronger ACE2 binding and faster S1 and S2 dissociation under force stimulation compared with wild-type spike protein. Two RBD mutations that impair force-dependent RBD–ACE2 binding compromised pseudovirus infection. The results suggest that force-activated spike–ACE2 recognition facilitates SARS-CoV-2 infection. A SARS-CoV-2-neutralizing, S1/S2-targeting antibody derived from convalescent patients with COVID-19 was shown to impede force-accelerated S1 and S2 detachment.

This study adds mechanical force as a regulator of SARS-CoV-2 host cell entry. *JW*

<https://doi.org/10.1038/s41556-021-00772-0>

CANCER

Uncovering spatial landscapes in colorectal cancer

Cell **18**, 4734–4752 (2021)

Mismatch repair-proficient (MMRp) and repair-deficient (MMRd) colorectal tumours are genetically varied subtypes that manifest distinct immune profiles and responses to immunotherapy, but the underlying mechanisms that account for these distinguishing features remain unclear. Pelka et al. characterize spatially resolved cellular networks and immune landscapes in these two subtypes.

Analysing over 370,000 cells from 35 MMRd and 29 MMRp specimens, the authors found immune cell, endothelial cell and fibroblast remodeling in both subtypes, with increased immune activation in monocytes and macrophages, more cytolytic T and natural killer cells and reduced bone morphogenetic protein (BMP)-expressing fibroblasts in MMRd tumours. Clustering analysis identified 7 and 9 co-varying multicellular hubs in MMRd and MMRp samples, respectively. Hub 3 was implicated in an inflammatory response at the luminal surface that engaged malignant epithelial cells, monocytes, neutrophils and stromal cells. By contrast, hub 6 showed interferon-stimulated genes, MHC class II programs and enriched CXCL10 and CXCL11 expression in myeloid and malignant cells with co-activity of CXCL13⁺ T cell programs.

This study further defines multicellular networks in colorectal cancer. *ZW*

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STEM CELLS

UV downregulates PRC1/2 to drive skin pigmentation

Dev. Cell <https://doi.org/10.1016/j.devcel.2021.08.006> (2021)

Ultraviolet (UV) light promotes skin pigmentation, but how exposure to physiological, low levels of UV activates pigment-producing melanocytes is poorly understood. Li et al. show that melanocyte activation relies on UVB-driven downregulation of gene expression repressors—the Polycomb repressive complex 1 (PRC1) and PRC2 in epidermal stem cells (EpSCs).

The authors found that exposure of mammalian (including human) skin to low-level UVB light coincides with reduced expression and PRC1 and PRC2 activity. In mice, PRC1 or PRC2 downregulation in EpSCs led to increased skin pigmentation, with concomitant activation of melanocytes and their migration to the epidermis.

PRC1–PRC2-repressed genes in EpSCs included secreted factors that, once de-repressed, could act in a paracrine manner to activate melanocytes. Extracellular matrix protein type II collagen was identified as a key factor in this EpSCs–melanocyte communication induced downstream of UVB exposure and was sufficient to drive skin pigmentation.

It will be interesting to explore how this PRC1–PRC2-dependent mechanism could be harnessed to modulate human skin pigmentation and how it may contribute to the development of skin cancers such as melanoma. *PS*

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