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Review Article

Targeting NRF2 to promote epithelial repair

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The transcription factor NRF2 is well known as a master regulator of the cellular stress response. As such, activation of NRF2 has gained widespread attention for its potential to prevent tissue injury, but also as a possible therapeutic approach to promote repair processes. While NRF2 activation affects most or even all cell types, its effect on epithelial cells during repair processes has been particularly well studied. In response to tissue injury, these cells proliferate, migrate and/or spread to effectively repair the damage. In this review, we discuss how NRF2 governs repair of epithelial tissues, and we highlight the increasing number of NRF2 targets with diverse roles in regulating epithelial repair.

Introduction

Epithelial cells are tightly packed cells, which exert a wide variety of different functions depending on the type of tissue and organ. Major functions of epithelial cells include the secretion/excretion of material, the absorption of nutrients as well as filtration. Some epithelial cells also act as a barrier to, and sensor of the external environment, and they are actively involved in inflammatory processes. The epithelium must therefore be equipped with efficient protective capabilities to handle diverse environmental challenges while maintaining its function, or in the case of injury, mounting an effective repair response [1]. Similar overarching mechanisms govern epithelial repair throughout the body, although tissue-specific processes also take place. Generally, a healing response is composed of three overlapping phases, which have been most thoroughly studied in the skin: inflammation, new tissue formation, and tissue remodeling [2,3]. During the repair process, the epithelium must effectively co-ordinate a combination of proliferation, migration, cell spreading and differentiation to restore the lost tissue and its functionality. Defects in any of these cellular processes can result in chronic tissue damage as seen for example in chronic skin ulcers, which remain a significantly challenging clinical problem [4,5]. A better understanding of the cellular and molecular mechanisms of epithelial cell behavior and dysfunction during tissue repair is important in order to address this challenge therapeutically.

Like all cell types, epithelial cells require complex cytoprotective signaling networks in order to sense and appropriately respond to different stressors that can accumulate immediately after injury and during tissue repair. In addition to directly sensing the stressor, epithelial cells also depend on nearby stromal and immune cells. These cells release growth factors, cytokines and extracellular matrix (ECM) molecules, many of which are up-regulated as a response to stress signals and promote survival, proliferation, migration and differentiation of epithelial cells [6].

The NRF2 transcription factor

One of the most important factors in regulating the cellular response to oxidative or xenobiotic stress is nuclear factor-erythroid 2-related factor 2 (NRF2; NFE2L2). It is a member of the cap`n collar family of transcription factors, which also includes NFE2, NRF1, NRF3, Bach1 and Bach2 [7]. NRF2 regulates the transcription of hundreds of genes, the bulk of which code for detoxification enzymes and antioxidant proteins, which help to alleviate cell damage, maintain the redox balance, and restore cellular homeostasis [7–10]. This cytoprotective function of NRF2 is conserved in different cell types, while additional NRF2 target genes that are not directly involved in cytoprotection, are frequently expressed in a cell type-specific manner [11–13].

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NRF2 activity is primarily regulated at the post-translational level via its chief antagonist Kelch-like ECH-associated protein 1 (KEAP1) [9,14,15]. During cellular homeostasis, KEAP1 binds to NRF2 in the cytoplasm, leading to the rapid ubiquitination and proteasomal degradation of NRF2 [9,15]. Activation of NRF2 requires the weakening of its interaction with KEAP1, which can occur through different mechanisms. The classic and most studied mechanism involves the accumulation of oxidizing compounds/electrophiles (e.g. as a result of cellular stress), which react with different cysteine residues in KEAP1 and form covalent modifications [9,15]. These modifications of KEAP1 results in a conformational change, which weakens the KEAP1–NRF2 interaction, thereby allowing newly synthesized NRF2 to accumulate in the nucleus. Once inside the nucleus, NRF2 forms a heterodimer with small MAF proteins and together with them binds to regions of DNA commonly referred to as antioxidant response elements (AREs), which are present in the promoter or enhancer regions of its target genes [7,15] (Figure 1). NRF2 competes with the related NRF1 and NRF3 transcription factors for binding to many of these AREs [16,17].

