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ROS in Ca²⁺ signaling and disease-part 2

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1. Introduction

This special issue entitled “**ROS in Ca²⁺ signaling and Disease**” focusses on the impact of ROS on Ca²⁺ signaling, cell function, and disease. A total of eighteen reviews written by experts in the respective areas have been compiled into two volumes. The first volume with reviews on state-of-the-art-methodologies in detection of ROS, ROS effects on intracellular calcium and ROS effects on plasma membrane Ca²⁺ entry channels has already been published (cell calcium, volume Xxx, number xxx). This second volume continues the discussion on ROS effects on cell function and disease, with focus on the mechanisms underlying ROS involvement in disease, new developments in identification of targets and novel therapy approaches. This volume comprises eight reviews that have been divided into two sections.

2. ROS in cell function and disease

The first section starts with a review by Taylor-Clark [1] that discusses the novel role of reactive oxygen species and TRP channels associated with the underlying inflammatory processes in the cough reflex. The cough reflex is evoked by noxious stimuli in the airways which is essential for health. However, it can also be triggered chronically in inflammatory and infectious airway disease. Transient receptor potential (TRP) channels such as ankyrin 1 (TRPA1) and vanilloid 1 (TRPV1) are polymodal receptors expressed on airway nociceptive afferent neurons. The review discusses the data that support key contributions by TRPA1 and TRPV1 channels in cough reflex associated with inflammatory airway disease. The second review by Di et al. [2] focuses on recent developments on the role of ROS-activated Ca²⁺ signaling mechanisms in the regulation of endothelial barrier function. Increased vascular permeability is a common pathogenic feature in many inflammatory diseases including acute lung injury (ALI) and acute respiratory distress syndrome, where lung microvessel endothelia lose their junctional integrity resulting in collapse of the endothelial barrier and accumulation of protein rich edema. Reactive oxygen species generated by neutrophils and other inflammatory cells play an important role in increasing endothelial permeability. The review presents recent concepts on the role of ROS signaling in controlling endothelial permeability with particular focus on ALI. Next, Espinosa et al. [3] present a review entitled “Reactive oxygen species and calcium signals in skeletal muscle: A crosstalk involved in both normal signaling and disease” which describes the molecular mechanisms that

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determine the precise amount of ROS needed for normal cell functioning in skeletal muscle. Excess ROS production (or diminished antioxidant defenses) plays a role in a number of pathological processes in skeletal muscle such as Duchenne muscular dystrophy, aging sarcopenia, and cancer cachexia. In addition, ROS is involved in obesity and muscle insulin resistance. The underlying mechanisms in these instances are discussed. The final review in this first section by Criddle [4] addresses the role of ROS and intracellular Ca^{2+} stores in acute pancreatitis with focus on possible therapeutic strategies. It has been well established that disruption of Ca^{2+} homeostasis leads to severe damage of the pancreas, with premature activation of digestive enzymes, vacuolization and necrotic cell death, features typical of acute pancreatitis. Therefore a fine balance between Ca^{2+} release from internal stores, Ca^{2+} entry and extrusion mechanisms is necessary to avoid injury. The author presents recent studies that demonstrate the alterations in Ca^{2+} handling at the level of mitochondria as a result of excess Ca^{2+} influx that leads to loss of ATP production and necrosis.

