NRF2 in COST Action 20121

Our quarterly newsletter attempts to provide our latest news and also aims at becoming a forum for analysis of relevant topics on the field of NRF2, and provide comments to some of the most relevant articles published during the quarter. Previous newsletters can be accessed at:
https://benbedphar.org/our-first-newsletter/
https://benbedphar.org/issue-2-abril-2022/
https://benbedphar.org/issue-3-july-2022/

This October issue links with the end of the first period of our COST Action, and provides a perfect opportunity to make some reflections and to have a critical analysis of our activities. In my opinion, our most important success so far is that, after just one year of activity, we are over 230 participants from 33 countries all over Europe. Among them, 67% are women and almost one third are young researchers. Looking back to the beginning of the Action, I think that the COST tools have significantly help to disseminate important concepts about the mechanistic regulation of NRF2, its participation in chronic diseases, and the multiple possibilities of pharmacological regulation.
Many other achievements were also reported during our last Management Committee meeting that was held in mixed format at the Victor Babes National Institute of Pathology, in Bucharest (Romania) in October 13. These achievements included our previous newsletters, webinars, meetings, etc. and an unexpectedly high number of collaborative reviews and some experimental papers published in our guest edited special issues. All these activities have paved the way to strengthen collaborative activities and the MC members encouraged BenBedPhar participants to look for ways to make use of COST tools to increase collaborative research, including STSMs, publication of joint research articles and preparation of grant application to private and public calls. In this regard, at least three grants have been awarded to collaborative projects among BenBedPhar participants.

At the verge of ending the first grant period, we had our scientific meeting, in October 13-15, at the Victor Babes National Institute of Pathology, in Bucharest, with title "Bench to Bedside for Pharmacological regulation of NRF2 in no communicable diseases". We gathered over 60 participants with 35 oral communications and a few poster presentations. This time the meeting was focused to enhance interactions among participants with the end goal of establishing collaborative agreements. You can access the programme and the abstract book at https://benbedphar.org/3rd-benbedphar-scientific-meeting/.

We are now facing the second grant period with lots of illusion and big expectations to strengthen the research interactions among the EU and international researchers interested in this transcription factor that some days we hate and most days we love. A day will soon come in which NRF2 research will conclusively be translated to the clinic and provide a therapeutic option for many chronic diseases that so badly impact our wellbeing.

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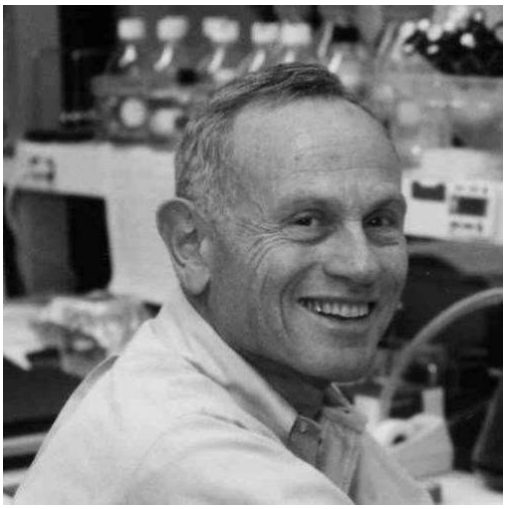
In Memoriam of Prof. Michael Sporn



On September 29, 2022, the NRF2 field lost one of its giant figures, Dr Michael B. Sporn, an internationally recognized cancer researcher, who passed away at his home in Tunbridge, Vermont (USA) at the age of 89. Dr. Sporn's scientific life was dedicated to developing new approaches for the prevention and treatment of cancer and chronic disease. He was the founding father of the concept of cancer chemoprevention defined as *"the use of pharmacologic or natural agents that inhibit the development of invasive cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred"*. Highlighting the importance of cancer prevention and challenging the existing dogma for cancer treatment based on treating end-stage disease, Dr. Sporn stated in his "Plea for Prevention" in a 1996 issue of *Scientific American*: "*An 'obsession' with curing advanced disease has blinded cancer researchers to the promise of prevention… The concept that people with cancer are healthy until a doctor tells them that they've got an invasive lesion makes no sense at all*."

