Introduction to Special Issue on “Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases”

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NRF2 (Nuclear factor erythroid 2-related factor 2) is a crucial transcription factor for regulation of cellular homeostatic functions [1]. We will soon celebrate the thirtieth anniversary of its discovery [2]. Its mode of action involves heterodimerization with other bZip transcription factors, of which the small MAF proteins F, G and K are the best characterized [3]. As illustrated in Fig. 1, the heterodimer activates the expression of genes that contain a specific enhancer, termed Antioxidant Response Element (ARE). These genes participate in protection against oxidative, inflammatory, metabolic or proteotoxic stress [4]. Given the tremendous impact of this protein in physiology and pathology, it is not surprising that it has attracted a great deal of attention by the biomedical community. Moreover, contrary to most transcription factors, NRF2 is amenable to pharmacological activation by selectively inhibiting its degradation. The main repressor of NRF2 is the druggable E3 ligase adapter Kelch-likeECH-associated protein1 (KEAP1). Under unstressed conditions, KEAP1 targets NRF2 for Rbx1/Cullin 3-dependent ubiquitination and proteasomal degradation, but this repressor activity is blocked when specific cysteine residues in this protein are oxidized, or form adducts with electrophilic molecules. A much less explored mechanism of NRF2 repression is its glycogen synthase kinase (GSK-3)-mediated phosphorylation, which creates a phosphorylation-dependent site for interaction with the E3-ligase adapter β-transducin repeat-containing protein (β-TrCP). Binding of beta-TrCP to GSK-3-phosphorylated NRF2 leads to Rbx1/Cullin1-mediated ubiquitination and proteasomal degradation of NRF2. Therefore, KEAP1 and β-TrCP complement each other in NRF2 regulation under oxidative stress and cell signaling, respectively.

A Special Issue published in Free Radical Biology & Medicine in 2016 highlighted some of the most important roles of NRF2 in physiology and pathology, as well as the regulation of its activity at several levels [5]. The current 2022 follow-up Special Issue is hosted by the European network CA20121 focused on "Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases (BenBedPhar)" (https://e-services.cost.eu/action/CA20121). Its four-year mission is to extend and share basic, pharmacological, and clinical knowledge about NRF2, and to integrate it into the stream of social, clinical and economic sectors with capacity for translation into innovative therapeutics for several non-communicable diseases. BenBedPhar currently includes more than 250 researchers from 33 countries.

This Special Issue contains nineteen invited review and primary research articles, covering basic concepts and state of the art knowledge of the role of NRF2 in physiology and pathology as well as its pharmacological regulation. The paper by Kopacz et al. [6] draws attention to essential issues for newcomers to the field, highlighting overlooked facts and clarifying potential misconceptions such as the unusual mobility of the NRF2 protein in SDS-PAGE, the need for the use of validated anti-NRF2 antibodies, the differences between the currently available Nrf2-knockout mice, the mechanistic interaction of the NRF2/KEAP1 pair, etc. A new and very promising tool for the study of NRF2 activation at the single cell level is reported in the experimental paper by Kitamura et al. [7], which describes a Neh2-Cre:tdTomato reporter mouse.

Current knowledge about the role of NRF2 in mitochondrial function and structure is reviewed in Ref. [8], with a focus on energy production, reactive oxygen species generation, calcium signaling, and cell death. Moreover, in the context of energy metabolism, a very exciting link between NRF2 and AMP-activated kinase (AMPK) is described by Petsouki et al. [9]. Regarding regulation of NRF2 by kinase cascades, another experimental paper is provided by Ishii et al. [10], which proposes that Cav1 serves as a hub for the control of H_2O_2-mediated phosphorylation of NRF2 by p38/nSMase2/ceramide signaling. Boorman et al. [11] gather current evidence about a role of NRF2 in regulation the neurogenic niches from early neural lineage specification and neural stem cell regulation to neuronal fate commitment and differentiation.

Accumulating evidence indicates a link between NRF2 and many chronic diseases. Moreover, pharmacological inhibition of KEAP1, leading to NRF2 activation, is providing proof of concept that NRF2 activation might be beneficial in many non-communicable diseases. Thus, Kopàz et al. [12] report that NRF2 deficiency leads to impairment of the gastrointestinal system in young females in connection with ERβ signaling. Current knowledge about the participation of NRF2 in physiology, pathophysiology and disease of the thyroid gland is analyzed by Chartoumpekis et al. [13]. A comprehensive review of the role of NRF2 in protection against non-alcoholic steatohepatitis and its potential use as a pharmacological target is provided in Batish et al. [14]. Another experimental paper by Gou et al. [15] shows that loss of NRF2 activity in periodontal ligament cells during bacterial and hypoxia events is tightly linked with periodontitis. In the context of neurodegenerative disease, the experimental paper by Anandhan et al. [16] reports that α-syn overexpression and NRF2 suppression lead to enhanced neuronal ferroptotic cell death in a model of Parkinson's disease. Manda et al. [17] discuss the involvement of NRF2 in rheumatoid arthritis according to findings from human transcriptomics and mouse models, and also consider a potential drawback of NRF2-based therapy due to increasing anti-rheumatic drugs efflux. The dark side of NRF2 hyperactivation is most evident in cancer because NRF2 makes tumor cells resistant to chemo-, immuno-, and radiotherapy, highlighting the need for NRF2 inhibitors. The review by Srivastava et al. [18] discusses novel

