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Pharmacological modulation of redox signaling pathways in disease

Free radicals and antioxidants have always been a hot topic in the field of translational pharmacology. Indeed, one of the earliest events in the defense against infection linked to the field of free radicals is the "oxidative burst" by different immune players. Inasmuch, new, but also old drugs acting on free radical generation and detoxification, are becoming powerful tools in the treatment of different chronic diseases, such as arthritis, cardiovascular, neurological disorders or even cancer. Therefore, the aim of this special edition is to bring knowledge on radicals and antioxidants to the pharmacological and other biomedical and clinical communities.

In this special issue, Mullen et al. [1] provide new insights in this field focusing on the role of oxidative changes in cell physiology and particularly in the field of the oxidoreductase enzymes activities in the context of the redox regulation of immunity. Nowadays it seems that therapeutic interventions in inflammatory diseases addressing alterations in the redox environment is probably more successful than the simple inhibition of reactive oxygen species (ROS) production.

In this regard, immunity plays a key role in the development of cardiovascular diseases (CVD). Among them, coronary heart disease and stroke, are the main causes of mortality in western countries [2], and atherosclerosis is the principal contributor to the pathogenesis of myocardial and cerebral ischemic disorders. In fact, changes in the style of life and therapeutic targets and strategies to prevent or to halt classical or non-classical cardiovascular risk factors are required. Of note, most of these cardiovascular risk factors cause endothelial dysfunction, a prothrombotic and proinflammatory state of the endothelium that precedes atherogenic events [3], which is closely associated with oxidant stress and vascular inflammation. The current knowledge on endothelial dysfunction, adverse redox signaling and oxidative stress have been addressed by Daiber & Chlopicki [4] in this issue. They have revisited CVD therapies and their link to endothelial dysfunction and oxidative stress as well as novel strategies for redox-based CVD therapies. In line with this topic, Piqueras & Sanz [5] in this issue, have complied the current knowledge on the pro-inflammatory activity of angiotensin-II (Ang-II), the main effector peptide hormone of the renin-angiotensin system. Given that Ang-II is intimately involved in the development of vascular lesions in CVD through the activation of different immune cells, the role of this peptide in the leukocyte recruitment cascade and the effects of drugs that impair Ang-II action in different CVD have been compiled.

Similarly, chronic kidney disease (CKD) is a high risk factor for developing CVD and infection. Indeed, CVD is often associated with vascular calcification, which has been attributed to hyperphosphatemia that could be initiated in mitochondria, inducing apoptosis, and accelerated by ROS. The production of oxygenated free radicals is linked to intracellular ferrous iron. Thus, Nakanishi et al. [6] in this issue, unravel different approaches to maintain adequate serum phosphate levels and minimize intracellular iron accumulation to diminish CKD complications.

Nrf2 (NFE2L2 – nuclear factor (erythroid-derived 2)-like 2) regulates the transcription of genes involved in redox balance, metabolism and inflammation. Nrf2 activation represents an adaptive mechanism to maintain homeostasis. This transcription factor is regulated by mechanisms such as the interaction with the redox-sensitive protein Keap1 (Kelch-like ECH- associated protein 1). An updated review of the structure, regulation and functions of the Nrf2/Keap1 axis is presented by Kopacz et al. [7] in this issue with a focus on the role of Keap1 and Nrf2 in the maintenance of cellular homeostasis. Activation of Nrf2 results in the synthesis of heme oxygenase-1 (HO-1) which catalyzes the formation of metabolites with antioxidant, cytoprotective and immunomodulatory properties. Recent translational studies in rodents and human liver transplant patients have provided novel insights into HO-1 mediated cytoprotection against sterile hepatic inflammation. Hirao et al. [8] in this issue have summarized the current knowledge on HO-1 molecular signaling and discuss their future therapeutic potential to mitigate ischemia-reperfusion injury in orthotopic liver transplantation. As Nrf2/HO-1 can regulate specific pathways involved in the pathophysiology of articular diseases, Alcaraz & Ferrándiz [9] in this issue discuss the current evidence supporting the interest of Nrf2 and HO-1 as therapeutic targets in conditions such as rheumatoid arthritis and osteoarthritis. Different pharmacological strategies focused on this pathway may complement other approaches for the prevention or treatment of a number of diseases leading to pain, functional limitation and physical disability.

On the other hand, the regulation of lysosomal dependent cell death can provide novel treatment strategies for autoimmune deficiency and diseases such as cancer or neurodegenerative conditions. In this respect, Eftekharpour et al. [10] in this issue analyze experimental and therapeutic pharmacological interventions targeting lysosomal structure and activation, and discuss key research points which may contribute to understand the role of lysosomes in health and disease.

Recent research has revealed the role of 4-hydroxy-2-nonenal (4-HNE) in mediating redox signaling during physiological and pathological processes. Jaganjac et al. [11] in this issue discuss the interest of 4-HNE regulation for stress- and age-associated diseases. In addition, its protein adducts are relevant bioactive markers which would allow the monitoring of specific pathophysiological processes. The potential of this approach has been explored to prevent the onset and progression of disease within an integrative medicine approach.

The potent metastasis suppressor N-myc downstream regulated gene-1 (NDRG1) inhibits epithelial-mesenchymal transition, cell migration and angiogenesis by modulation of different oncogenes. Pharmacological targeting of NDRG1 signaling represents a promising therapeutic strategy in cancer. Park et al. [12] in this issue summarize

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major issues with regard to the regulation of NDRG1 in cancer cells including the mechanisms underlying its induction and their pleiotropic roles. Interestingly, NDRG1 plays a critical role in mediating anti-tumor activity of novel anti-cancer therapeutics, di-2-pyridylketone thiosemicarbazones.

Oxidative stress contributes to the most prevalent diseases and offers a wide range of opportunities for pharmacological modulation, as discussed by experts working in the field from different approaches. This special issue provides novel insights into the pathophysiology of diseases in which free radicals play a key role and how different therapeutic tools can modulate disease onset and/or progression acting at different redox signaling pathways.

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