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REVIEW

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NRF2-dependent stress defense in tumor antioxidant control and immune evasion

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Abstract

The transcription factor NRF2 is known as the master regulator of the oxidative stress response. Tumor entities presenting oncogenic activation of NRF2, such as lung adenocarcinoma, are associated with drug resistance, and accumulating evidence demonstrates its involvement in immune evasion. In other cancer types, the KEAP1/NRF2 pathway is not commonly mutated, but NRF2 is activated by other means such as radiation, oncogenic activity, cytokines, or other pro-oxidant triggers characteristic of the tumor niche. The obvious effect of stress-activated NRF2 is the protection from oxidative or electrophilic damage and the adaptation of the tumor metabolism to changing conditions. However, data from melanoma also reveal a role of NRF2 in modulating differentiation and suppressing anti-tumor immunity. This review summarizes the function of NRF2 in this tumor entity and discusses the implications for current tumor therapies.

KEYWORDS
immune evasion, KEAP1, Nrf2, oxidative stress

1 | INTRODUCTION

Exposure to oxidants is a widespread event in cells of every tissue origin. Cellular oxidants commonly grouped under the term reactive oxygen species (ROS) encompass an array of reduced forms of molecular oxygen, such as superoxide ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\cdot -}$). Most of these species are sufficiently reactive to undergo spontaneous reactions with lipids, DNA, or proteins. At low levels, ROS can serve as signaling modulators and impact an ever-growing list of cellular functions. ROS-dependent oxidation of proteins, including H_2O_2-dependent oxidation of accessible cysteine residues, results in altered activity of signaling proteins such as NF-kB, prolyl hydroxylases, phosphatases such as SHP-1/2 or PTEN, and many others, thereby acting as a stimulator of pro-survival and pro-proliferative pathways (Berra et al., 2003; Lee et al., 2002; Meierjohann, 2014; Oliveira-Marques et al., 2009; Weibrecht et al., 2007). ROS-dependent oxidation of lipids leads to the generation of lipid-derived electrophiles including 4-hydroxynonenal (4-HNE), the so-called second messenger of free radicals, which acts as pleiotropic modulator of several signaling pathways (Csala et al., 2015). Furthermore, by activating AMP kinase in response to glucose intake, ROS can drive proliferation, as shown previously for colorectal cancer cells (Gutierrez-Salmeron et al., 2020).

In contrast, ROS lose their beneficial cellular function at high concentrations. Elevated levels of radical ROS species can eventually lead to difficult to control chain reactions and cellular damage. ROS are commonly produced during oxidative phosphorylation in mitochondria, for example, when electrons are accidentally transferred to O_2, thus forming $O_2^{\cdot -}$ (Dan Dunn et al., 2015), but they can also be generated by cells of the innate immune system such as macrophages or neutrophil granulocytes (Morel et al., 1991). In the skin, there are additional sources of ROS. UV exposure, in particularly the long-wave UV-A, can invade the epidermal layer and can drive the transfer of electrons and

energy from cellular photosensitizers including melanin to oxygen (Panich et al., 2016; Ravanat et al., 2001). Furthermore, melanin, although very efficient in shielding the nucleus from UV-B irradiation, can serve as ROS amplifier under certain conditions. For example, UV exposure was shown to induce nitric oxide synthase (NOS), as well as NAPDH oxidases, resulting in the generation of nitric oxide ($NO^{\cdot}$) and superoxide. Both free-radical species can easily react leading to the formation the highly reactive peroxynitrite ($ONOO^{-}$), which can subsequently cause DNA damage in a melanin-dependent manner (Premi & Brash, 2016). Accordingly, when compared to other cell lineages such as keratinocytes and fibroblasts, melanocytes harbor elevated basal ROS levels (Jenkins & Grossman, 2013). Next to the black-brownish eumelanin, which is the focus of most ROS-related studies, the reddish cysteine-containing pheomelanin is also an important source of ROS. Pheomelanin is prevalent in people with red hair and fair skin, a population group characterized by distinct inactivating mutations in the melanocortin receptor MC1R, which is crucial for the response to melanocyte-stimulating hormone MSH. While a high activity of MC1R leads to the predominant formation of eumelanin, low MC1R activity results in pheomelanin formation (Valverde et al., 1995). This phenotype is reflected in mouse models, where *Mc1r* mutations also lead to a red hair/fair skin phenotype. Interestingly, the mouse models revealed that this phenotype leads to elevated ROS levels, probably due to aberrant cysteine incorporation into pheomelanin, resulting in UV-independent melanoma development (Mitra et al., 2012).