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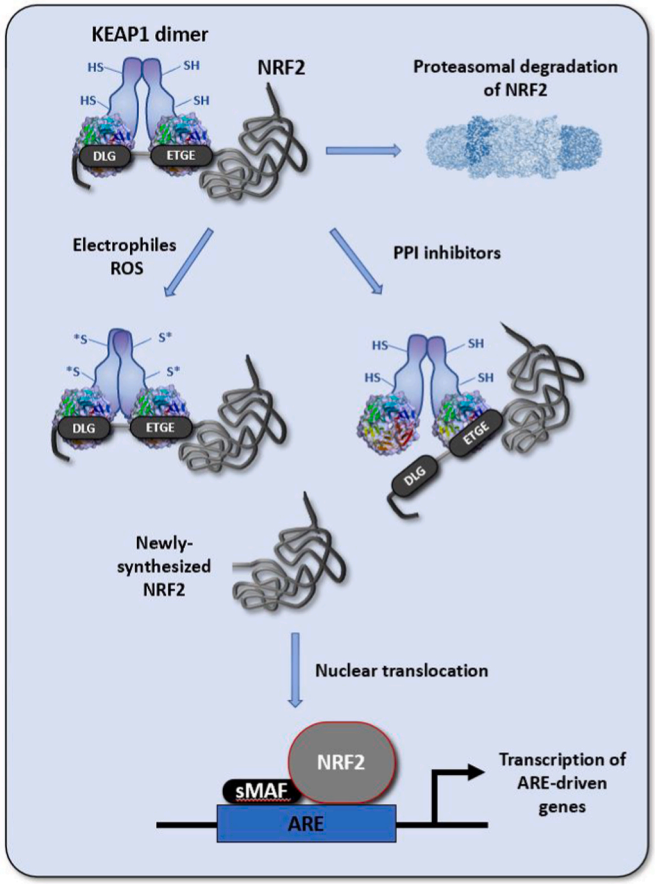

Fig. 1. Regulation of NRF2 by KEAP1. Dimeric KEAP1 binds to the 'DLG' and 'ETGE' motifs of NRF2 and targets the transcription factor for ubiquitination and proteasomal degradation. Electrophiles and reactive oxygen species (ROS) modify specific cysteines in KEAP1, disabling its substrate adapter function without disrupting the KEAP1–NRF2 interaction. By contrast, KEAP1–NRF2 protein-protein interaction (PPI) inhibitors disrupt the DLG–KEAP1 interaction preferentially to the ETGE–KEAP1 interaction. Consequently, newly-synthesized NRF2 accumulates, translocates to the nucleus, forms a heterodimer with a small MAF transcription factor, and the heterodimer activates the transcription of genes that contain antioxidant response elements (AREs) in their regulatory regions. SH = reduced cysteine; S* = modified cysteine.

approaches to inhibit NRF2 by enhancing with molecular glues its interaction with the main repressors KEAP1 and β-TrCP.

Three studies deal with significant challenges to mankind caused by environmental factors. Thus, Bayo-Jiménez et al. [19] discuss the impact of noise and air pollution on the circadian rhythm and the interactions of NRF2 and its target heme oxygense-1 (HO-1) with the circadian clock. Kahremany et al. [20] comment on the damage to skin by ultraviolet radiation and how NRF2 activators might protect against cutaneous photodamage and photodermatoses. In a similar context, Wakamori et al. [21] provide experimental evidence that pharmacological activation of NRF2 protects against radiation-induced oral mucositis via antioxidation and keratin layer thickening.

Most of these articles address the pharmacological regulation of NRF2 with a wide armamentarium of small molecule activators. Moreover, we also present three novel NRF2 activators. The paper by Yao et al. [22] uses panaxatriol saponin to ameliorate myocardial infarction-induced cardiac fibrosis in a NRF2/KEAP1 dependent manner. Yilmaz et al. [23] report that cycloastragenol activates telomerase in a NRF2-dependent manner, suggesting an anti-ageing effect. Finally, Moreno et al. [24], show that a biotinylated derivative of an acetylenic tricyclic bis(cyanoenone), but not its parent compound, exhibits bifunctional effects, activating NRF2 and inhibiting BACH1, a transcriptional repressor of a subset of NRF2-target genes.

The longer-term objective of Free Radical Biology & Medicine is to provide readers with informed updates of this important research field every 4 years.

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