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EDITORIAL

Novel paradigms of mitochondrial biology and function: potential clinical significance in the era of precision medicine

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Mitochondria represent one of the key organelles in a cell, wherein they orchestrate multiple functional activities including intracellular energy production, cellular metabolism, growth signaling, cell proliferation and differentiation, as well as cell death. The mitochondrion is a double-layered membranous entity with their own hereditary fingerprint, the mitochondrial DNA (mtDNA). Mitochondrial dysfunction has been recognized to contribute to multitude of diseases, through the occurrence of disorders in respiratory chain, mitochondrial dynamics, mitophagy, metabolism, or specific oncogenic or tumor suppressive alterations in mtDNA. The current issue of the journal has a specific focused coverage on the significance of mitochondrial function and dysfunction, regulation of mitochondrial dynamics, interaction between mitochondria and endoplasmic reticulum (ER), mitochondria-associated cell death, and mitochondrial improvement.

Mitochondria are highly dynamic organelles and can readily alter their morphology by fusion or fission in order to meet cellular responses to various challenges. Kumar and colleagues (Kumar et al. 2021b) reviewed the clinical significance of mitochondrial dynamics in cancer, outlined their roles as critical functional regulators, as well as highlighted their potentials as therapeutic targets and predictive biomarkers in clinical settings. Among the variety of the cellular activities, tumor metastasis involves the ability of the extracellular matrix to regulate oxidative stress, mitochondrial fission, and morphology of cancer cells (Romani et al. 2022). More specifically, the increases in mitochondrial fission alter cellular movement and promote the capacity of cancer cells to undergo accelerated metastasis and acquire enhanced drug resistance. In this regard, the inhibition of mitochondrial fission-related proteins dynamin-related protein 1(Drp1) was suggested to be one of strategies to eradicate disseminated cells (Romani et al. 2022). In addition, mitochondrial dynamics could also regulate inflammation in lung tissues (Chen et al. 2021b). Tumor necrosis factor-α can stimulate the occurrence of mitochondrial dysfunction, including decreased mitochondrial membrane potential and

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increased mitochondrial fission and mitophagy. Regulation of mitochondrial fission can be an effective alternative to improving the severity of non-cancerous diseases. Intriguingly, the application of vitamin D could alleviate the inflammatory response in lung epithelial cells by inhibiting mitochondrial fission and mitophagy (Chen et al. 2021b). The disruption of mitochondrial fission by bisphenol-induced Ca^{2+} influx increases cardiac hypertrophy which can result in compromised cardiac function (Cheng et al. 2021). These findings indicate that the regulation of mitochondrial dynamics can be a novel and previously unrecognized potential approach for discovering and developing next generation of targeted drugs and tailor precision therapies.

Mitophagy is an important process in the mitochondria-associated activities, which allows elimination of damaged mitochondria and maintains mitochondrial function and homeostasis in a cell at a given time. The induction of optineurin-dependent mitophagy can serve as an alternative to unravel new class of targeted therapies, since mitophagy has been unequivocally shown to be a critical mechanism by which mitogen-activated protein kinase (MAPK) inhibitor pemetrexed and cisplatin synergize with PD-1/PD-L1 antibodies in non-small cell lung cancer (Limagne et al. 2022). Mitophagy induces mtDNA release in the cytoplasm, to promote CXCL10 production and $CD8^+$ cell recruitment by activating Toll like receptor-9 and sensitization of cells to immune checkpoint therapy. The disruption of mitophagy process could result in the initiation of mitochondrial dysfunction in various degenerative diseases, such as respiratory chain deficiency and accumulation of pathogenic mtDNA variants. Rapamycin, an inhibitor of mTOR signaling pathway, has been shown to augment mitophagy and in restoring mitochondrial turnover, in order to alleviate the severity of mitochondrial pathology in mammalian muscles (Mito et al. 2022). This is of particular functional and clinical relevance, as the mTOR pathway plays an important role in the regulation of mitophagy and mitochondrial function. A growing school of thought now supports the notion that mitochondrial cargo associated with mitophagy (e.g., RNA, DNA, and proteins) will likely garner increased attention from the scientists in the coming years, to innovate mitophagy-targeted interferences and/or development of novel therapies for improving aging-associated lifespan and other diseases including cancer. Of those regulators, direct inducers of mitophagy could promote key mitophagy-associated pathways including the PINK1/Parkin pathway, increase the survival and functionality of glutamatergic and cholinergic neurons, abrogate amyloid-β and tau pathologies, and improve the life quality of patients with Alzheimer's disease (Xie et al. 2022). The mitochondria-derived vesicles—an ancient pathway of mitochondrial quality control—can also serve as an additional factor for balancing the contents between intramitochondrial and intracellular spatial compartments (Konig et al. 2021). The formation and scission of mitochondria-derived vesicles depend on the activation of mitochondrial fission-related proteins and corresponding receptors. The processes and involved factors, during such vesicles-mediated mitochondrial quality control, are important not only for understanding molecular mechanisms of diseases like neurodegenerative disorders, but also for identifying new biomarkers and therapeutic drug targets.