Dr Sporn graduated from Harvard and subsequently from the University of Rochester School of Medicine. He then worked at the National Cancer Institute (NCI) where he became Chief of the Lung Cancer Branch and later Chief of the Laboratory of Chemoprevention. During that time, he made ground-breaking discoveries on retinoids and Transforming Growth Factor β (TGFβ). In 1995, he became Professor of Pharmacology and Medicine at Dartmouth Medical School where he pioneered

the development of the cyanoenone semi-synthetic triterpenoids as extremely potent anti-inflammatory agents and NRF2 activators. To date, this class of compounds represents the most potent NRF2 activators known, which have shown protective effects in numerous models of human disease. In 2018, Dr Sporn founded the company Triterpenoid Therapeutics, Inc. to develop and commercialize new compounds for cancer prevention and treatment.

For his outstanding scientific achievements, Dr Sporn received several prestigious awards, including the inaugural American Association for Cancer Research (AACR) and the Cancer Research Foundation of America Award for Excellence in Cancer Prevention Research, a Medal of Honor from the American Cancer Society, the Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research, the Lila Gruber Award for Cancer Research from the American Academy of Dermatology, the Komen Brinker Award for Scientific Distinction. In 2004, he was named by the NCI as its first Eminent Scholar. In 2007, he was a member of the Cancer Advisory Board of the President of the United States.

Dr Sporn was a passionate scientist and an enthusiastic mentor and collaborator. He will be greatly missed by the scientific community for his gigantic intellect, enormous contributions and commitment to science, entrepreneurial spirit, and generosity in sharing his ideas, discoveries, and materials, and in supporting the next generation of cancer researchers.

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Comments from the Working groups

Role of inflammation and redox status on doxorubicin-induced cardiotoxicity in infant and adult CD-1 male mice

Doxorubicin (DOX) is a topoisomerase II inhibitor commonly used in the treatment of several types of cancer. Despite its efficacy, DOX can potentially cause fatal adverse effects, like cardiotoxicity. This work aimed to assess the role of inflammation in DOX-treated infant and adult mice and its possible link to underlying cardiotoxicity. Two groups of CD-1 male mice of different ages (infants or adults) were subjected to biweekly DOX administrations, to reach a cumulative dose of 18.0 mg/kg, which corresponds approximately in humans to 100.6 mg/m2 for infants and 108.9 mg/m2 for adults a clinically relevant dose in humans. The classic plasmatic markers of cardiotoxicity increased, and that damage was confirmed by histopathological findings in both groups, although it was higher in adults. Moreover, in DOX-treated adults, an increase of cardiac fibrosis was observed, which was accompanied by an increase in specific inflammatory parameters, namely, macrophage M1 and nuclear factor kappa B (NF-κB) p65 subunit, with a trend toward increased levels of the tumor necrosis factor receptor 2 (TNFR2). On the other hand, the levels of myeloperoxidase (MPO) and interleukin (IL)-6 significantly decreased in DOX-treated adult animals. In infants, a significant

increase in cardiac protein carbonylation and in the levels of nuclear factor erythroid-2 related factor 2 (Nrf2) was observed. In both groups, no differences were found in the levels of tumor necrosis factor (TNF-α), IL-1β, p38 mitogen-activated protein kinase (p38 MAPK) or NF-κB p52 subunit. In conclusion, using a clinically relevant dose of DOX, our study demonstrated that cardiac effects are associated not only with the intensity of the inflammatory response but also with redox response. Adult mice seemed to be more prone to DOX-induced cardiotoxicity by mechanisms related to inflammation, while infant mice seem to be protected from the damage caused by DOX, possibly by activating such antioxidant defenses as Nrf2.