Melanomas are transformed melanocytes with a highly malignant potential and belong to the most frequent malignant tumor entities in the Northern Hemisphere. Importantly, most melanomas are still able to produce melanin and are additionally prone to produce even more ROS as a result of increased proliferation, elevated mitochondrial activation or oncogenic BRAF or NRAS, which are also a source of ROS (DeNicola et al., 2011; Haq et al., 2013; Leikam et al., 2008). Furthermore, like many other cancer types, melanomas have a strongly elevated glucose consumption, a feature which is diagnostically employed by using ^{18}F-fluorodeoxyglucose PET to detect metastases. The consumption of glucose in the glycolysis can also contribute to enhanced ROS, for example, as a result of increased production of lactate during anaerobic glycolysis (Doherty & Cleveland, 2013; Gutierrez-Salmeron et al., 2020; Tauffenberger et al., 2019). ROS also play an important role in determining the metastatic potential of tumor cells. Several lines of evidence indicate that melanoma cells experience elevated oxidative stress during the process of metastasis into the bloodstream or even distant organs. Consequently, the treatment with the antioxidant N-acetylcysteine or with inhibitors of ferroptosis can improve metastatic efficacy (Piskounova et al., 2015; Ubellacker et al., 2020). Thus, an efficient ROS defense system might make the difference between inefficient and efficient metastasizers in melanoma.

2 | ANTIOXIDANT DEFENSE MECHANISMS

To cope with the cellular sources of increased ROS, cells are equipped with a large set of enzymes and antioxidant cofactors that allow them to efficiently buffer their ROS levels and revert oxidative damage. The most abundant intracellular antioxidant is the tripeptide glutathione (GSH) or γ-glutamyl-cysteinyl-glycine. It is synthesized in an ATP-dependent two-step reaction. Due to the reactive SH group of the central cysteine, whose sufficient supply by import or de novo synthesis is crucial, GSH is very reactive and is involved in numerous redox and detoxification processes, where it serves as cofactor for a large set of enzymes, including glutathione peroxidases (GPX) and glutathione S transferases (GST). Thus, GSH is central for the reduction of H_2O_2, lipid peroxides, and mixed persulfides as well as for biotransformation. An analogous system is the thioredoxin system, where cysteine residues from reduced thioredoxin serve as cofactor for thioredoxin reductases. In both systems, the cofactors are recycled after oxidation by NADPH-dependent glutathione or thioredoxin reductase, respectively. Accordingly, NADPH supply, for example by the oxidative branch of the pentose phosphate pathway or by malic enzyme, is crucial to maintain the cellular redox balance. In addition, the cytosolic Cu/Zn superoxide dismutase (SOD1), mitochondrial Mn SOD (SOD2), and catalase are further enzymes that detoxify superoxide to H_2O_2 (SOD) or H_2O_2 to water and O_2 (catalase; reviewed in Hayes et al., 2020). Many of these antioxidant systems were shown to be required for melanoma maintenance (Cassidy et al., 2015; Jessen et al., 2020; Khamari et al., 2018; Leikam et al., 2014; Lokaj et al., 2009; Sato et al., 2020; Schmitt et al., 2015). Stress-induced transcription factors are major contributors for triggering these antioxidant pathways in response to ROS stress. These include hypoxia-inducible factor 1 α (HIF1α), activator protein 1 (AP-1), nuclear factor κB (NF-κB), p53, and activating transcription factor 4 (ATF4) (Marinho et al., 2014; Paul et al., 2018). However, the most potent effector of the oxidative stress defense is nuclear factor erythroid 2-like 2 (NFE2L2, more commonly termed NRF2).

3 | THE TRANSCRIPTION FACTOR NRF2

NRF2 is a member of the Cap "n" Collar basic leucine zipper transcription factor family. Together with NRF1 and NRF3, NRF2 belongs to a subgroup of this transcription factor family responding to cellular stress. All three have been associated with pro-tumorigenic processes (Kim et al., 2016; Kobayashi, 2020; Rojo de la Vega et al., 2018), but the function of NRF2 is by far the best understood.

NRF2 serves as major determinant for counteracting and preventing oxidative damage and is therefore deemed the master regulator of the oxidative stress response. It induces the transcription of genes involved in all major metabolic pathways that are instrumental in relieving oxidative or electrophilic stress and enabling detoxification, such as the glutathione and thioredoxin-dependent detoxification pathways, the pentose phosphate pathway, as well as phase I and phase II detoxification enzymes (reviewed in He et al., 2020; Figure 1).

