ANNUAL REVIEWS

Annual Review of Cancer Biology

The Pleiotropic Role of the KEAP1/NRF2 Pathway in Cancer

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Annu. Rev. Cancer Biol. 2020. 4:413–35

The *Annual Review of Cancer Biology* is online at cancerbio.annualreviews.org

https://doi.org/10.1146/annurev-cancerbio-030518-055627

Keywords

KEAP1, *NRF2/NFE2L2*, reactive oxygen species, cancer metabolism, autophagy, tumor microenvironment, immunometabolism, therapy

Abstract

The unregulated proliferative capacity of many tumors is dependent on dysfunctional nutrient utilization and ROS (reactive oxygen species) signaling to sustain a deranged metabolic state. Although it is clear that cancers broadly rely on these survival and signaling pathways, how they achieve these aims varies dramatically. Mutations in the KEAP1/NRF2 pathway represent a potent cancer adaptation to exploit native cytoprotective pathways that involve both nutrient metabolism and ROS regulation. Despite activating these advantageous processes, mutations within *KEAP1/NRF2* are not universally selected for across cancers and instead appear to interact with particular tumor driver mutations and tissues of origin. Here, we highlight the relationship between the KEAP1/NRF2 signaling axis and tumor biology with a focus on genetic mutation, metabolism, immune regulation, and treatment implications and opportunities. Understanding the dysregulation of KEAP1 and NRF2 provides not only insight into a commonly mutated tumor suppressor pathway but also a window into the factors dictating the development and evolution of many cancers.

INTRODUCTION

The disruption of cellular redox state and nutrient metabolism is a crucial barrier to tumorigenesis that widely intersects with pathways regulating cell proliferation, stress response, genome stability, and bioenergetics. Mutations of the KEAP1/NRF2 pathway are commonly selected for in order to overcome these obstacles during the course of cancer development. In order to understand how this pathway is used in a context-dependent fashion to deal with the unique challenges facing tumors, we begin by briefly addressing the function of the KEAP1/NRF2 pathway in normal physiology and development. This serves as a useful conceptual framework for subsequent sections where we discuss how cancer cells hijack *KEAP1/NRF2* function in pathophysiology. The KEAP1/NRF2 pathway plays a central role in supporting and driving tumorigenesis; understanding the molecular and physiological factors governing this pathway will provide deeper insights into the biology and successful treatment of cancer.

KEAP1/NRF2 FUNCTION

KEAP1 (Kelch-like ECH-associated protein 1) is a member of the BTB (Broad complex, Tramtrack, and Bric-à-brac)-Kelch domain family of protein adaptors that provides substrate specificity for the CUL3 (Cullin 3)/RBX (RING box 1) E3 ubiquitin ligase complex (Itoh et al. 1999). KEAP1 serves as the major negative regulator of the master antioxidant transcription factor NFE2L2 (nuclear factor erythroid 2–like 2), also known as NRF2; KEAP1 homodimerization is necessary to bind to both DLG and ETGE degron motifs within the Neh 2 (NRF2-ECH homology 2) domain and facilitates NRF2 proteasomal degradation under basal conditions, ultimately preventing NRF2 nuclear translocation (**Figure 1*a***) (Itoh et al. 1999, Kobayashi et al. 2004, Zhang et al. 2004). The detailed biochemical mechanisms underlying the KEAP1/NRF2 interaction have been the focus of intense study, and the reader is directed to several reviews discussing this topic in greater depth (Baird et al. 2014, Suzuki & Yamamoto 2015). In response to the accumulation of reactive species, sulfhydryl groups of key cysteine residues on KEAP1 become modified and impair targeting of NRF2 for degradation (**Figure 1*b***) (Kobayashi et al. 2004, Zhang et al. 2004). Sulfhydryl modifications not only include classic hydroxyl reactive oxygen species (ROS) and nitrosyl reactive nitrogen species, but also metabolic intermediates from the tricarboxylic acid (TCA) cycle (fumarate, succinate, and itaconate), lipid metabolism, glycolysis (methylglyoxal and glycosylation), and undoubtedly additional factors that have yet to be identified (**Figure 2**, **Table 1**) (Adam et al. 2011, Bollong et al. 2018, Kinch et al. 2011, Mills et al. 2018, Ooi et al. 2011). The vast and varied nature of these modifications allows KEAP1/NRF2 signaling to respond not only to xenobiotic stressors and ROS but also to other insults to cellular physiology such as proteotoxicity or the disruption of endogenous metabolism. Nevertheless, these signals ultimately converge to abrogate KEAP1-directed inhibition of NRF2 and activate a potent cytoprotective response network.

NRF2 is a Cap'n'collar transcription factor family member that provides target specificity to small MAF proteins toward antioxidant response elements and activates a battery of detoxification, metabolic, and DNA damage response enzymes that reestablish cellular redox homeostasis (Igarashi et al. 1994, Itoh et al. 1997). The major mediators of this redox defense system include enzymes involved in the metabolism of glutathione (GSH), NADPH, redoxin protein family members (e.g., TXN, PRDX, SRXN), drug biotransformation and efflux multidrug resistance–associated proteins, and enzymes involved in iron homeostasis (**Figure 3**). Increased production of the cofactor NADPH is essential to support the redox cycling mechanisms of these enzymes that work to detoxify ROS and xenobiotics (**Figure 3**) (DeNicola et al. 2015, Mitsuishi et al. 2012).