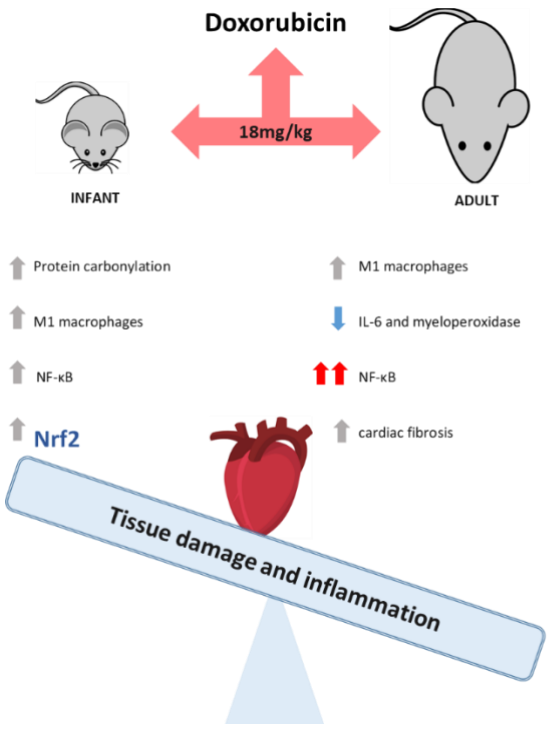

Figure 1. Doxorubicin's cardiotoxic effects were strongly attenuated in **infant mice by Nrf2 activation, whose role on future pharmacological treatment of cancer** patients dealing with cardiac adverse effects requires further research.

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Another way to skin the cat: Small molecule inhibitors of the β-TrCP-NRF2 interaction as a strategy for activation of NRF2

Under homeostatic conditions, NRF2 is a short-lived protein that is continuously targeted for ubiquitination and proteasomal degradation. Three known ubiquitin ligase systems mediate the degradation of NRF2: (i) Kelch-like ECH associated protein 1 (KEAP1), a substrate adaptor protein for Cullin3 (Cul3)/Rbx1-based Cullin-RING E3 ubiquitin ligase and a cysteine-based sensor for NRF2 inducers; (ii) the E3 ubiquitin ligase Hrd1, which resides in the endoplasmic reticulum (ER), and degrades NRF2 during ER stress; (iii) β-transducin repeat-containing protein (β-TrCP), a substrate adaptor for Skp1-Cullin1 (Cul1)/Rbx1-based Cullin-RING E3 ubiquitin ligase (Holmström et al. 2016). Notably, degradation of NRF2 by β-TrCP requires the formation of a phosphodegron on NRF2

following phosphorylation catalyzed by glycogen synthase kinase 3 (GSK3) (Rada *et al.* 2011). Most pharmacological NRF2 activators known to date target KEAP1, by either modifying its cysteine sensors or disrupting its interaction with NRF2. In a new study, Fernández-Ginés *et al.* adopted an alternative strategy for the development of pharmacological NRF2 activators, namely by targeting the β-TrCP-NRF2 protein-protein interactions (Fernández-Ginés *et al.* 2022). After *in silico* screening of ~1 million compounds, they identified a small molecule, named PHAR (**Figure 2**), which selectively inhibits the interaction between β-TrCP and the phosphodegron in NRF2. In cells, PHAR was protective against hydrogen peroxide-induced oxidative stress and liposaccharide (LPS)-mediated pro-inflammatory stress. *In vivo*, intraperitoneal (*i.p.*) administration of PHAR activated NRF2 in the mouse liver, attenuated the increase of pro-inflammatory cytokines following LPS challenge; this was accompanied by reduced activation of Kupffer cells, the liver resident macrophages. This study supports the value of pharmacological NRF2 activators as protective agents against oxidative stress and inflammation and provides a proof-of-principle that such protection can be achieved without inhibition of KEAP1.

