Mitochondrial signaling tunes malignancy via the metabolism and immunity in the hostile tumor microenvironment

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Mitochondria play the important role in tumorigenesis because of the dysregulation of metabolism and reactive oxygen species (ROS). The tumor microenvironment (TME) is affected by hypoxia and elevated ROS status, which leads to adaptive mechanism of chronic inflammation and immunoescape. ROS signaling is included in the mitochondrial information processing system (MIPS). Mitochondrial chaperone Lon interacts with pyrroline-5-carboxylate reductase 1 (PYCR1) and NDUFS8 to induce mitochondrial ROS (mtROS) that consequently triggers epithelial mesenchymal transition (EMT), metastasis and inflammation in cancer. For example, Lon-mediated mtROS promoted metastasis and inflammation via NF-κB-TGF-β and mitochondrial DNA (mtDNA)-IFN signaling, respectively. However, it remains unclear how Lon-PYCR1 metabolism/metabolites is related to metastasis and immunity in the TME.

Using the metabolomics analysis, the Lon-PYCR1 complex induces proline metabolism that induces collagen biosynthesis in cancer and fibroblast cells in the TME. Proline metabolism plays an oncogenic role in inducing cancer collagen biosynthesis, EMT, and metastasis. In addition, Lon induces the secretion of extracellular vesicles (EVs), which carry mtDNA, PD-L1, and metabolites and further attenuate macrophage, CD8+ T cells, and dendritic cells (DCs) in the TME. Furthermore, Lon-induced secretion of cytokines IL-6/IL-10 and EVs affects the function of DCs, which promotes the regulatory phenotypes of DC (regDCs) via STAT3. The metabolites in the EVs may regulate the regDCs in the TME, which were identified as Phenylalanine, Tryptophan, Tyrosine, and Arginine. In short, the mitochondria play an oncogenic role in regulating mtROS that regulate proline/ glutamate-mediated metabolism and EVs secretion to mediate metastasis and immunosuppression in the TME. Thus, mitochondria and metabolic pathways may act as imaging diagnostic tools and combine with immunotherapy to provide a therapeutic synergy for cancer patients.