As a transcription factor usually responding to emergencies, NRF2 is fine-tuned at a post-translational level and has a short half-life of 15–20 min. In the cytosol, NRF2 is bound by its interaction

partner Kelch-like ECH-associated protein 1 (KEAP1), which recruits the cullin 3 (CUL3)/RBX E3 ubiquitin ligase complex, eventually leading to proteasomal degradation of NRF2 (Cullinan et al., 2004; Kobayashi et al., 2004). Consequently, events that impair the physical interaction between KEAP1 and NRF2 constitute the main switch for activating NRF2, as they allow stabilization and nuclear accumulation of newly synthesized NRF2. Oxidative or electrophilic stress leads to the modification of cysteine residues in KEAP1, in particular Cys151, Cys226, Cys273, and Cys288, leading to a conformational change and impaired interaction with NRF2 (Baird et al., 2013; Li et al., 2012; McMahon et al., 2010; Zhang, & Hannink, 2003). Interestingly, the immunometabolite itaconate, which plays an important role in macrophage reprogramming, also modifies Cys residues in KEAP1 via alkylation and serves as potent NRF2 activator (Mills et al., 2018). In addition, the interaction between KEAP1 and NRF2 can be blocked by other means, such as binding of the autophagy marker p62/SQSTM1 to KEAP1 (Komatsu et al., 2010) or binding of p21CIP1 to NRF2 (Chen et al., 2009). Inhibiting the KEAP1-NRF2 interaction is furthermore the basis for a number of pharmacological NRF2 activators such as sulforaphane, curcumine, or tert-butylhydroquinone (Abiko et al., 2011; Kensler et al., 2013; Shin et al., 2020).

In several tumor entities such as bladder cancer, esophageal carcinoma, and (non-) small-cell lung cancer, NRF2 is found constitutively activated, either due to genetic loss or due to point mutations in KEAP1 or NRF2, resulting in impaired interaction between both proteins (Kerins & Ooi, 2018; Kim et al., 2010; Shibata et al., 2008; Singh et al., 2006). In melanoma, such mutations are found only sporadically (Miura et al., 2014), with no oncogenic NRF2 mutation and only two oncogenic KEAP1 mutations reported in the TCGA skin cutaneous melanoma dataset (Akbani et al., 2015; www.cbioportal.org). When NRF2 is activated—for example, in response to oxidative stress or due to mutational activation—it still requires an interaction partner to be transcriptionally active. The small MAF (sMAF) proteins MAFG, MAFF, and MAFK serve as NRF2 dimerization partners that enable the binding to antioxidant response elements (ARE) on the promoters of a wide array of genes (Hirotsu et al., 2012; Katsuoka et al., 2005). Additionally, MAFG was also reported to enhance the nuclear retention of NRF2 by masking the NESzip motif of NRF2, which encompasses the nuclear export signal (Li et al., 2008).

4 | NRF2 ACTIVATION IN MELANOCYTES AND MELANOMAS

Given the important contribution of UV radiation for ROS formation, it is not surprising that NRF2 activity is induced by UV in

