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EDITORIAL

Subcellular Organelles and Cellular Molecules: Localization, Detection, Prediction, and Diseases

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1 Subcellular Organelle Dysfunction and Disease Progression

The precise organization of subcellular organelles is important for maintaining cellular homeostasis. Compartmentalization orchestrates metabolic processes, signal transductions, and stress responses. Disturbances in organelles, including the nucleus, mitochondria, lysosomes, and endoplasmic reticulum, can lead to widespread intracellular dysfunction and contribute to diverse pathologies. For example, mitochondrial reactive oxygen species (ROS) exacerbate endoplasmic reticulum (ER) stress, as demonstrated in studies linking ROS-mediated mitochondrial dysfunction to apoptosis in neurodegenerative diseases, cancer, and inflammatory diseases [1–4]. ER stress has also been implicated in cardiac hypertrophy [5], lung fibrosis [6], liver fibrosis [7], and ulcerative colitis [8].

Emerging evidence highlights ferroptosis as a "double-edged sword" in tumor immunity, closely tied to the tumor microenvironment [9]. Mitochondria-targeted therapies, such as Mitoquinone for cigarette smoke-induced airway inflammation [10,11] and Mesaconine for PINK1-dependent mitophagy in doxorubicin-induced cardiotoxicity [12], underscore the therapeutic potential for restoring mitochondrial homeostasis. Additionally, lysosomal impairment obstructs autophagic clearance of damaged organelles, as seen in Parkinson's disease models where defective lysosomal degradation promotes protein aggregation [13–15]. Nanomedicine based approaches, such as autophagy-activating aluminum hydroxide nanovaccines, have been developed to enhance antigen presentation in tumor immunotherapy [16,17]. Conversely, lysosomal autophagy inhibition by hydroxychloroquine [18], nanoparticles [19], or small-molecule kinase modulators [20] demonstrates the dual role of lysosomal pathways in disease modulation.

Despite extensive research, the mechanistic links between organelle dysfunction and disease progression remain only partially elucidated. This special issue brings together recent advances in subcellular biology, focusing on the regulatory mechanisms underlying organelle dysfunction and its pathophysiological implications. The collection includes studies that dissect organelle-specific pathologies, explore cross-compartmental interactions, and suggest novel therapeutic strategies.

2 Key Advances and Contributions

2.1 Epigenetic Regulation in Pediatric Asthma (Wu et al.)

Wu et al. examine the role of the transcription factor RFX5 in dendritic cells and its interaction with histone deacetylase 2 (HDAC2) in pediatric asthma. Their data reveal that allergen exposure upregulates RFX5, which in turn downregulates HDAC2, thereby enhancing MHC II-mediated antigen presentation and driving a Th2-mediated inflammatory response. This finding suggests that the RFX5/HDAC2 axis may represent a novel therapeutic target in asthma. Notably, HDAC2 also regulates STAT3 nuclear translocation [21].

2.2 Noncoding RNA in Ovarian Cancer Chemoresistance (Jiang et al.)

Jiang et al. report that the ultra-conserved noncoding RNA uc.243 plays a critical role in ovarian cancer chemoresistance. Their findings indicate that uc.243 enhances cisplatin resistance by modulating drug efflux transporters ABCB1 and ABCC2 through the inhibition of miR-155 maturation. This study underscores the significance of noncoding RNA regulatory networks in tumor drug resistance and highlights potential targets for overcoming chemoresistance. In recent, antibody-drug conjugate (ADC) resistance is linked to intracellular trafficking defects, lysosomal dysfunction, and ATP-binding cassette (ABC) transporter-mediated efflux [22].

2.3 CKLF1 in Myocardial Ischemia (Feng et al.)

Feng et al. evaluate the expression dynamics of chemokine-like factor 1 (CKLF1) in myocardial infarction. Their results reveal that CKLF1 is elevated in infarcted tissues, particularly in association with macrophages and neutrophils, suggesting a key role in post-infarction inflammatory processes. These findings position CKLF1 as both a biomarker and a therapeutic target in ischemic heart disease. As a member of the CKLF-like MARVEL transmembrane domain-containing family (CMTM), CKLF1 is involved in vesicles-mediated secretion [23].

