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Oxidative Medicine and Cellular Longevity

Special Issue on

NRF2 as an Emerging Therapeutic Target

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The transcription factor nuclear factor erythroid 2 related factor 2 (NRF2) is the master regulator of the basal and inducible expression of a large network of cytoprotective genes. As a result, NRF2 plays a key role in antagonising a range of pathological insults including reactive oxygen species and toxic xenobiotics. Consistent with this, dysregulation of NRF2 signalling is associated with an increased susceptibility to and/or accelerated progression of a range of experimental diseases in mice.

In recent years, NRF2 has shown promise as a novel therapeutic target in human diseases, particularly those with underlying oxidative and inflammatory stress components. Indeed, several NRF2 inducers have recently entered the clinic. Key examples include dimethyl fumarate (trade name Tecfidera), recently licensed in the US and Europe for the treatment of relapsing remitting multiple sclerosis; bardoxolone methyl and other triterpenoid derivatives, currently in clinical trials as novel therapies in a range of diseases; and Sulforadex, a synthetic version of the natural NRF2 inducer sulforaphane that will imminently be tested in a phase II trial for its ability to improve recovery after subarachnoid haemorrhage. A unifying chemical feature of the vast majority of NRF2 inducers is reactivity towards cysteine sulfhydryl, and it has been suggested that the modification of cysteine residues in the redox-sensitive repressor Kelch-like ECH-associated protein 1 (KEAP1) at least partly underlies the ability of the above compounds to stimulate NRF2 signalling.

Evidence that mutations in the NRF2 or KEAP1 genes that cause constitutive NRF2 activation are frequent occurrences in non-small-cell lung cancer and other common malignancies is emerging. As hyperactive NRF2 signalling has been linked to cancer cell proliferation and resistance to chemo- and radiotherapies, there is an increasing interest in the value of NRF2 inhibitors as novel treatments in the subsets of cancer patients, although relatively few such compounds have been described to date.

At present, the benefits and risks of modulating NRF2 pathway activity in patients are not fully understood, and it is known that NRF2 and KEAP1 may cross-talk with other signalling pathways, such as NF-$\varkappa$B. Indeed, many NRF2 inducers directly influence the activities of these pathways, and thus it will be important to establish the true therapeutic value of modulating NRF2 per se in man. The goal of the special issue is to publish high-quality research communications, as well as review articles, in which the value of NRF2 as a novel therapeutic target is further defined.

Potential topics include but are not limited to the following:

- Physiological functions of NRF2 and KEAP1
- Regulatory mechanisms within the NRF2 pathway
- Influence of NRF2 on disease susceptibility and/or progression
- Pharmacological targeting of NRF2 in the context of disease
- Crosstalk between NRF2/KEAP1 and other signalling pathways
- Contribution of NRF2, relative to other signalling pathways, to the beneficial effects of synthetic and natural agents that repress oxidative stress and/or inflammation

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