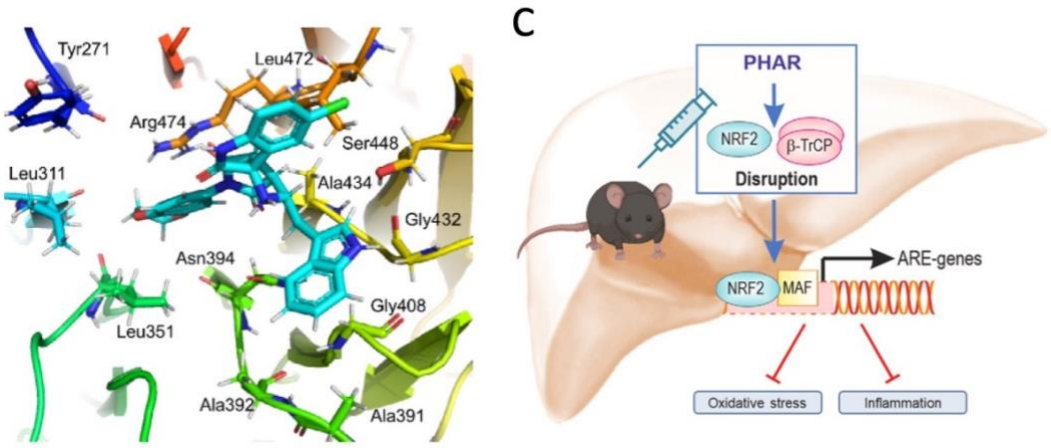

Figure 2: (A) Spatial localisation of the amino acids of β-TrCP that form hydrophobic or electrostatic interactions with PHAR based on molecular docking simulations; (B) PHAR inhibits the interactions between NRF2 and β-TrCP, activates NRF2-mediated transcription in the mouse liver, and suppresses oxidative stress and inflammation. Figure adapted from: Fernández-Ginés *et al.* 2022.

References: Fernández-Ginés R, Encinar JA, Hayes JD, Oliva B, Rodríguez-Franco MI, Rojo AI, Cuadrado A. An inhibitor of interaction between the transcription factor NRF2 and the E3 ubiquitin ligase adapter β-TrCP delivers anti-inflammatory responses in mouse liver. Redox Biol. 2022 Jul 11;55:102396. Holmström KM, Kostov RV, Dinkova-Kostova AT. The multifaceted role of Nrf2 in mitochondrial function. Curr Opin Toxicol. 2016 Dec;1:80-91. Rada P, Rojo AI, Chowdhry S, McMahon M, Hayes JD, Cuadrado A. SCF/ β-TrCP promotes glycogen synthase kinase 3-dependent degradation of the Nrf2 transcription factor in a Keap1-independent manner. Mol Cell Biol. 2011 Mar;31(6):1121-33.

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A matter of gender: The lack of transcriptionally active Nrf2 triggers colon dysfunction in female mice – The role of estrogens

The proper functioning of the gastrointestinal system relies on an intricate crosstalk between a plethora of cell types and signaling pathways. Recently we identified that the lack of NRF2 transcriptional activity (NRF2 tKO) triggers significant colon microscopical alterations, still they do not affect the general functioning of mice. Therefore, in this study, we aimed to address the gender-dependent impact of NRF2 transcriptional deficiency on colon function and relate them to an established model of inflammatory bowel disease (IBD). In the study we subjected 3- and 6-month-old mice deficient in IL-10 and NRF2 transcriptional activity and wild-type counterparts to tests assessing colon functionality, and histological analyses. To address the role of estrogens, we attempted to rescue the phenotype by the delivery of 17β-estradiol through subcutaneous implants. In females, NRF2 transcriptional abrogation, like IL-10 deficiency, triggers a functional and microscopic phenotype, that resembles IBD. The females are significantly more affected by the dysfunctional phenotype, and the functional impairment decreases with age. We found that NRF2 transcriptional activity influences 17β-estradiol level and the estrogen receptors expression and location. Exogenous delivery of 17β-estradiol normalized colon motility in the NRF2 tKO mice, which is related to enhanced ERβ signaling. Summing up, in this study, we underline that NRF2 transcriptional deficiency or the lack of IL-10 results in pronounced GI functional decline in young females. Mechanistically, we show that the impaired distal colon motility is dependent on ERβ signaling. Targeting estrogen signaling seems a promising therapeutic strategy to counteract colonic dysfunction.