The interactions between mitochondria and other organelles play decisive roles in transportation of metabolites, exchange of regulatory signals, and maintenance of intracellular homeostasis. The autophagosome and lysosome interaction controls the process of mitophagy by selectively engulfing mitochondria and performing subsequent catabolism. The interaction between mitochondria and endoplasmic reticulum membranes (MAMs) mainly contributes to calcium and lipid regulation by complex mechanisms (Zhang et al. 2021). In the present issue, T. Wang et al (2021a, b) reported that IP3R-Grp75-VDAC1 tethers in MAMs are associated with the mitochondrial calcium uptake from ER, which could induce autophagy in neuronal cells. In addition, mitochondrial dysfunction and metabolism could affect the ER expansion and stress response, inducing the inflammation in autoimmune diseases (Wu et al. 2021). The mitochondria-derived aspartate could regulate GRP78/BiP, a master regulator for the ER stress response, and act upon the tumor necrosis factor (TNF) biogenesis and tissue inflammation (Wu et al. 2021). The mitochondria-ER intercommunication is responsible for many pathophysiological processes and can be another potential alternative source for the identification and development of promising therapeutic targets. For example, irisin could upregulate the mitochondrial ubiquitin ligase MARCH5 located in MAMs and protect cardiomyocytes from ER stress,

reactive oxygen species, and mitochondrial dysfunction in myocardial ischemia–reperfusion injury (Lu et al. 2020).

Mitochondrial dysfunction also plays central roles in the initiation and development of cell death, e.g., apoptosis, ferroptosis, autophagy, and mitophagy. Niu et al (2021) reported acetaminophen-induced hepatocyte ferroptosis and injury through oligomerization of the voltage-dependent anion channel. The mitochondrial dysfunction initiates the process of ferroptosis by impairing energy generation, tricarboxylic acid cycle, fatty acid β-oxidation, and metabolism of ceramide and cardiolipin, which was alleviated by the treatment VDAC oligomerization inhibitor and ferroptosis inhibitor (Niu et al. 2021). Tsvetkov et al (2022) found that dysfunction of mitochondrial respiration and metabolism plays a central role in copper-induced cell death (cuproptosis) subsequent to the binding of copper with lipoylated components of the tricarboxylic acid cycle. This particular study indicates that the mechanism of cuproptosis can be a fascinating approach for developing copper-dependent therapy for diseases. In viral myocarditis, calpain-induced imbalance of mitochondrial dynamics led to cardiomyocyte apoptosis and myocardial dysfunction (Shi et al. 2021). Calpain can cleave and activate calcineurin A to dephosphorylate Drp-1 at Ser637 site and promote its accumulation in the mitochondria, leading to mitochondrial fission and dysfunction. The induction of mitochondria-dependent apoptosis, ferroptosis, or cuproptosis may become one of the newest classes of mechanisms for developing anticancer therapy. Chen et al (2021a) demonstrated that mitochondrial biosynthesis was inhibited by overexpression of hypoxia inducible factor-1α in tamoxifen-resistant breast cancer cells, which was prevented by baicalein to explore a new way to overcome the occurrence of drug resistance.