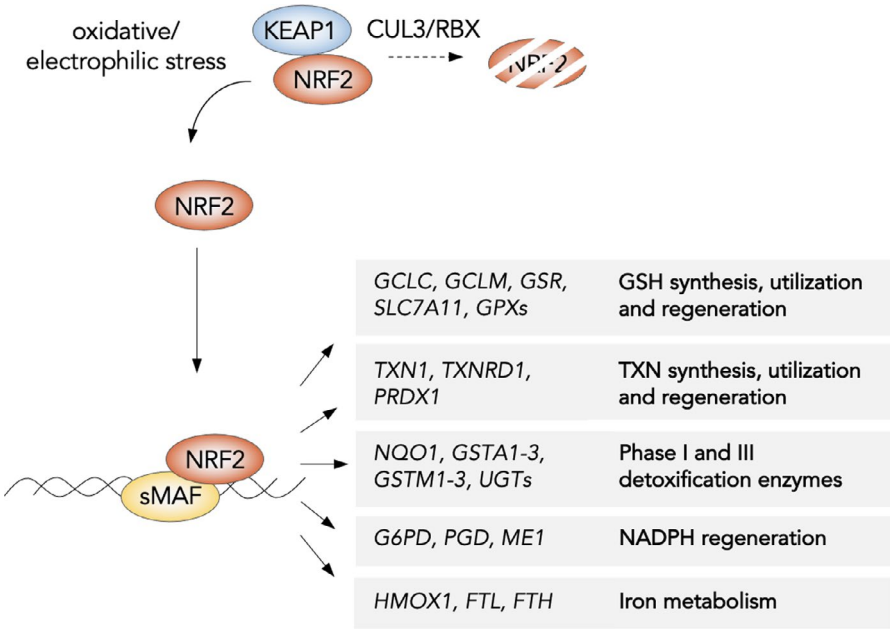

FIGURE 1 Overview of NRF2 activation and NRF2 target genes. Schematic overview of NRF2 regulation by KEAP1. In the absence of stress, NRF2 is bound by KEAP1, which serves as adapter of the CUL3/RBX complex, thus initiating NRF2 ubiquitination and degradation. Under conditions of oxidative or electrophilic stress, KEAP1 is oxidized at various Cys residues, leading to its dissociation from NRF2 and the stabilization of NRF2, which can then act as transcription factor in concert with small MAF proteins. The well-known target genes of NRF2 are instrumental for glutathione (GSH) and thioredoxin (TXN) synthesis, utilization, and regeneration, as well as detoxification, NADPH regeneration and iron metabolism. *FTH*, ferritin, heavy chain; *FTL*, ferritin, light chain; *G6PD*, glucose 6-phosphate dehydrogenase; *GCLC*, glutamyl-cysteinyl ligase, catalytic; *GCLM*, glutamyl-cysteinyl ligase, modulatory; *GPX*, glutathione peroxidase; *GSR*, glutathione reductase; *GSTA1-3*, glutathione S transferase A1-3; *GSTM1-3*, glutathione S transferase M1-3; *HMOX1*, heme oxygenase 1; *ME1*, malic enzyme 1; *NQO1*, NAD(P)H quinone dehydrogenase 1; *PGD*, phosphogluconate dehydrogenase; *PRDX1*, peroxiredoxin 1; *SLC7A11*, solute carrier family 7 member 11 (cystine-glutamate antiporter); sMAF, small MAF proteins (MAF BZIP transcription factors isoform F, G, or K); *TXN1*, thioredoxin 1; *TXNRD1*, thioredoxin reductase 1; *UGT*, UDP glucuronosyltransferase

melanocytes. The most prominent effect is caused by the ROS-generating UV-A, but UV-B has also been reported to stabilize NRF2, though to a lesser extent (Kim et al., 2017; Marrot et al., 2008; Sample et al., 2018; Zhu et al., 2018). UV-A leads to a ROS-dependent induction of autophagy (Zhao et al., 2013), resulting in the accumulation of the autophagy cargo adapter p62, also called sequestosome 1 (SQSTM1), in melanocytes and melanoma cells. This causes an increase in NRF2 (Sample et al., 2018), because p62 has the ability to bind KEAP1 and thereby blocks its inhibitory interaction with NRF2 (Komatsu et al., 2010). As SQSTM1 contains an ARE promoter element and is a direct target gene of NRF2, both are connected in a positive feedback loop (Jain et al., 2010; Sample et al., 2018). In conclusion, NRF2 has an important role in survival and stress tolerance of melanocytes, which frequently encounter cell-damaging stress due to their epidermal location. In addition to the relief of oxidative stress and the induction of autophagy, NRF2-mediated survival might also be a consequence of the ability of NRF2 to increase the expression of anti-apoptotic proteins such as BCL-2 (Jian et al., 2011; Niture & Jaiswal, 2012).

A central function of NRF2 for melanocyte resilience is also visible in vitiligo, a skin condition with progressive loss of melanocytes, leading to patches of depigmented skin. The onset of vitiligo can be triggered by exogenous oxidative stressors including sunburn (Picardo & Bastonini, 2015), and compared to melanocytes from control subjects, those from vitiligo patients suffer from hypersensitivity to oxidative stress such as H_2O_2 (He et al., 2017; Qiu et al., 2014). Interestingly, nuclear translocation and activation of NRF2 after H_2O_2-induced oxidative injury were impaired in melanocytes from vitiligo patients, and serum levels of heme oxygenase 1, an indicator for NRF2 activity, were significantly reduced in a large patient cohort of 114 vitiligo patients compared to controls (Jian et al., 2014). Along the same lines, a polymorphism in the promoter region of NRF2 was associated with elevated vitiligo risk in a Han Chinese population (Guan et al., 2008), thus implying that Nrf2 plays an active role in the pathogenesis of vitiligo. However, as NRF2 knockout mice show normal pigmentation, NRF2 is not required for melanocyte survival under unstressed conditions, but rather seems to be relevant under conditions of exogenous stress such as UV exposure (Chan et al., 1996).