As an alternative to the canonical activation pathway, NRF2 can become activated during autophagy via p62-dependent autophagosomal degradation of KEAP1 [18]. Phosphorylated p62 can also directly interact with KEAP1 and interfere with binding to NRF2, allowing for NRF2 stabilization and nuclear accumulation [19–22]. Several other proteins have also been reported to activate NRF2 in a similar manner by disrupting the KEAP1–NRF2 interaction by binding to either KEAP1 or NRF2 [23–28]. These mechanisms have been reviewed previously [29,30] and are summarized in Figure 1. Furthermore, phosphorylation of NRF2 by different kinases can positively or negatively regulate NRF2 activity [31].

NRF2 in repair of epithelial tissues

The role of NRF2 in the protection of epithelial and other cell types from various insults has been researched extensively and previously reviewed [7–9,32,33]. Here, we will summarize the increasing evidence for a direct involvement of NRF2 in repair processes after the injury has occurred (summarized in Table 1) and the relevant NRF2 target genes, whose function extend beyond cytoprotection. We report on tissues and organs, for

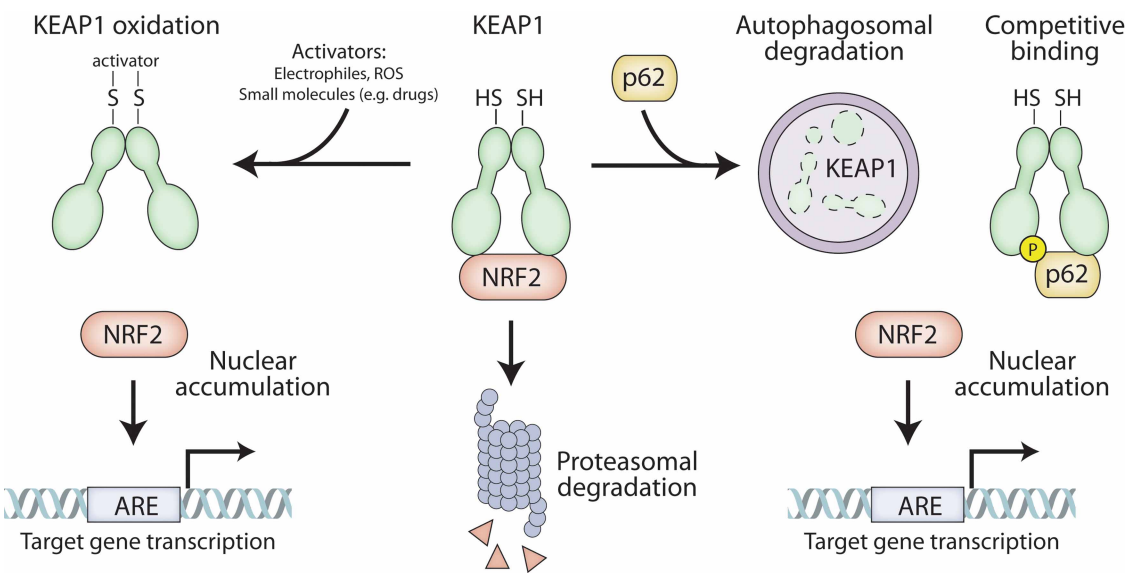

Figure 1. Mechanisms of NRF2 activation.

NRF2 binds to KEAP1 during cellular homeostasis, resulting in its rapid proteasomal degradation. Left: The classical (canonical) mechanism for NRF2 activation relies on the accumulation of intracellular electrophilic or oxidative compounds, which are common by-products during cellular stress. These compounds react with cysteine residues in KEAP1, which weakens the KEAP1–NRF2 interaction, allowing NRF2 to accumulate in the nucleus and facilitate transcription of its target genes by binding to AREs. Right: Non-canonical mechanisms of NRF2 activation involve p62-dependent degradation of KEAP1 during autophagy. Alternatively, phosphorylated p62 and several other proteins can compete with NRF2 for binding to KEAP1, allowing NRF2 to accumulate in the nucleus.

