## Journal Scan:

### Mitochondrial redox signaling enables repair of injured skeletal muscle cells

Strain and physical trauma to mechanically active cells, such as skeletal muscle myofibers, injures their plasma membranes, and mitochondrial function is required for their repair. We found that mitochondrial function was also needed for plasma membrane repair in myoblasts as well as nonmuscle cells, which depended on mitochondrial uptake of calcium through the mitochondrial calcium uniporter (MCU). Calcium uptake transiently increased the mitochondrial production of reactive oxygen species (ROS), which locally activated the guanosine triphosphatase (GTPase) RhoA, triggering F-actin accumulation at the site of injury and facilitating membrane repair. Blocking mitochondrial calcium uptake or ROS production prevented injury-triggered RhoA activation, actin polymerization, and plasma membrane repair. This repair mechanism was shared between myoblasts, nonmuscle cells, and mature skeletal myofibers. Quenching mitochondrial ROS in myofibers during eccentric exercise ex vivo caused increased damage to myofibers, resulting in a greater loss of muscle force. These results suggest a physiological role for mitochondria in plasma membrane repair in injured cells, a role that highlights a beneficial effect of ROS.

#### Comment

Horn et al., 2017 reported that during membrane injury of muscle and tissue elevates mitochondrial calcium levels and activates mitochondrial ROS signaling which further repairs plasma membrane. Severe membrane injury leads to apoptosis in various cancers, neurodegenerative and infectious diseases. These findings may be applied to develop novel therapeutics by selecting mitochondrial ROS signaling pathway enzymes.

*A. Horn, J H. Van der Meulen, A. Defour, M. Hogarth, S. Chandra Sreetama, A. Reed, L. Scheffer, N S. Chandel, J K. Jaiswa. Mitochondrial redox signaling enables repair of injured skeletal muscle cells. Sci.Signal.2017 Sep 5;10(495). doi: 10.1126/scisignal.aaj1978.*

### Cancer-associated arginine-to-histidine mutationsconfer a gain in pH sensing to mutant proteins

The intracellular pH (pHi) of most cancers is constitutively higher than that of normal cells and enhances proliferation and cell survival. We found that increased pHi enabled the tumorigenic behaviors caused by somatic arginine-to-histidine mutations, which are frequent in cancer and confer pH sensing not seen with wild-type proteins. Experimentally raising the pHi increased the activity of R776H mutant epidermal growth factor receptor (EGFR-R776H), thereby increasing proliferation and causing transformation in fibroblasts. An Arg-to-Gly mutation did not confer these effects. Molecular dynamics simulations of EGFR suggested that decreased protonation of His776 at high pH causes conformational changes in the aC helix that may stabilize the active form of the kinase. An Arg-to- His, but not Arg-to-Lys, mutation in the transcription factor p53 (p53-R273H) decreased its transcriptional activity and attenuated the DNA damage response in fibroblasts and breast cancer cells with high pHi. Lowering pHi attenuated the tumorigenic effects of both EGFR-R776H and p53-R273H. Our data suggest that some somatic mutations may confer a fitness advantage to the higher pHi of cancer cells.

**Online access**
http://svimstpt.ap.nic.in/jcsr/jul-sep17_files/js.pdf

## Comment

White et al., 2017 selected human cancers targets (EGFR and p53) to study the impact of intracellular pH (pHi) on cancer proliferation, cell survival and metastasis. Their findings suggested that Arg>His mutations confer pH-sensitive functions and lowering pHi effectively limited the tumorigenic effects. Further studies are required to alleviate the tumorigenicity by giving vitamin C supplement which may reduce the pHi in wild type and mutant cancer cells.

*K A. White, Diego G. Ruiz, Z A. Szpiech, N B. Strauli, R D. Hernandez, M P.Jacobson, D L. Barber.Cancer-associated arginine-to-histidine mutations confer a gain in pH sensing to mutant proteins. Sci. Signal. 2017 Sep 5; 10(495). doi:10.1126/scisignal.aam9931.*

## Bacterial d-amino acids suppress sinonasal innate immunity through sweet taste receptors in solitary chemosensory cells

In the upper respiratory epithelium, bitter and sweet taste receptors present in solitary chemosensory cells influence antimicrobial innate immune defense responses. Whereas activation of bitter taste receptors (T2Rs) stimulates surrounding epithelial cells to release antimicrobial peptides, activation of the sweet taste receptor (T1R) in the same cells inhibits this response. This mechanism is thought to control the magnitude of antimicrobial peptide release based on the sugar content of airway surface liquid. We hypothesized that d-amino acids, which are produced by various bacteria and activate T1R in taste receptor cells in the mouth, may also activate T1R in the airway. We showed that both the T1R2 and T1R3 subunits of the sweet taste receptor (T1R2/3) were present in the same chemosensory cells of primary human sinonasal epithelial cultures. Respiratory isolates of Staphylococcus species, but not Pseudomonas aeruginosa, produced at least two d-amino acids that activate the sweet taste receptor. In addition to inhibiting P. aeruginosa biofilm formation, d-amino acids derived from Staphylococcus inhibited T2R-mediated signaling and defensin secretion in sinonasal cells by activating T1R2/3. d-Amino acid–mediated activation of T1R2/3 also enhanced epithelial cell death during challenge with Staphylococcus aureus in the presence of the bitter receptor–activating compound denatonium benzoate. These data establish a potential mechanism for interkingdom signaling in the airway mediated by bacterial d-amino acids and the mammalian sweet taste receptor in airway chemosensory cells.

## Comment

Generally during bacterial infection Toll like receptors-4 (TLR-4) recognize the pattern recognition receptors (Lipo polysaccharides) and activates immune system to kill the pathogen. T2R has similar role of TLR-4 and T1R has contrast role to suppress immune response. Lee et al., 2017 studied the effect of D-amino acids produced by bacteria on airway epithelial innate immune responses (T2R and T1R) to understand influence host-pathogen interactions in the upper respiratorytract. Further research is required to enhance immune response during bacterial infection by overcoming the effect of bacterial D-amino acids on T1Rs present on throughout the body of other cell types.

*R J. Lee, B M. Hariri, B Derek. M C Mahon, B Chen, L Doghramji, N D. Adappa, J N. Palmer, D W. Kennedy, P. Jiang, R F. Margolskee, N A. Cohen. Bacterial d-amino acids suppress sinonasal innate immunity through sweet taste receptors in solitary chemosensory cells. Sci.Signal. 2017 Sep 5;10(495). doi: 10.1126/scisignal.aam7703.*

**Reviewers**

**V. Suresh, A. R. Bitla**

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