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Cell signaling and fate through the redox lens

The Hungarian endocrinologist, Hans Selye, was way ahead of his time when he remarked in a landmark publication [1], "*Experiments on rats show that if the organism is severely damaged by acute non-specific nocuous agents such as exposure to cold, surgical injury, production of spinal shock (transcision of the cord), excessive muscular exercise, or intoxications with sublethal doses of diverse drugs (adrenaline, atropine, morphine, formaldehyde, etc.), a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed, and represent rather a response to damage as such.*" The implied 'syndrome' referred to therein was a reference to a generalized phenomenon that, once triggered rippled through the entire organism, irrespective of the insult. Almost two decades later [2], Selye made reference to a similar generalized stress associated with human disease states that could not be specifically linked to the causative organism or agent, and therefore presented a therapeutic challenge for the physicians. Based on our current understanding of cellular redox metabolism, it won't be unreasonable to speculate that an altered redox state could ideally fit the bill as the underlying mechanism for the systemic manifestations. Tremendous advances in technology have made it possible to study redox reactions in cells and their effects on organelles, macromolecules and metabolic pathways, which not only provide a novel insight into cellular and systemic responses, but also have implications for the design of therapies aimed at regulating the redox microenvironment. The long-held dogmatic view of redox stress as an insult, invariably associated with cellular/tissue injury, damage and death, has not only been challenged but also dispelled. Changes of cellular redox milieu have been linked to a plethora of biological responses and processes that dictate cell fate decisions. Such a beautiful landscape of redox-mediated signaling networks, based on effects from regulation of transcription and gene expression to post-translational modification of proteins (elegantly reviewed in Ref. [3]), provides a novel facet to homeostasis and its deregulation, manifesting as pathological states.

This special issue presents a snapshot of the interplay between cellular redox milieu and diverse signaling networks and metabolic pathways. A mixture of original reports and critical reviews provides the reader with a pretty good account of the wide-ranging effects of redox modulations during normal homeostasis and in the pathophysiology of a variety of disease states.

Foo, J and Pervaiz, S. review the interplay between the oncoprotein Ras and cellular redox status and their associated signaling networks during cancer initiation and progression. A brief summary of the advances in the field is presented together with emerging redox-based strategies to target Ras-driven cancers.

Srinivas, U. S. et al. discuss the current knowledge on the effect of ROS in the DNA damage response, and its clinical relevance. Relatedly, in their original work, Liu, T. et al. employed a siRNA library targeting more than six thousand genes and identified Ku80, the DNA repair associated protein product of XRCC5, in the pathophysiology of malignant melanoma. Notably, the group reports that Ku80 activated PDK1 transcription in HIF1-α dependent manner, thus highlighting a potentially targetable node in the therapeutic management of melanoma treatment.

Li, H.S. et al. report findings linking hypoxia and exposure to H_2O_2 to the translocation of HIF-1α to the mitochondria, which prevented oxidative stress induced-apoptosis via transcription-independent mechanism. On a somewhat related theme, Worley, B.L. et al. link high GPx3 expression with poor patient survival and advanced stage disease in ovarian cancer. Notably, GPx3 is necessary to guard against exogenous oxidant insults via its ability to scavenge H_2O_2.

Ren, Y. and Shen, H-M. critically review the link between cellular energy supply and demand and redox metabolism, specifically focusing on glucose metabolism and AMPK activity in the setting of carcinogenesis and its therapeutic management. Complementing that, Lee, M. et al. discuss the metabolic switch to OXPHOS in therapy-resistant oncogene-addicted cancers and its relationship to STAT3 activation. They also underscore the need to identify novel OXPHOS inhibitors as well as the simultaneous targeting of these two effector pathways in refractory cancers. Corroborating that, Hirpara, J. et al. present experimental evidence to demonstrate the crosstalk between STAT3 activation and OXPHOS. This original study shows that the metabolic switch to mitochondrial OXPHOS is a key driver of targeted drug resistance in oncogene-addicted cancers. They also report the identification of a novel complex I targeting OXPHOS inhibitor, which shows promise in the clinical setting.

Pal, A. et al. delve into the connection between intracellular redox metabolism and rhabdomyosarcoma (RMS), the most common soft tissue sarcoma that accounts for 5–8% of malignant tumours in children and adolescents. This review discusses recent developments highlighting key pathways, in particular the crosstalk between cellular redox status and epigenetic alterations that could form the basis for developing novel molecularly targeted therapies in RMS. Emphasizing the importance of redox milieu in epigenetics, Li, B.W. et al. review the literature on the role that intracellular ROS plays in the metabolic plasticity of cancer stem cells (CSC), more importantly the redox-dependent changes in the CSC epigenome that could bestow upon them a survival advantage in the harsh tumor microenvironment.

Wong, S. C. et al. discuss the recent findings linking inflammation and cancer and the dichotomous role of immune cell infiltration and cytokines in shaping the tumor microenvironment. By implication, a better understanding of the multifaceted roles of various immune cell types holds tremendous promise for the development of innovative immune targeted cancer therapies. Similarly, Doridot, L. et al. discuss the crosstalk between autoimmunity and redox metabolism,

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particularly from the standpoint of inflammatory and fibrotic cutaneous and visceral manifestations of systemic sclerosis. They also summarize novel redox targeting strategies for the therapeutic management of systemic sclerosis. In a different though related context Shi, J. et al. present the results of an interesting study linking advanced oxidation protein products (AOPP) to intestinal epithelial cell cycle (IEC) arrest in the pathogenesis of Crohn's disease. Interestingly, plasma AOPP levels were elevated in active CD patients and correlated with IEC G1 phase arrest. These data argue in support of targeting AOPPs as a novel approach to managing Crohn's disease.

Pohl, S et al. analyzed mRNA co-expression and methylation patterns, as well as performed survival analysis and gene set enrichment analysis, on gastrointestinal cancer data sets to decipher the link between heat shock proteins (HSP) activity and cellular redox status. Specific combinatorial co-expression patterns were shown to significantly alter patient survival outcomes, thus making the case for targeting HSPs as a potential therapeutic strategy for gastrointestinal cancers. Sticking with the stress sensing and response theme, Zhang, Z. et al. provide a redox perspective on the regulation of unfolded protein response (UPR) and the underlying redox modifications of UPR sensors/transducers in the ER in the context of cell fate.

Haberle, I. B. and Tome, M.E. provide an excellent account of the chemistry, biology and clinical potential of superoxide dismutase (SOD) mimetics, specifically focusing on Mn porphyrins. These compounds are under clinical evaluation as radioprotectors of normal tissue during chemotherapy. The authors summarize data indicating the diverse reactions of Mn porphyrins *in vivo*, which form the basis for the observed biological effects and the potential therapeutic use even in pathological states that are not associated with aberrant SOD activity. Continuing along similar lines, MacKinney, A. et al. describe the potential therapeutic application of redox-active Mn porphyrin in sickle cell disease. Their work provides novel insights into the deleterious cycle created by NOX-dependent ROS and MAPK activation within RBCs upon hypoxia/reoxygenation leading to vascular occlusion, which could be disrupted by Mn porphyrins.

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