Melanomas harbor additional NRF2 triggers. Many melanomas express oncogenic $BRAF^{V600E/K}$ or $NRAS^{Q61K/R}$, which are present in approximately 50% and 20% of cutaneous melanomas, respectively (Appenzeller et al., 2019; Akbani et al., 2015). Oncogenic $BRAF^{V619E}$, the murine counterpart of $BRAF^{V600E}$, can elevate NRF2-dependent transcription of target genes, an observation that was confirmed for inducible $BRAF^{V600E}$ in melanocytes (DeNicola et al., 2011; Jessen et al., 2020). As oncogenic $KRAS^{G12D}$ has a similar effect (DeNicola et al., 2011), it is plausible to assume that an activation of the MAPK pathway by RAF or RAS isoforms could be generally regarded as bona fide NRF2 activator.

5 | LINK BETWEEN NRF2 AND PIGMENTATION

Next to protecting from UV stress, NRF2 activity is also linked to melanocyte and melanoma differentiation and pigmentation, which are largely regulated by the microphthalmia-associated transcription factor MITF. MITF is a basic helix-loop-helix leucine zipper protein specifically binding to E boxes (5′-TCACGTGA-3′) and M boxes (5′-TCATGTG-3′) that are found in the promoter region of genes involved in melanin synthesis and melanosome formation such as tyrosinase (*TYR*) and Melanoma Antigen Recognized by T cells 1 (*MART1 or MLANA*), respectively (Bentley et al., 1994; Du et al., 2003). Several lines of evidence indicate that NRF2 limits differentiation features in melanocytes. In neonatal human dermal melanocytes (NHEM), NRF2 overexpression decreased the protein expression of pigmentation markers including *TYR*, resulting in a reduction in melanin content, while KEAP1 overexpression had the opposite effect (Shin et al., 2014). In another study focusing on the role of autophagy for melanocyte biology, it was found that a lack of autophagy mediated by ATG7 knockout led to an increase in oxidative stress and the induction of NRF2 targets, which correlated with dedifferentiation (Qiao et al., 2020). As already mentioned, UV-A exposure leads to an induction of NRF2 in melanocytes as well as in melanoma cells (Chaiprasongsuk et al., 2016). UV-A exposure has also been associated with an increase in tyrosinase protein and consequently melanin content. This increase was further enhanced when NRF2 levels were reduced by shRNA, thereby supporting an inhibitory effect of NRF2 on pigmentation (Chaiprasongsuk et al., 2016). The biological benefit of the NRF2-mediated dedifferentiation in melanocytes is not yet understood. However, it is possible that it helps to support melanocyte proliferation under conditions of stress recovery, as lowered MITF levels in melanocytes were shown to enhance proliferation in a zebrafish model (Taylor et al., 2011).

An influence of NRF2 on pigmentation was also shown for melanoma. In a recent study comparing the transcriptome of human melanoma cells transfected with control and NRF2-specific siRNA, the process “pigmentation” was found to be upregulated in NRF2 silenced cells (Jessen et al., 2020). While differentiation genes *TYR*, *DCT*, and *MLANA* were increased, expression levels of MITF were unaltered, which was consistent with the observation that NRF2 does not bind to the MITF promoter. However, NRF2 inhibited MITF transcriptional activity in a *TYR* promoter-driven luciferase assay, indicating that NRF2 counteracts MITF by a yet to be defined mechanism (Jessen et al., 2020). This underscores the role of NRF2 for melanoma malignancy, as melanomas with dedifferentiated features have a less favorable outcome (Takeuchi et al., 2003), and fits the observation that high nuclear NRF2 correlates with worse overall survival in melanoma (Hintsala et al., 2016).