3. ROS – techniques, targets, and therapies

The first chapter in this section by Mishra [5] discusses the critical interphase between mitochondrial dynamics and disease. Mitochondria display dynamic behaviors including fusion, division (or fission), directed transport, and targeted destruction (mitophagy). Intriguingly, a common theme is that these behaviors do not function in isolation, but influence one another either directly or indirectly. The second review by El-Hattaba and Scaglia [6] presents new concepts in mitochondrial cytopathy as it relates to diagnosis and treatment of mitochondrial diseases. While most of the proteins in the mitochondria are encoded by the nuclear DNA (nDNA), a very small fraction is encoded by the mitochondrial DNA (mtDNA). Mutations in mtDNA or mitochondria-related nDNA genes can result in mitochondrial dysfunction, which leads to a wide range of cellular perturbations including aberrant Ca^{2+} homeostasis, excessive ROS production, dysregulated apoptosis, and insufficient energy generation. Such impairment of mitochondrial function leads to multi-organ manifestations of mitochondrial diseases including epilepsy, intellectual disability, skeletal and cardiac myopathies, hepatopathies, endocrinopathies, and nephropathies. The review also discusses recent treatment strategies. Next, Magenta et al. [7] discuss oxidative stress, microRNAs, and cytosolic Ca^{2+} homeostasis. Reactive oxygen species increase cytosolic Ca^{2+} concentration and modulate the expression of microRNAs (miRNAs). This review discusses three groups of miRNAs that are associated with changes in ROS and Ca^{2+} . The effects of these miRNAs on cell signaling, cell function and diseases, such as psoriasis and atopic dermatitis, are also discussed.

In the final chapter of this volume Joshi et al. [8] present the current understanding of the ER-mitochondrial axis as it relates to neurodegeneration and possible new developments for therapy that target this organellar interaction. Endoplasmic reticulum (ER) and mitochondrial functions have been shown to be critical events in neurodegenerative diseases. The ER mediates protein folding, maturation, sorting as well acts as Ca^{2+} storage. The unfolded protein response (UPR) is a stress response of the ER that is activated by the accumulation of misfolded proteins within the ER lumen. Although the molecular mechanisms underlying ER stress-induced apoptosis are not completely understood, increasing evidence suggests that ER and mitochondria cooperate to signal cell death.

Similarly, Ca^{2+} -mediated mitochondrial function and dynamics contribute to ATP generation and Ca^{2+} buffering and are central to decision of cell fate. This review summarizes the latest therapeutic strategies that target these essential organelles in the context of neurodegenerative diseases.

4. Conclusion

In recent years, mitochondria have been the focus for studies related to regulation of various aspects of cell physiology. The discovery of the components of mitochondrial Ca^{2+} transport proteins as well as those involved in PTP transition have fuelled these studies. Further, the generation of new sensors that detect mitochondrial function have proved to be critical in the progress of this field. It is now well accepted that the mitochondria play critical roles in the mechanism and development of disease. The role of these organelle as check points in cell fate decisions is a concept that is gaining much attention and propelling studies towards development of mitochondria-directed therapies. Emerging studies demonstrate that mitochondria are dynamic, interacting with intracellular organelles as well as the plasma membrane. Thus, they can respond to local changes within cellular domains. Interactions between mitochondria and the ER have been well demonstrated and correlated with neuronal degradation and disease. Recent studies have provided evidence for dynamic physical interactions between the mitochondrial and ER membranes that underlie the onset of conditions such as ER stress and unfolded protein response that determine neuronal degenerative diseases. Changes in mitochondrial DNA as well as epigenetic changes that alter mitochondrial functions have also been identified and associated with disease onset and progression. Almost all these disease related mitochondrial changes involve effects on mitochondrial ROS and Ca^{2+} . Loss of homeostasis in these two critical factors lead to severe consequences that can lead to cell death.

We believe that the two volumes we have compiled in this special issue of ROS and Ca^{2+} Signaling and Disease provide an insight into the new developments in this area. The reviews are of particular relevance as they pertain to relatively new areas of research which are extremely critical in understanding the underlying mechanisms of several human diseases. Emerging studies are described that provide greater understanding of the exact details and specific mechanisms that underlie the cellular processes that regulate ROS and Ca^{2+} . Further, the reviews also describe in detail the cellular functions/dysfunction that are impacted by ROS and Ca^{2+} . Such information should provide new avenues in the development of treatment strategies for several critical diseases including cancer, pancreatitis, diabetes, autoimmune and neurodegenerative diseases, muscular dystrophy, cardiovascular defects.

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