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Redox pathways in cancer drug discovery

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Editorial Overview

Various forms of sulfur have unique properties and these contribute in making it a critical element in support of biological life forms. Its variable valency states and flexible nucleophilic properties permit a number of lower phyla to use sulfur as a metabolism mainstay. In higher eukaryotes, including mammals, sulfur metabolism controls redox balance, a critical facilitator of the use of endogenous oxygen to provide energy. Thiol:disulfide balance underlies basic cellular homeostasis and also serves to protect cells from exogenous reactive oxygen and nitrogen species (ROS/RNS). The complexity and functional redundancy of these pathways continue to provide a fertile area for ongoing research and form the framework for the contributions in this COP issue.

The “free radical theory” of aging and degenerative diseases has been applied to a broad range of human pathologies. Oxidative stress results in reactive oxygen and nitrogen species (ROS/RNS) and these are known to influence a multiplicity of disease states that include, general organ-system aging, atherosclerosis, neurodegenerative syndromes, hypertension, asthma, chronic obstructive pulmonary disease (COPD) and cancer. Oxidative stresses cause the cell to respond uniquely and are inherently difficult to assay because normal metabolic processes generate potentially deleterious ROS/RNS, oxidative damage and inflammation, which increase with age and probably contribute to senescence. Oxidative stress and inflammation biomarkers, as well as anti-oxidants and anti-inflammatory factors, need to be measured concurrently, since the metabolic processes overlap and the lack of balance between these stressors and protectors may lead to development or progression of disease. At the cellular level, thiol:disulfide balance influences a multitude of events including, protein folding, detoxification, membrane structure and transporter function. Thiol homeostasis is a function of many de novo and salvage reactions and the enzymes that control these make plausible targets for therapeutic intervention strategies. In turn, there are also major opportunities in translational studies in these areas. In particular, biomarkers for assessing the acute, and perhaps more importantly, chronic exposure to ROS will be of great value in monitoring patients and populations exposed to these stresses. Furthermore, the connection of oxidants with a number of redox sensitive proteins creates a number of opportunities to dissect out critical cell signaling pathways. Interestingly, a number of linkage points are emerging where sulfur and phosphorus mediated signaling events may converge. For example, the post-translational addition of glutathione to target cysteine residues can regulate the activity of phosphatases, which in turn can reverse the phosphorylating activity of a variety of kinases.

Our contributors have provided succinct reviews representing how some of the nodal points within redox pathways can be targeted for possible drug therapies. For example, work from the Herzenberg group describes the value of n-acetyl cysteine in treatment of a variety of disorders. Huber and Parzefall extend this principle in their discussion of the role of sulfur containing natural products can influence chemoprevention of cancer. Pharmacogenetics of Phase II metabolism genes, particularly glutathione S-transferases can influence response to cancer therapies (Dr Ali-Osman). Thioredoxins (Drs Powis and Kirkpatrick) and peroxiredoxins (Dr. Neumann) are emergent targets for drug design and development. In addition, the growing body of literature on the role of thiol mediated signaling has been summarized in two complementary reviews from the laboratories of Drs. Ghezzi and Mieyal. These illustrate how reversible S-glutathionylation can influence numerous important regulatory pathways and might provide linkage to kinase/phosphatase signaling pathways. Emerging research from the Zunino laboratory has implicated g-glutamyl transpeptidase in hydrogen peroxide mediated signaling providing a further piece of the puzzle with respect to thiols and cell signaling events.

We are indebted to the authors of the articles in this issue. Without their admirable abilities to conceptualize a complex field, conveying the subject matter in a clear fashion would have been challenging.

Biography

Kenneth Tew is Chairman Dept. of Cell and Molecular Pharmacology and Experimental Therapeutics and John C. West Chair in Cancer Research. His main interests are in anticancer drug discovery/development, drug resistance and redox pathways, with particular focus glutathione pathways.