6 | INTERFERENCE OF NRF2 WITH THE IMMUNE SYSTEM

Many of the MITF-regulated pigmentation markers such as TYR, DCT, and MLANA give rise to strongly antigenic surface peptides that are readily presented by major histocompatibility complex type I (MHCI) membrane proteins (Coulie et al., 1994; Fassler et al., 2019). Dedifferentiated melanomas, characterized by a $MITF^{low}$ signature, can therefore more likely escape immune control by cytotoxic T cells (Landsberg et al., 2012). The cytokine tumor necrosis factor α (TNFα) was reported as a potent trigger of dedifferentiation, as shown in cell culture and mouse studies (Landsberg et al., 2012; Riesenberg et al., 2015), and this inflammation-induced dedifferentiation contributed to the resistance to adoptive T-cell transfer in melanoma patients (Mehta et al., 2018). Falletta and colleagues have revealed that extended timespans of TNFα treatment coincided with activation of the transcription factor ATF4, the effector of the integrated stress response, which drives the $MITF^{low}$ signature and the dedifferentiating effect of TNFα (Falletta et al., 2017). ATF4 serves as hub for integrating the response to various cellular stressors including ER stress, amino acid depletion, heme depletion, and viral infection. These stressors lead to the activation of the eIF2α kinases PERK, GCN2, HRI, and PKR, respectively, resulting in phosphorylation of eIF2α on position serine 51. While this blocks translation initiation and thereby global protein synthesis, the translation of ATF4 is enabled by a concerted mechanism involving the usage of an upstream open reading frame, which allows the correct ribosomal scanning and translation of the ATF4 transcript (Pakos-Zebrucka et al., 2016). As ATF4 responds to these various stress sources, it becomes activated under many conditions. Interestingly, TNFα is not only a trigger for ATF4, but also serves as potent activator of NRF2, which furthermore contributes to the dedifferentiation effect (Jessen et al., 2020). ATF4 and NRF2 are reported to physically interact and activate a subset of downstream genes interdependently (DeNicola et al., 2015; He et al., 2001), thus both transcription factors seem to jointly coordinate the TNFα-initiated stress response in melanoma. As illustrated by the example of the cytokine TNFα, melanoma cells can be driven into an $MITF^{low}$ state by external stress. This is also observed under therapy pressure, for example, in case of sustained BRAF or BRAF/MEK inhibition (Kemper et al., 2014; Muller et al., 2014). In particular, $MITF^{low}$ melanomas are characterized by the increased expression of receptor tyrosine kinases (RTK), such as AXL and EGFR, that contribute to the resistance of $BRAF^{V600E}$-mutant melanomas to BRAF/MEK inhibition (Ji et al., 2015; Muller et al., 2014). Notably, NRF2 supports the expression of EGFR in $MITF^{low}$ melanoma cells, thereby implicating that NRF2 is establishing and/or maintaining an $MITF^{low}/EGFR^{high}$ state (Jessen et al., 2020). Although the causes and consequences of NRF2-mediated EGFR expression in melanoma are not yet understood, data from KEAP1-mutant NSCLC support a role of NRF2 in RTK signaling, as NRF2 leads to elevated levels and activation of several RTKs including IGF1R, ERBB3, and EGFR in this tumor subtype (Chio et al., 2016; Vartanian et al., 2019).

In addition to altering the availability of differentiation antigens, NRF2 also has the capacity to block tumor immunity by several other means. UV exposure of melanocytes triggers the expression of the immune checkpoint ligand programmed death-like 1 (PD-L1), which mediates inhibitory interactions between tumor cells and effector T cells in an NRF2-dependent manner (Zhu et al., 2018). Reversely, shRNA-mediated depletion of NRF2 increases CD4+ and CD8+ T cells and suppresses melanoma progression in vivo (Zhu et al., 2018). In our own study, the in vivo function of NRF2 in melanomas was addressed by knocking out endogenous NRF2 in BRAF-mutant murine melanoma cells before injecting them subcutaneously into immune-competent mice (Jessen et al., 2020). In accordance with the study by Zhu et al. (2018), reduced melanoma growth and increased immune cell infiltration were observed. However, the effect was stronger, and several mice injected with NRF2-ko melanomas did not develop tumors at all, which is most likely due to the complete lack of tumor NRF2. RNA sequencing analysis revealed a striking upregulation of the gene set "defense to virus," an innate immune response gene signature responding to cytosolic DNA, in NRF2-ko melanomas (Jessen et al., 2020). The presence of cytosolic DNA is typically observed in response to viral infections, where it triggers the cGAS/STING pathway, resulting in the induction of type I interferons, cytokines, helicases, and other virus defense genes (Ni et al., 2018). Interestingly, it was previously described that infection with DNA viruses such as Herpes simplex in NRF2-deleted mice is severely impaired due a strongly increased capacity to induce type I interferon response, which largely overlaps with the "defense to virus" response. This led to a significantly reduced virus load in NRF2-deficient MEFs (Gunderstofte et al., 2019) and shows that NRF2 also contributes to the suppression of the innate immune response. Similar observations were made in human cells, where NRF2 repressed STING RNA and protein expression (Olagnier et al., 2018). In cancer, cytosolic DNA can be caused by damage of nuclear or mitochondrial DNA. Importantly, tumor immunogenicity has been reported to be strongly enhanced by activation of the cGAS/STING pathway (Schadt et al., 2019) and STING activation can break resistance to PD-1 blockade in mice (Fu et al., 2015). It is therefore likely that by suppressing the cGAS/STING pathway, NRF2 promotes an immune-cold microenvironment.