Table 1 Effects of targeting NRF2 on epithelial repair in different organs and cell types

Organ	Cell type	Activation status	Impact on epithelial repair	Refs.
Skin	Keratinocytes	Activation	Increased proliferation of hair follicle stem cells, faster re-epithelialization	[50]
			Improved wound closure in diabetic rodents	[39,41–44]
			Improved epithelial repair in wounds of healthy, non-diabetic mice	[45–47]
		Dominant-negative Nrf2	No effect	[36]
		Inducible knockout	Reduced keratinocyte proliferation, migration — delayed wound closure	[37]
	Fibroblasts	Activation	Increased proliferation of keratinocytes, faster re-epithelialization, fibroblast senescence	[52]
	Global	Knockout	Prolonged wound inflammation	[34]
Eye	Retinal epithelium	Activation	Reduced EMT, less fibrosis	[60]
	Corneal epithelium	Activation	Faster healing in diabetic mice	[62]
	Global	Knockout	Delayed corneal healing, defective corneal keratinocyte migration	[61]
Lung	Lung cells (general)	Activation	Improved recovery following ALI More severe emphysema	[66,67,70,76]
	Airway basal stem cells	Activation	Optimal Notch expression, proliferation/ renewal	[71]
	hAMSCs	Over-expression	Improved recovery following ALI, increased type II alveolar cell differentiation	[68]
	Club cells	Knockout	Impaired resolution of inflammation following ALI, worse recovery	[73]
	Global	Knockout	Impaired lung regeneration following ALI, increased mortality Pro-fibrotic response to irradiation injury	[72,74]
Liver	Liver cells (general)	Activation	Faster regeneration following partial hepatectomy	[87]
	Hepatocytes	Activation	Impaired liver regeneration following partial hepatectomy Reduced cell proliferation, differentiation	[84–86]
		Inhibition	Increased progenitor cell differentiation	[84]
	Global	Knockout	Delayed liver regeneration following acute toxic injury or partial hepatectomy, increased cell death Reduced Notch1 expression, De-differentiation of hepatocytes	[79–83]
Kidney	Kidney cells (general)	Activation	Protection of proximal tubular cells from ferroptosis following kidney injury	[89]
		Inhibition	Improved repair following ischemia/ reperfusion injury	[91]

which such data are available, including skin, eye, lung, liver and kidney. Roles of NRF2 in the repair of additional epithelial tissues are likely, but remain to be determined.

Skin

A possible role for Nrf2 in wound repair was first addressed using global *Nrf2* knockout (*Nrf2* KO) mice [34]. These mice develop normally with no major phenotypic abnormalities [35]. Similarly, upon skin wounding, no obvious differences in wound closure, re-epithelialization or granulation tissue formation were observed, despite Nrf2 being highly expressed in the wound epithelium as well as in stromal and immune cells of wild-type mice [34]. The only observed difference was a prolonged inflammatory response in the KO mice [34]. To address the issue of potential compensation by Nrf1 and Nrf3, transgenic mice were generated, which express a dominant-negative Nrf2 mutant in keratinocytes. This truncated protein still binds to DNA and thereby

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competes for binding of endogenous Nrf1, Nrf2 and Nrf3, but it lacks the transactivation and Keap1 binding domains [36]. These mice also showed no major defects in wound re-epithelialization, suggesting Nrf2 activation in keratinocytes is not essential for re-epithelialization of a normal skin wound, and that potential long-term compensation may occur independently of Nrf1 or Nrf3 [36]. Indeed, when *Nrf2* was conditionally deleted in keratinocytes of adult mice using a tamoxifen-inducible system, thereby reducing the time/potential for compensatory mechanisms to become engaged, delayed wound healing was observed [37]. A role for Nrf2 in epithelial wound repair is not restricted to mice, since RNAi-mediated knock-down of Nrf2 caused delayed closure of laser-inflicted wounds in *Drosophila* embryos as a consequence of slower epithelial cell migration [1].

Additional studies have shown a more pronounced role for Nrf2 during impaired wound healing, which occurs for example in diabetic rodents or humans [38]. Mice injected with streptozotocin (STZ) develop diabetes and experience delayed wound closure, a phenotype that was exacerbated in mice lacking Nrf2 [39]. This same study also found that the NRF2 activating compounds sulforaphane or cinnamaldehyde were both sufficient to improve wound closure when administered to diabetic mice, but they had no significant impact when administered to healthy, non-diabetic mice [39]. *In vitro*, keratinocytes cultured in hyperglycemic conditions showed reduced proliferation and migration, which was worsened or rescued when Nrf2 was inhibited or activated, respectively [39]. The NRF2 activator dimethyl fumarate, approved by the Food and Drug Administration for the treatment of multiple sclerosis [40], also accelerated wound closure in STZ-induced diabetic, but not in healthy control mice [41]. Several other substances capable of activating NRF2 have shown similar improvements to re-epithelialization in the STZ-induced diabetes model [42–44].