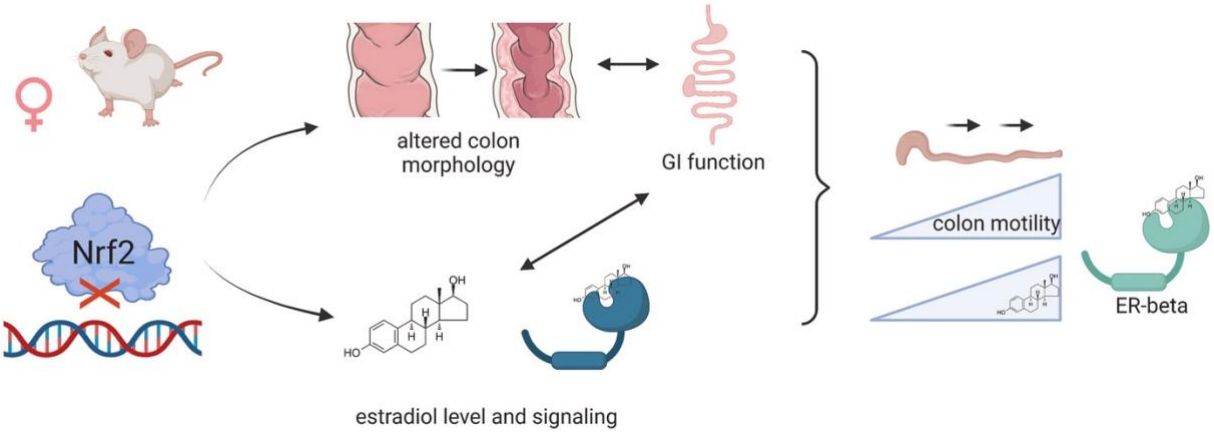

Figure 3. The lack of transcriptionally active Nrf2 triggers colon dysfunction in female mice by influencing levels of 17β-estradiol and the expression of estrogen receptors.

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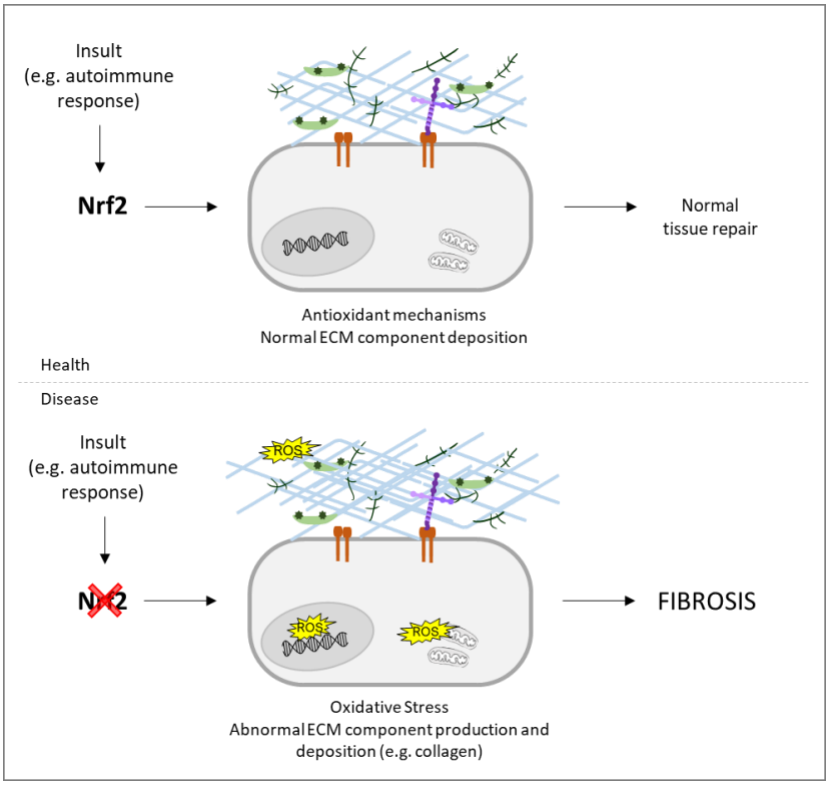
The protective role of NRF2 against fibrosis