This theory is further supported by the observation that NRF2 serves as potent inducer of cyclooxygenase 2 (COX2), an enzyme that converts phospholipid-derived arachidonic acid into prostaglandin H2 (PGH2), which is the precursor for PGE2. PGE2 has been shown to block the activation of T cells by attenuating T-cell receptor (TCR) signaling and thereby provides an immune-evasive tumor environment (Wiemer et al., 2011). In addition, the induction of the innate immune response is reduced by PGE2 (Zelenay et al., 2015). In mouse models of melanoma, successful tumor growth depends on the tumor's ability to secrete PGE2, which mediates immune

tolerance, for example, by impairing the infiltration of type I dendritic cells into the tumor and limiting T-cell-mediated tumor elimination (Bottcher et al., 2018; Zelenay et al., 2015). Basal as well as H_2O_2- and TNFα-induced COX2 induction is dependent on NRF2, and a strong reduction in PGE2 is observed in NRF2-depleted human melanoma cells and mouse melanomas (Jessen et al., 2020). COX2 is encoded by the gene prostaglandin endoperoxide synthase 2 (*PTGS2*). The *PTGS2* promoter does not bind NRF2, but has a binding site for ATF4, which serves as strong activator of *PTGS2* expression downstream of NRF2. Importantly, forced overexpression of NRF2 or ATF4 leads to a robust upregulation of *PTGS2*, but only in presence of the respective other partner (Jessen et al., 2020 and unpublished results). Thus, the joint activation of ATF4 and NRF2 is required for the induction of immune-suppressive COX2. These observations underline the tight linkage of these two stress-induced transcription factors. This is further supported by studies of the PERK-mediated ER stress response. Next to activating ATF4 translation by phosphorylating eIF2α, PERK also phosphorylates NRF2, resulting in dissociation from KEAP1 and NRF2 stabilization (Cullinan et al., 2003). Further, ATF4 can also induce the transcription of NRF2 under conditions of ER stress (Sarcinelli et al., 2020). Although this was not investigated, it is therefore highly likely that ER stress will also serve as potent trigger of COX2 in melanoma.

7 | POTENTIAL ROLE OF NRF2 IN TARGETED THERAPY RESISTANCE AND FERROPTOSIS

It is known from KEAP1 mutated lung cancer that activation of the NRF2 pathway enables the development of resistance to chemotherapy as well as EGFR-targeted therapy (Frank et al., 2018; Park et al., 2018). Elevated NRF2 activity was also detected in A375 melanoma cells with acquired resistance to BRAF inhibitor, where it contributed to vemurafenib resistance (Khamari et al., 2018). After extended BRAF/MEK inhibition for several days, a small fraction of melanoma cells is able to withstand targeted cancer therapy and forms a resilient cancer cell pool until acquired resistance develops. This initial drug-tolerant state has acquired a dedifferentiated and mesenchymal-like signature (Tsoi et al., 2018; Viswanathan et al., 2017), features reminiscent of the changes caused by NRF2. It was demonstrated that dedifferentiated melanoma cells are particularly sensitive to ferroptosis inducers such as inhibitors of the selenocysteine containing enzyme glutathione peroxidase 4 (GPX4) or the xCT cystine-glutamate antiporter system, an intracellular cysteine source for the generation of glutathione (GSH). Ferroptosis is caused by iron-dependent peroxidation of unsaturated membrane lipids, which triggers a toxic chain reaction ultimately leading to cell death (Friedmann Angeli et al., 2019; Nehring et al., 2020). GPX4 detoxifies oxidized lipids and is therefore one of the main players in preventing ferroptosis (Friedmann Angeli et al., 2014; Yang et al., 2014), along with pathways supplying the GPX4 cofactor GSH (Dixon et al., 2012). Furthermore, other lipid radical scavengers such as coenzyme Q10 as well as factors determining availability of cellular iron or unsaturated membrane lipids have been reported to contribute to ferroptosis sensitivity (Doll et al., 2017, 2019; Friedmann Angeli et al., 2019). NRF2 induces a large set of ferroptosis-relevant genes including *GPX4* and the gene encoding the xCT cystine-glutamate antiporter *SLC7A11* (Figure 1 and Dai et al., 2020), and NRF2-ko melanoma cells show a marked sensitivity to GPX4 inhibitors (unpublished observations). How can these contrasting roles of NRF2 be reconciled? On the one hand, NRF2 supports melanoma dedifferentiation, a state, which reportedly sensitizes cancer cells to ferroptosis. On the other hand, NRF2 is a potent inducer of genes enabling ferroptosis resistance. Possibly, NRF2 serves as a marker of permanent oxidative stress, indicating a state where cells are particularly close to a maximal pro-oxidant threshold and can be easily driven into ferroptosis. Although anti-ferroptotic processes are already running, these might not be sufficient to tolerate the additional stress caused by GPX4 inhibitors. Future studies will be required to clarify the role of NRF2 in ferroptosis-sensitive drug-tolerant cells.