In contrast with the studies described above, other substances capable of activating NRF2 are suggested to improve cutaneous wound healing even in non-diabetic, healthy mice, and they promoted epithelial repair and epidermal integrity in mouse models and 3D organotypic culture models for atopic dermatitis [45–47]. This is of potential relevance in humans, since reduced NRF2 activity was detected in the epidermis of patients with this chronic inflammatory skin disease [48].

While the use of NRF2-activating compounds can provide useful insight into how NRF2 regulates epithelial repair, potential off-target effects of these compounds or medicines often make the precise role of NRF2 difficult to interpret. One strategy to overcome this problem is through the use of genetic models. One such model uses a mutated form of Nrf2, which lacks the Keap1-binding domain and is therefore constitutively active [49]. Transgenic mice with constitutively active Nrf2 (caNrf2) expressed in keratinocytes show increased expression of classical and newly identified Nrf2 target genes in the epidermis. Excisional wounds in these mice re-epithelialized significantly faster compared with wounds of control mice [49,50]. While this is beneficial, it should be considered that constitutive activation of Nrf2 induced hyperkeratosis in the non-injured epidermis of the caNrf2-transgenic mice and also in *Keap1* KO mice [49,51].

Interestingly, activation of the Nrf2 pathway in fibroblasts by expression of caNrf2 also promoted wound re-epithelialization without aggravating scar formation. This was caused by Nrf2-mediated fibroblast senescence during wound healing and the subsequent release of a senescence-associated secretome, which promoted migration and proliferation of keratinocytes, leading to faster re-epithelialization [52].

In addition to the classical Nrf2 target genes that regulate the cellular redox balance, additional Nrf2 target genes not directly related to cytoprotection continue to be identified in keratinocytes and some of them are also important regulators of tissue repair. For example, in mice with keratinocyte-specific expression of caNrf2, the activated Nrf2 targeted the gene coding for epigen, which signals via the epidermal growth factor receptor to enhance proliferation of hair follicle stem cells. These cells contribute to re-epithelialization, and their hyperproliferation therefore promoted this process [50]. In another study, Nrf2 was shown to target the gene coding for C-C motif chemokine ligand 2 (Ccl2) in keratinocytes following injury. Overexpression of this chemokine promoted the recruitment of macrophages to the wound site. Macrophages then provided signals that stimulate keratinocyte proliferation and re-epithelialization [37]. In wounds of genetically diabetic *db/db* mice, Nrf2 activation was impaired, resulting in defects in macrophage recruitment and wound closure. This was rescued by administration of Ccl2, pointing to a role for keratinocyte-derived Nrf2 in regulating keratinocyte proliferation indirectly via Ccl2-mediated recruitment of macrophages [37]. In fibroblasts, Nrf2 directly targets *Serpine1*, the gene encoding plasminogen activator inhibitor-1 (PAI-1) [52]. PAI-1 is a known inducer of senescence in fibroblasts, a key event during wound healing, which can promote the proliferation and migration of nearby epithelium via its senescence-associated secretome [52–54]. Nrf2 also targets genes coding for miRNAs in keratinocytes and fibroblasts [55,56], which are capable of regulating the expression of a wide variety of proteins that may affect repair. Interestingly, many Nrf2 target genes, particularly those that are non-classical

targets, may be cell-type specific. One reason for this could be the co-ordinated action of Nrf2 with other transcription factors that are expressed or become activated in a cell-type specific manner or context. For example, NRF2 and p63 work synergistically in human keratinocytes to drive expression of common target genes, thereby promoting keratinocyte proliferation [57]. This finding suggests that their combined activation may offer even greater potential for improving epithelial repair.

Eye

In the eye, retinal detachment can occur as a result of injury, disease or normal aging, and treatment usually requires emergency surgery [58]. Potential complications following surgery include a fibrotic response termed proliferative vitreoretinopathy (PVR), which includes increased proliferation of retinal epithelial cells and epithelial to mesenchymal transition [59]. While this typically requires further surgery, one study found that the use of a synthetic, bio-functional polymer was sufficient to activate Nrf2 and reduce EMT in retinal epithelial cells in a rabbit model of PVR, suggesting a possible therapeutic role for activated NRF2 in the promotion of healthy repair and prevention of PVR following retinal detachment surgery [60].