The regulation of signaling pathways and factors in mitochondrial function is the critical part of molecular mechanisms and also provides a rationale for developing novel therapeutic targets. Hao et al (2021) reported that the activation of transcription factor 4 could suppress the nuclear respiratory factors (NRF1)-mitochondrial transcription factor A (TFAM) signaling pathway in alcohol-induced liver injury. TFAM, a downstream target of NRF1, is a crucial factor in the transcription and stabilization of mtDNA and the maintenance of mitochondrial function, since the inactivation of TFAM caused mitochondrial injury (Hillen et al. 2018). The activation of AKT/IRS-1/GSK-3β accompanied with the inhibition of signal transducer and activator of transcription (STAT) 3/Cyp-D signaling pathway could protect mitochondria from diabetes-induced pancreatic β-cell injury (Wang et al. 2021a). On the contrary, the increase in STAT3 phosphorylation and nuclear accumulation resulting from its binding with DYRK1B can impair mitochondrial bioenergetics through the downregulation of peroxisome proliferator-activated receptor gamma coactivator-1α (Zhuang et al. 2022). The activation of AMPKα2/mTORC1 signaling pathway could stabilize the mitochondrial function and reduce oxidative stress by promoting transcription factor EB nuclear translocation (Che et al. 2021). Selenium sulfide suppressed C-MET/STAT3, AKT/mTOR, and MAPK signaling pathways and triggered Bcl-2/Cyto C/Caspase-mediated intrinsic mitochondrial apoptosis to inhibit the growth of hepatocellular carcinoma (Yang et al. 2021b). Noncoding RNAs regulate mitochondrial function, evidenced by the finding that microRNA-210 targeting glycerol-3 phosphate dehydrogenase could improve cardiac function by controlling mitochondrial metabolism and production of reactive oxygen species in myocardial ischemia–reperfusion injury (Song et al. 2022). Nicotinamide adenine dinucleotide (NAD^+) is an important factor for regulating mitochondrial function through SIRT3-dependent pathway, including oxidative phosphorylation, mitochondrial dynamics, and membrane potential (Yang et al. 2021a). The supplementation of NAD^+ precursor could alleviate the obesity-induced oocyte mitochondrial dysfunction and offspring metabolic abnormalities. In fact, there is a growing list of new regulators of mitochondrial function that are being selected as candidates for drug discovery or supplementations for clinical trials. Kumar et al (2021a) reported a pilot clinical trial of the supplementation combined glycine with N-acetylcysteine for improving the mitochondrial dysfunction and oxidative stress in aged participants, on the basis of deficiency of those regulators in aging. It is obvious that as our understanding of the molecular underpinnings of mitochondrial biology evolve, this will allow as to better appreciate their functional significance as well as allow development of novel therapies for mitochondria-associated diseases.

In conclusion, this special issue of the journal continuously emphasizes the importance of mitochondria in cell biology and toxicology and marks the journal with a highly specific focus. The current issue presents molecular mechanisms and regulators of mitochondrial dynamics and potential therapies for mitochondria-associated cellular and organ dysfunction. These exciting reports clearly highlight that this is merely the tip of the iceberg, and greater opportunities lie ahead, which will allow us to uncover intricate details of mitochondrial biology as well as their roles as disease-specific biomarkers and potential therapeutic targets. This will all be better appreciated in the context of mitochondria on their own, as well as during the interactions between mitochondria and other organelles, delivery of mitochondria-derived vehicles, and development of mitochondria-dependent cell death. These findings also set the stage to also focus on patterns of mitochondrial multi-omic profiles, crosslink between transcriptomic regulations and mitochondrial metabolisms, dynamic networks of inter-organelle transports and signals, and genetic controls between mitochondria and nucleus. Thus, mitochondrial discovery provides new insights for understanding molecular mechanisms of mitochondrial biomedicine—a fascinating start to a new and exciting journey ahead as we usher into the area of precision medicine.

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