The mitochondrial stress signaling tunes the immunity, organelle crosstalk, and metabolism in a hostile tumor microenvironment

The response and efficacy to immunotherapy and chemotherapy of cancer is influenced by their status of tumor microenvironment (TME). Hypoxia and elevated Reactive Oxygen Species (ROS) status in the TME lead to adaptive mechanism of cell survival and immunoescape. ROS produced mainly from mitochondria and are the major mediator for tumorigenesis in different aspects, such as invasion, inflammation, and immunoescape. Mitochondria are the major organelles for mitochondrial information processing system (MIPS) in sensing cellular stress, integrating, and signaling the output cell response. Mitochondrial Lon is a stress protein that participates in protein quality control and mitochondrial DNA (mtDNA) stability, and the chaperone activity of Lon cooperates pyrroline-5-carboxylate reductase 1 (PYCR1) and NDUFS8 to induce mitochondrial ROS (mtROS). Here we will show the role of mitochondrial signaling by mtROS, mtDNA, organelle crosstalk via calcium flux, vesicle transportation, and metabolites in the TME. Using RNAseq analysis, we found that Lon induces NF-κB and interferon (IFN) signal pathways in a ROS-dependent manner. The results show that Lon induces mtROS that promote inflammation and metastasis via NF-κB-TGF-β and mtDNA-IFN signaling. Lon also induces the secretion of extracellular vesicles (EVs), which carry mtDNA and PD-L1 and further attenuate the immunity in the TME. We next found that the ER-mitochondria contacts (EMC) trigger Ca^{2+}-dependent mitophagy under hypoxia. Finally, mitochondrial Lon-PYCR1 play an oncogenic role in regulating glutamate/proline level and proline-mediated collagen biosynthesis of fibroblast cells to mediate metastasis and immunosuppression in the TME. Our studies imply an insight into the MIPS under ROS and hypoxia stress and suggest a therapeutic synergy between mitochondria/metabolism-targeting therapy and immunotherapy in cancer.