The epithelium of the cornea must also withstand from environmental stress and rapidly recover from injury. In this tissue, wound healing was also investigated using *Nrf2* KO mice [61]. Unlike skin, global *Nrf2* deficiency significantly delayed corneal wound healing, featuring a defective migratory ability of corneal keratinocytes [61]. Another study suggests that certain compounds may improve corneal wound healing during diabetes by activating Nrf2 [62]. In this study, the authors used STZ-induced diabetic mice, which show delayed corneal wound healing and reduced Nrf2 activity. Topical application of the lipid mediator resolvin D1 led to activation of Nrf2, as seen by increased expression of Nrf2 target genes, reduced ROS levels and accelerated repair [62]. These findings suggest similar benefits of Nrf2 activation in corneal keratinocytes as seen in skin, particularly during diabetic wound healing.

Lung

Damage to the lung epithelium can occur due to a variety of factors, including infection, inflammation or inhalation of toxic fumes. Several lines of evidence suggest NRF2 activation can regulate repair of the lung epithelium, and pharmaceutical activators of NRF2 have shown promise in preventing and treating lung injury and disease (e.g. COVID-19) due to their antioxidant and anti-inflammatory properties [63,64]. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are inflammatory lung disorders, resulting in damage to the lung epithelium [65]. Efforts to treat these conditions in mice with various Nrf2-activating compounds yielded promising results [66,67]. Strategies to treat ALI/ARDS have also incorporated Nrf2 activation as part of cell-based approaches. In one study, injection of NRF2-overexpressing human amniotic mesenchymal stem cells (hAMSC) into mice resulted in improved recovery following ALI induced by lipopolysaccharide compared with normal hAMSCs [68]. NRF2 overexpression led to increased differentiation of these cells into type II alveolar cells and faster resolution of fibrosis [68].

Lung injury can also result from ischemia and subsequent reperfusion in the brain, an injury that frequently extends to distant organs and tissues [69]. In a rodent model, lung injury following cerebral ischemia/reperfusion was associated with increased activation of Nrf2 in lung tissue, whose cytoprotective function likely combats further injury while facilitating repair [70]. Another study found that Nrf2 became activated in airway basal stem cells following an increase in ROS and was essential for optimal Notch expression and subsequent proliferation and self-renewal [71]. *Nrf2* KO mice responded worse to ALI resulting from hypoxia, showing increased mortality and impaired regeneration of alveolar structures [72]. Loss of Nrf2 specifically in Club cells, which are exocrine epithelial cells within the bronchi, also lead to worse outcomes following hypoxia-induced ALI. This included reduced protection from injury and an impaired resolution of inflammation during repair [73]. Nrf2 deficiency also impaired the mobilization of progenitor cells following irradiation injury of the lung and shifted repair to a more fibrotic response [74].

In contrast with its beneficial effects, Nrf2 activation in the lung may be detrimental in some cases. For example, in a mouse model of emphysema, Nrf2 activation suppressed ROS-mediated platelet-derived growth factor receptor B (Pdgfrb) signaling, which functions to maintain alveolar homeostasis [75,76]. In this model, knockout of the short isoform of latent transforming growth factor (TGF)-β-binding protein 4 (Ltbp4S) resulted in decreased levels of active TGF-β, which under normal conditions inhibits Nrf2 indirectly by blocking sestrin 2-mediated autophagosomal degradation of Keap1. *Ltbp4S* knockout mice therefore showed elevated expression of Nrf2 target genes, reduced Pdgfrb signaling and severe emphysema [75]. Such adverse effects

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should to be taken into consideration when NRF2-activating compounds are applied to promote repair of the lung, but also of other tissues as detailed below.