Fibrosis is characterized by the accumulation of extracellular matrix, often in the context of chronic inflammation, leading to pathological conditions in many organs such the lung, liver and heart. These conditions can be triggered by different stimuli, being oxidative stress, persistent infection, and autoimmune reactions some examples (Cho et al., 2004; Hao et al., 2022; Wynn, 2008). As a key player in the antioxidant defense response, NFR2 plays a major role in preventing the generation of fibrotic tissue. In the myocardium, Nrf2 is responsible for the activation of the glutathione pathway that contributes for the maintenance of the redox balance, preventing increased inflammation, fibroblast activation and myocardial fibrosis. The activation of Nrf2-dependent antioxidant mechanisms and consequent reduction of oxidative stress levels also prevents epithelial-mesenchymal transition, a known characteristic of fibrosis, and acute injury in the lung and reduce insulin resistance and attenuate fibrosis in the liver. Interestingly, Nrf2 role is not limited to antioxidant mechanisms. In fact, Nrf2 was shown to be responsible to inhibit the activation of pathways such as TGF-β/SMADs, which lead to the production and accumulation of collagen. In the lung, Nrf2 is important during the immune response by influencing cytokine production, and, in the liver, *Nrf2* knockdown was shown to stimulate extracellular matrix synthesis leading to fibrosis. Not surprisingly, the important role of NRF2 to counter fibrosis has promoted several research groups to explore the potential of targeting NRF2 pathway to treat fibrosis. A promising compound is oltipraz, a well-known NRF2 activator, shown to have an impact in preclinical and clinical trials in the reduction of fibrosis. Other NRF2 activators have also been shown to reduce fibrosis in the context of different diseases, including sulforaphane or tanshinone IIA. Being fibrosis such a common outcome in the pathology of a wide range of diseases, research on NFR2 has an enormous potential to uncover new lines of treatment.



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Hot from Pubmed

Glutaminase inhibition effect in CD8 T cell activation

Glucose and glutamine in the tumor microenvironment (TME) are essential for the development and activation of effector T cells that exert antitumor function. Immunotherapy potentiates T cell antitumor function. However, a significant proportion of patients does not benefit from this treatment. In patients with KRAS-mutant lung adenocarcinoma, KEAP1 and STK11/Lkb1 co-mutations are associated with impaired response to immunotherapy. To investigate the metabolic and immune microenvironment of KRAS-mutant lung adenocarcinoma, the authors generated murine models that reflect the KEAP1 and STK11/Lkb1 mutational landscape in these patients. Degradation of glutamine into glutamate is promoted by the NRF2 target gene glutaminase and in this work, it was showed that increased glutamate abundance in the Lkb1-deficient TME is associated with CD8 T cell activation in response to anti-PD1. Moreover, combined treatment with the glutaminase inhibitor CB-839 inhibited clonal expansion and activation of CD8 T cells, negatively impacting CD8 T cells activated by anti-PD1 immunotherapy.
Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35504291/

A CRISPR screen identifies redox vulnerabilities for KEAP1/NRF2 mutant non-small cell lung cancer

The redox regulator NRF2 is hyperactivated in a large percentage of non-small cell lung cancer (NSCLC) cases, which is associated with chemotherapy and radiation resistance. However, NRF2 control in ROS detoxification is complex and redundant. To investigate redox vulnerabilities, Jiang and collaborators conducted a CRISPR-Cas9-based negative selection screen for antioxidant enzyme genes whose loss sensitized cells to sub-lethal concentrations of the superoxide (O2•-)-generating drug β-Lapachone. Besides identifying expected hits in the pentose phosphate pathway, the thioredoxin-dependent antioxidant system and glutathione reductase, the mitochondrial superoxide dismutase 2 (SOD2) was identified as one of the top hits. Importantly, SOD2 loss enhanced the efficacy of β-Lapachone due to loss of iron-sulfur protein function, loss of mitochondrial ATP maintenance and deficient NADPH production. Moreover, inhibition of mitochondrial electron transport activity sensitized cells to β-Lapachone, demonstrating a therapeutic potential in the modulation of ROS sensitivity.
Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35667246/