2.4 Galectin-2 and JAK/STAT3 Signaling in OSCC (Feng and Xiao)

Feng and Xiao investigate the tumor-suppressive role of galectin-2 (LGALS2) in oral squamous cell carcinoma (OSCC). They demonstrate that decreased LGALS2 expression is associated with hyperactivation of the JAK2/STAT3 pathway, leading to enhanced tumor proliferation, migration, and chemoresistance. LGALS2 is thus proposed as a potential biomarker and therapeutic target in OSCC. STAT3 signaling is also implicated in ER stress-mediated hepatic ischemia/reperfusion injury [24]. Furthermore, selenium nanoparticles mitigate septic lung injury by inhibiting STAT3 and enhancing mitochondrial transfer in bone marrow mesenchymal stem cells [25].

2.5 ERRα in Metabolic and Degenerative Disorders (Wang et al.)

Wang et al. present a comprehensive review of estrogen-related receptor alpha (ERRα), a key regulator of cellular metabolism, angiogenesis, and osteogenesis. By linking ERRα to conditions such as osteoporosis, arthritis, and vascular diseases, the review emphasizes its therapeutic potential in addressing metabolic and degenerative disorders. Elevated glucose levels promote glycolysis and cholesterol synthesis via ERRα while suppressing the autophagy-lysosomal pathway in cancer cells [26].

2.6 Melatonin and CK1α in Endocrine Regulation (Wang et al.)

Wang et al. investigate the effect of melatonin on thyroid-stimulating hormone (TSH) regulation via casein kinase 1α (CK1α). Their findings show that melatonin suppresses CK1α activity, leading to activation of the PKC/ERK/CREB pathway and enhanced TSH transcription. This study provides insights into circadian regulation of endocrine function and suggests CK1α as a potential target for thyroid disorders. Pyrvinium inhibits NLRP3 inflammasome and flammatory pyroptosis via the CK1α-β-catenin-NF-κB and CK1α-NRF2-mitochondrial OXPHOS pathways [27].

2.7 Immune-Related lncRNAs in Dilated Cardiomyopathy (Bai et al.)

Bai et al. employ transcriptomic analyses and machine learning to identify immune-related long non-coding RNAs (lncRNAs) associated with dilated cardiomyopathy (DCM). Their work distinguishes two DCM subtypes: one characterized by heightened immune activation and another by suppressed immune responses, underscoring the nucleus as a critical hub for lncRNA-mediated regulation of immune pathways and myocardial remodeling. Notably, the lncRNA NORAD modulates STAT3/STAT1 balance in human cells, influencing innate immune responses [28].

3 Emerging Themes and Future Directions

The interdependence of organelles is evident in pathologies such as ferroptosis, where mitochondrial lipid peroxidation and lysosomal membrane destabilization converge [29–32]. Targeting these pathways, such as activating Nrf2 to mitigate oxidative stress [29,33–36], offers promising therapeutic avenues. Furthermore, non-coding RNAs (e.g., uc.243 in ovarian cancer chemoresistance) and epigenetic modifiers (e.g., METTL3-mediated m6A in cholangiocarcinoma) exemplify nuclear-cytoplasmic crosstalk in disease progression [29].

The studies presented in this issue underscore that organelle dysfunction is rarely an isolated event. Rather, it initiates cross-compartmental cascades that exacerbate disease progression. For example, mitochondrial ROS may amplify ER stress, while lysosomal impairment can obstruct the autophagic clearance of damaged organelles [37]. These interdependencies offer promising translational avenues: targeting specific pathways such as RFX5 in asthma, LGALS2 in OSCC, CKLF1 in myocardial infarction could facilitate precision medicine approaches. In addition, leveraging immune-related lncRNAs in DCM, employing mitochondrial antioxidants in kidney disease [38], stabilizing lysosomes in acute pancreatitis [39], and modulating ferroptosis in cancer [29,31,32] represent promising therapeutic avenues.

Collectively, the insights presented in this issue not only enhance our understanding of organelle dysfunction in a variety of disorders but also pave the way for novel diagnosis and therapeutic strategies, highlighting the need for continued exploration in this evolving field.

4 List of Contributions

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