Liver

In contrast with other mammalian organs, the liver has a remarkable regenerative capacity and can completely regenerate after limited acute injury without formation of scar tissue [77]. Loss of liver tissue as a consequence of surgery or toxin- or virus-mediated injury initiates a repair program that ultimately restores the original liver mass, while still allowing the organ to perform its important metabolic functions. *In vivo* imaging in transgenic reporter mice that express luciferase under control of an ARE-regulated promoter showed strong Nrf2 activation in the liver after partial (two-thirds) hepatectomy (PH), with a peak activity on day 3. In addition, Nrf2 accumulated in the nucleus of hepatocytes after PH [78]. These findings demonstrate that Nrf2 is activated in the regenerating liver and suggest its functional involvement in this process. This was confirmed using mice with a global KO of *Nrf2*, which showed delayed liver regeneration as a consequence of enhanced death and delayed proliferation of liver cells. This resulted from oxidative stress-mediated resistance of hepatocytes to insulin/insulin-like growth factor signaling [79]. Loss of Nrf2 also reduced the levels of Notch1, which contributed to the impaired regeneration after PH [80]. Other studies revealed that Nrf2 is involved in maintaining hepatocytes in a fully differentiated state during the regeneration process [81] and also ensures the timely entry of replicating hepatocytes into mitosis by regulating the expression of cyclin A2 and the Wee1/Cdc2/cyclin B1 pathway [82]. The important role of Nrf2 in liver regeneration was confirmed in a model of acute injury induced by the hepatotoxin CCl_4, where loss of Nrf2 also delayed the repair process [83]. On the other hand, silencing or inhibition of Nrf2 promoted hepatic progenitor cell activation and differentiation, which is required after severe and chronic liver injury. *Vice versa,* activation of Nrf2 in the biliary tract repressed the injury-induced ductular reaction, in which hepatic progenitor cells acquire hepatocyte or cholangiocyte phenotypes [84]. These results point to different functions of Nrf2 in different cell types and different liver injury models.

The important role of endogenous Nrf2 in liver regeneration suggested that further activation of Nrf2 in the liver may be beneficial. However, hepatocyte-specific expression of caNrf2 in mice, which increases target gene expression to a level seen upon activation of endogenous Nrf2, caused a surprising impairment of liver regeneration after PH without affecting liver development and homeostasis [85]. This resulted from Nrf2-mediated up-regulation of the cyclin-dependent kinase inhibitor p15 and the pro-apoptotic protein Bcl2l11 (Bim) in the regenerating liver of caNrf2 transgenic mice, whose genes were identified as direct Nrf2 targets [85]. Consistent with these results, heterozygous deficiency in *Keap1*, which resulted in increased Nrf2 activity, caused a delay in S-phase entry, disruption of S-phase progression and loss of mitotic rhythm of replicating hepatocytes after PH [86]. However, liver re-growth was not significantly affected in these mice [86], possibly because of a weaker activation of Nrf2 in hepatocytes of heterozygous *Keap1* KO mice compared with caNrf2 expressing mice. Both studies, however, suggest that activation of Nrf2 in the liver does not promote liver regeneration and even impairs this process. In contrast with these studies, pharmacological activation of Nrf2 by bardoxolone methyl (CDDO-Me) accelerated liver regeneration and improved liver function after PH in wild-type, but not in *Nrf2* KO mice [87]. This was associated with more pronounced hepatocyte hypertrophy, enhanced hepatocyte proliferation and reduced liver inflammation. These findings suggest that transient and limited activation of Nrf2 in all cells of the liver may be beneficial for the regeneration process. In the future, it will be important to determine the optimal extent and duration of Nrf2 activation in the regenerating liver and the relevance of Nrf2 in different cell types during the regeneration process.

Kidney

Similar to other tissues, activation of Nrf2 protected the kidney from acute or chronic tissue injury [88]. However, a potential role of Nrf2 in kidney repair has only been addressed very recently. In one study, the authors demonstrated that sex differences in resilience to ferroptotic cell death underlie the reduced kidney injury and enhanced repair of this organ in female vs. male mice [89]. Importantly, Nrf2 activation was identified as a female resilience mechanism against ferroptosis, and activation of Nrf2 in male mice protected proximal tubular cells from ferroptosis and improved cellular plasticity to the extent seen in female mice [89]. Nrf2 activation may also promote repair following ischemia/reperfusion injury in the kidney, where Nrf2 activation is suppressed [90]. This appears to be mediated by hypoxia-inducible factor 1-alpha (HIF-1α), which promotes activation of Nrf2 in nutrient-rich, or mild ischemic conditions, but suppresses Nrf2 activation in nutrient-deficient or severe ischemic conditions [91]. These studies identify Nrf2 as a potential therapeutic target to promote renal repair after acute kidney injury.