8 | IMMUNE THERAPY: THERAPEUTIC IMPLICATIONS

The link between NRF2 and immune tolerance has already been indicated in lung adenocarcinoma, where KEAP1 mutations are present in up to 20%, leading to permanent NRF2 activation (Cancer Genome Atlas Research, 2014; www.cbioportal.org). RNA sequencing revealed that KEAP1 mutated non-small-cell lung cancers show a reduced expression of a T-cell-inflamed gene expression signature (GEP) independent of tumor mutational burden (Cristescu et al., 2018), thus supporting an immune-suppressive role of NRF2 in cancer. This is relevant for cancer therapy, as the T-cell-inflamed GEP correlated with responsiveness toward anti-PD-1 immune therapy (Cristescu et al., 2018). An inhibition of the immune-evasive effects of NRF2 might therefore have the potential to trigger the endogenous anti-tumor response or increase the responsiveness to existing checkpoint inhibitor therapy. NRF2 itself is currently not targetable, as available inhibitors lack specificity.

However, downstream effectors of NRF2 such as COX2 or STING are attractive targets, with inhibitors and agonists, respectively, already approved or in clinical trials. In a $BRAF^{V600E}$ mouse model, COX inhibition with aspirin strongly synergized with anti-PD-1 immune therapy (Zelenay et al., 2015). Similar observations were made with the COX2 inhibitor celecoxib, which sensitized pancreatic cancer to immune checkpoint blockade in mouse models (Markosyan et al., 2019). In humans, a retrospective study revealed an increased time to progression in checkpoint inhibitor-treated melanoma patients if they also co-administered COX inhibitors (Wang et al., 2020). Clinical phase II trials are underway to test the effect of aspirin in combination with PD-1 and CTLA4-targeting checkpoint inhibitors in melanoma (www.clinicaltrials.gov).

In addition, the negative effect of NRF2 on the cGAS/STING pathway might constitute a targetable Achilles heel. Although

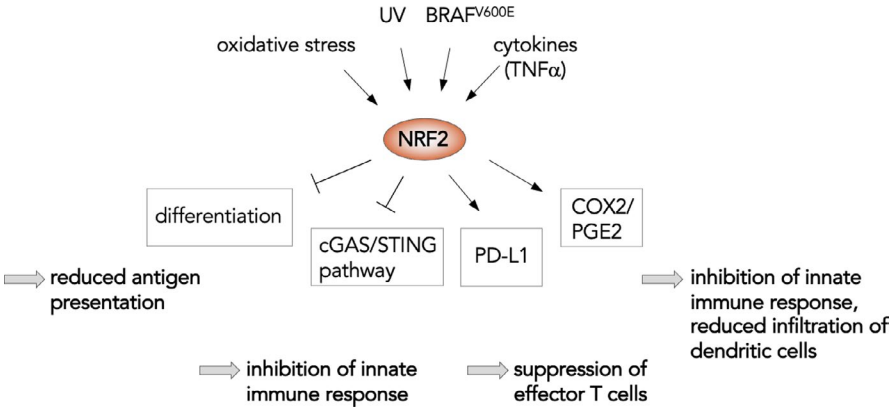

FIGURE 2 Activators of NRF2 and immune-relevant effects in melanoma, as discussed in this review

reduced pathway activation correlates with reduced immunogenicity (Schadt et al., 2019), it sensitizes to viral infection, as already mentioned (Gunderstofte et al., 2019; Olagnier et al., 2018). Interestingly, a recent report described the susceptibility of STING-deficient melanoma cells to Talimogene laherparepvec (T-VEC), an oncolytic Herpes simplex virus engineered to express granulocyte–macrophage colony-stimulating factor (GM-CSF), which is approved for melanoma therapy (Bommareddy et al., 2019). A T-VEC therapy might therefore serve as promising approach after previous stimulation of NRF2, for example, by oxidative stress inducers or cytokine treatment.

In summary, it emerges that NRF2 is a central hub, not only to counteract acute oxidative stress on the cellular level, but also to prevent immune recognition and cell clearance of the damaged cells (Figure 2). This protective system is hijacked in tumors like melanoma and non-small-cell lung cancer, where it contributes to immune evasion and therapy resistance.

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CONFLICT OF INTEREST

The authors have no conflict of interest in relation to this work.

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