Guidelines for measuring ROS and oxidative damage in cells and in vivo

Researchers from different fields are now studying reactive oxygen species (ROS) due to their involvement in different pathologies. Indeed, there are many assays and commercial kits available, but their use and interpretation are challenging and open to artefacts, specially by those working outside the area. As such, a consensus statement was created highlighting problems that can arise with many commonly used approaches for measurement of ROS and oxidative damage, along with the proposal of guidelines for best practice. The goal is that these strategies will be useful to those

who find their research requiring assessment of ROS, oxidative damage and redox signaling in cells and in vivo.
Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35760871/

NRF2 pathway activation attenuates ageing-related renal phenotypes

Oxidative stress is strongly related to age-induced functional decline in cells and tissues. The KEAP1-NRF2 system plays a central role in the regulation of redox balance, and NRF2 activation exerts anti-aging effects by controlling oxidative stress in aged tissues. α-Klotho was identified as an ageing suppressor protein based on the premature ageing phenotypes of its mutant mice, and its expression is known to gradually decrease during ageing. Because α-klotho has been shown to possess antioxidant function, ageing-related phenotypes of α-klotho mutant mice seem to be attributable to increased oxidative stress at least in part. To examine whether NRF2 activation antagonizes ageing-related phenotypes caused by α-klotho deficiency, α-klotho-deficient (Kl-/-) mice was crossed with a Keap1-knockdown background, in which the NRF2 pathway is constitutively activated in the whole body. NRF2 pathway activation in Kl-/- mice extended the lifespan and improved ageing-related renal phenotypes with elevated expression of antioxidant genes accompanied by an oxidative stress decrease, namely through the inhibition of oxidative stress accumulation, fibrosis, calcification and apoptosis. Thus, NRF2 is demonstrated to have an antiageing function by attenuating renal pathologies originating from α-klotho deficiency.
Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35137128/

NRF2 activation mediates the anti-inflammatory properties of a subset of over-the-counter and prescription NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX) enzymes and are ubiquitously used for their anti-inflammatory properties. However, COX inhibition alone fails to explain numerous clinical outcomes of NSAID usage. Screening commonly used NSAIDs in primary human and murine myeloid cells demonstrated that NSAIDs could be differentiated by their ability to induce growth/differentiation factor 15 (GDF15), independent of COX specificity. The group of Eisenstein demonstrated that NSAID-mediated GDF15 induction was dependent on the activation of NRF2 in myeloid cells and that sensing by KEAP1 was required for NSAID activation of NRF2 and subsequent anti-inflammatory effects both in vitro and in vivo. This work highlights a noncanonical NRF2-dependent mechanism of action for the anti-inflammatory activity of a subset of commonly used NSAIDs.
Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35588739/

Neuroprotective effect of the Nrf2 in spinal cord injury

Spinal cord injury (SCI) is associated with chronic neuroinflammation and redox imbalance. Oxidative stress is one of the main hallmarks of secondary injury of SCI which is tightly regulated by nuclear factor E2-related factor 2/antioxidant response element (Nrf2/ARE) signaling. Moreover, miRNA expression is temporally altered after SCI, and these alterations may have a critical effect on the pathogenesis of SCI by regulating inflammation, demyelination, and apoptosis. The work from Ebrahimy and collaborators suggests that astrocytic hyperactivation of Nrf2 exert neuroprotective effects at least in part through the upregulation of miRNA145-5p, a negative regulator of astrocyte proliferation.

Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35750202/

Nrf2 protects against radiation-induced oral mucositis via antioxidation and keratin layer thickening

Radiation-induced oral mucositis is one of the most common adverse events in radiation therapy for head and neck cancers, but treatments for oral mucositis are limited to palliative and supportive care. Given previous reports on Nrf2 cytoprotection against oxidative and electrophilic stresses and regulation of keratin layer thickness in mouse tongues, Wakamori and collaborators demonstrated that Nrf2 activation by genetic Keap1 knockdown alleviated radiation-induced DNA damage by increasing antioxidation. In agreement with the genetic Nrf2 activation model, a Nrf2 inducer prevented irradiation damage to the tongue epithelium.
Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35753588/

Fisetin Attenuated Oxidative Stress-Induced Cellular Damage in ARPE-19 Human Retinal Pigment Epithelial Cells Through Nrf2-Mediated Activation of Heme Oxygenase-1

Oxidative stress-induced retinal disorders are thought to play an important role in the pathogenesis of irreversible vision loss-related diseases, including retinitis pigmentosa, diabetic retinopathy and age-related retinal degeneration. Fisetin is a bioactive flavonol, present in fruits such as strawberries and apples, and is known to act as a potent free radical scavenger. Its effect in human retinal pigment epithelial (RPE) cells injured with hydrogen peroxide was investigated. Indeed, fisetin alleviated mitochondrial dysfunction and enhanced phosphorylation and nuclear translocation of Nrf2, which was associated with increased expression and activity of heme oxygenase-1 (HO-1). Accordingly, fisetin protective effects were reversed with a HO-1 inhibitor, suggesting that Nrf2-mediated activation of antioxidant enzyme HO-1 may play an important role in the ROS scavenging activity of fisetin in retinal pigment epithelial cells.
Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35784747/

Modulating Nrf2 as part of a multifaceted therapeutic approach for Alzheimer's disease

The etiology of Alzheimer's disease (AD) includes amyloid β (Aβ) amyloidosis, metal–Aβ42 complex formation, ROS, oxidative stress, mitochondrial damage, and neuroinflammation. Thus, multifunctional modulators were designed by integrating pharmacophores for metal chelation, antioxidant and anti-inflammatory properties, and modulation of Aβ42 aggregation on the naphthalene monoimide (NMI) scaffold. Treatment with one of the synthesized molecules synergistically modulated metal-independent and -dependent amyloid toxicity, quenched the ROS and reduced oxidative stress, accompanied by the reduced the translocation of Nrf2 to the nucleus in neuronal cells. This work further supports the importance of modulating Nrf2 in AD therapeutics.
Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35759686/

Carbocysteine modulation of Nrf2/HO-1 in the treatment of ulcerative colitis

Current therapies for ulcerative colitis (UC), an inflammatory bowel disease with multifaceted pathophysiology, lack efficacy. It has been well documented that modulating the Nrf2/NFκB is a

promising therapeutic target in inflammation. Moreover, carbocisteine is a mucoregulatory medication and its efficacy in COPD was found to be more closely related to its antioxidant and anti-inflammatory properties. In this work, it was investigated the potential coloprotective role of carbocisteine in acetic acid-induced colitis in rats. The results revealed that carbocisteine attenuated colon shortening and augmented colon antioxidant defense mechanisms via upregulating catalase and HO-1 enzymes. The myeloperoxidase activity was suppressed indicating inhibition of the neutrophil infiltration and activation. Consistent with these findings, carbocisteine boosted Nrf2 expression along with NFκB inactivation. Consequently, carbocisteine downregulated the proinflammatory cytokines IL-6 and TNF-α and upregulated the anti-inflammatory cytokine IL-10. Concomitant to these protective roles, carbocisteine displayed anti-apoptotic properties as revealed by the reduction in the Bax: BCL-2 ratio. In conclusion, carbocisteine inhibited oxidative stress, inflammatory response, and apoptosis in acetic acid-induced UC by modulating the Nrf2/HO-1 and NFκB interplay in rats. Therefore, the current study provides a potential basis for repurposing a safe and a commonly used mucoregulator for the treatment of UC.

Access to the original article: https://pubmed.ncbi.nlm.nih.gov/35754464/

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