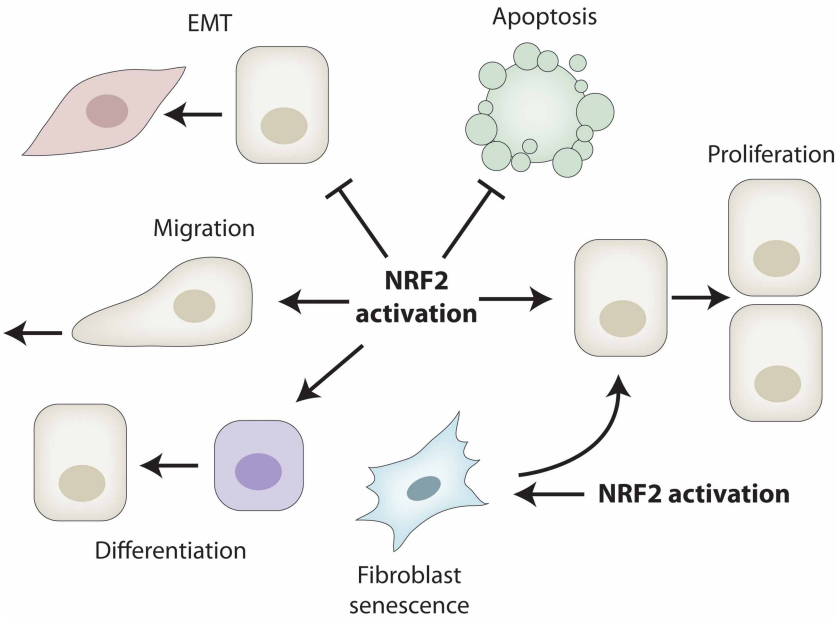

Figure 2. Cellular processes regulated by NRF2 with implications for epithelial repair.
NRF2 activation can promote proliferation of epithelial cells in multiple tissues and organs. In contrast, constitutive NRF2 activation promotes fibroblast senescence, which leads to increased proliferation of neighboring epithelium via the senescence-associated secretome. NRF2 activation can also encourage epithelial cell differentiation and migration, while at the same time limit complications that contribute to impaired healing by reducing epithelial to mesenchymal transition (EMT) and subsequent fibrosis, and protecting cells from apoptosis.

Summary

Recent advances in the field have cemented the view of NRF2 as a multifaceted regulator of epithelial repair in different animal models. This has been aided by the identification of a number of cell type-specific target genes with diverse roles in regulating a variety of cellular processes important for efficient healing (Figure 2). While downsides to NRF2 activation were observed in some occasions, it is often beneficial for the repair process of epithelial tissues. However, the precise level of activation of NRF2 as well as the duration of the treatment will most likely determine the final outcome. In addition, potential pro-tumorigenic effects of long-term NRF2 activation should be taken into consideration [52,92,93] before NRF2 activators are used in the clinic to promote tissue repair. With these limitations in mind, use of precisely targeted NRF2 activators with well-characterized specificity is a promising new strategy to promote repair of injured tissues.

Perspectives

- Defective epithelial repair can lead to long-term tissue damage, which represents a substantial clinical challenge.
- The NRF2 transcription factor is a key regulator of tissue repair, and its pharmacological activation is a promising therapeutic strategy for impaired healing. A beneficial effect of NRF2 activation on epithelial repair was confirmed in multiple studies; however, prolonged activation negatively impacted repair of the lung, liver and kidney under certain conditions.
- Compounds or treatment regimens that allow a precise timing of the extent and duration of NRF2 activation are required for the promotion of tissue repair. In addition, identification of further NRF2 target genes and their function could help to predict for what tissues or injury situations NRF2 activation may offer the greatest benefit.

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Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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Abbreviations

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; AREs, antioxidant response elements; EMT, epithelial to mesenchymal transition; KEAP1, Kelch-like ECH-associated protein 1; PAI-1, plasminogen activator inhibitor-1; PVR, proliferative vitreoretinopathy; STZ, streptozotocin; TGF, transforming growth factor.

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