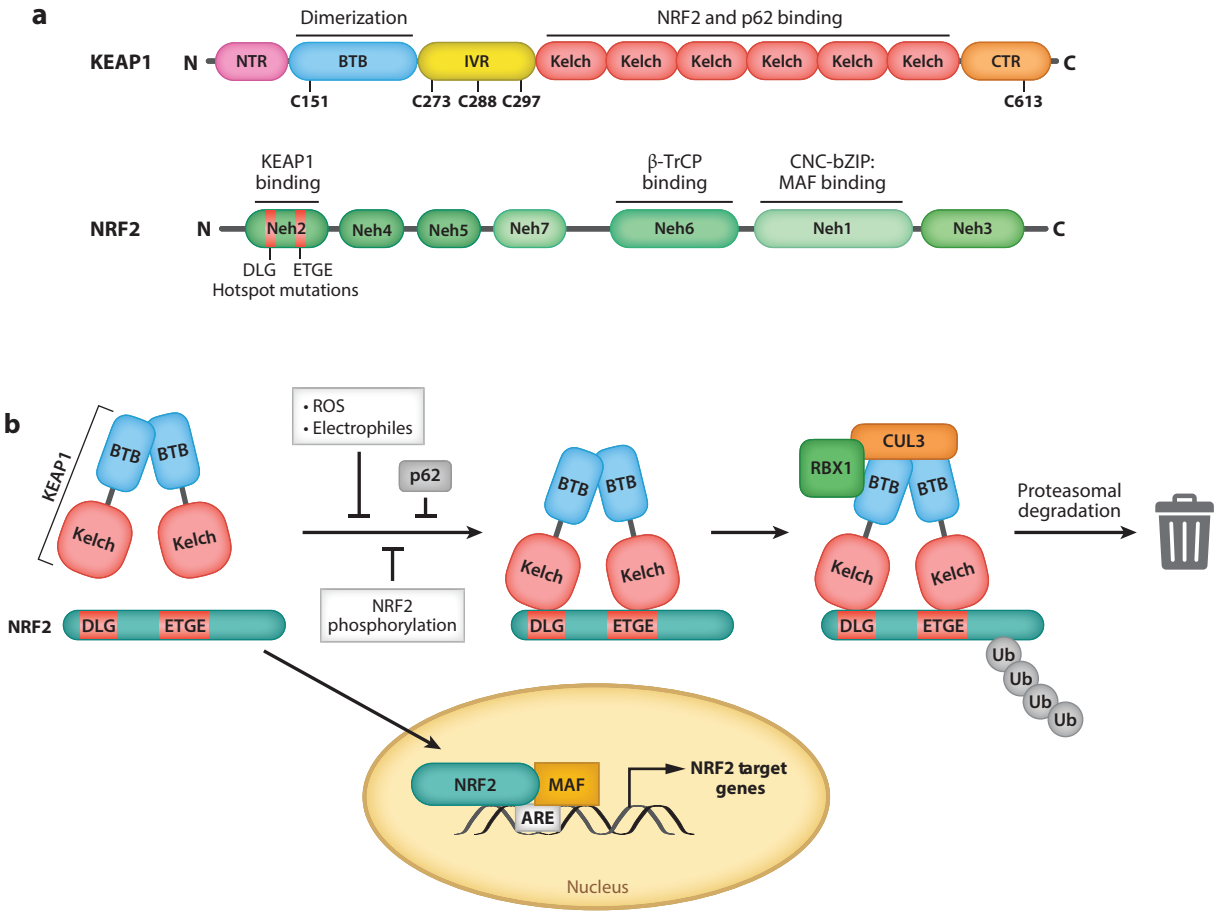

Figure 1

KEAP1/NRF2 signaling pathway. (*a*) NRF2 and KEAP1 protein domains. KEAP1 contains an amino-terminal region (NTR; *purple*), a broad complex/Tramtrack/Bric-à-brac (BTB; *blue*) domain, an intervening region (IVR; *yellow*), six Kelch domains (*red*), and the C-terminal region (CTR; *orange*). Annotated across KEAP1 are cysteine residues posttranslationally modified to enable NRF2 activation. NRF2 contains seven NRF2-ECH homology (Neh; *green*) domains. Highlighted in red in the Neh2 domain are the two most frequently mutated NRF2 codons, DLG and ETGE. (*b*) KEAP1 homodimerizes through the BTB domain, and through the Kelch domains KEAP1 interacts with NRF2 at the ETGE and DLG motifs. KEAP1 binds CUL3 (Cullin 3) and RBX1 (RING box 1) to form an E3 ubiquitin ligase complex that ubiquitinates NRF2 and promotes its proteasomal degradation in the cytoplasm. Multiple posttranslational modifications on KEAP1 cysteines by reactive oxygen species (ROS) or electrophiles (see **Table 1**) lead to stabilization and release of NRF2 from KEAP1 and the nuclear translocation of NRF2. Additionally, p62 can bind to KEAP1 and sequester it from NRF2, therefore leading to NRF2 stabilization. Phosphorylation of NRF2 can also lead to its release from KEAP1. Upon stabilization, NRF2 enters the nucleus where it dimerizes with the transcriptional activator MAF and induces expression of target genes that contain the ARE (antioxidant response element) motif.

In order to sustain this requirement for NADPH and other substrates, NRF2 diverts glutamine, glucose, and glycolytic intermediates into anabolic pathways such as the pentose phosphate pathway, glutaminolysis, de novo serine synthesis, and de novo purine synthesis (**Figure 2**) (DeNicola et al. 2015, Mitsuishi et al. 2012, Sayin et al. 2017). The KEAP1/NRF2 pathway orchestrates a dramatic reorganization of cellular metabolism in order to efficiently combat redox stressors and preserve cellular homeostasis.

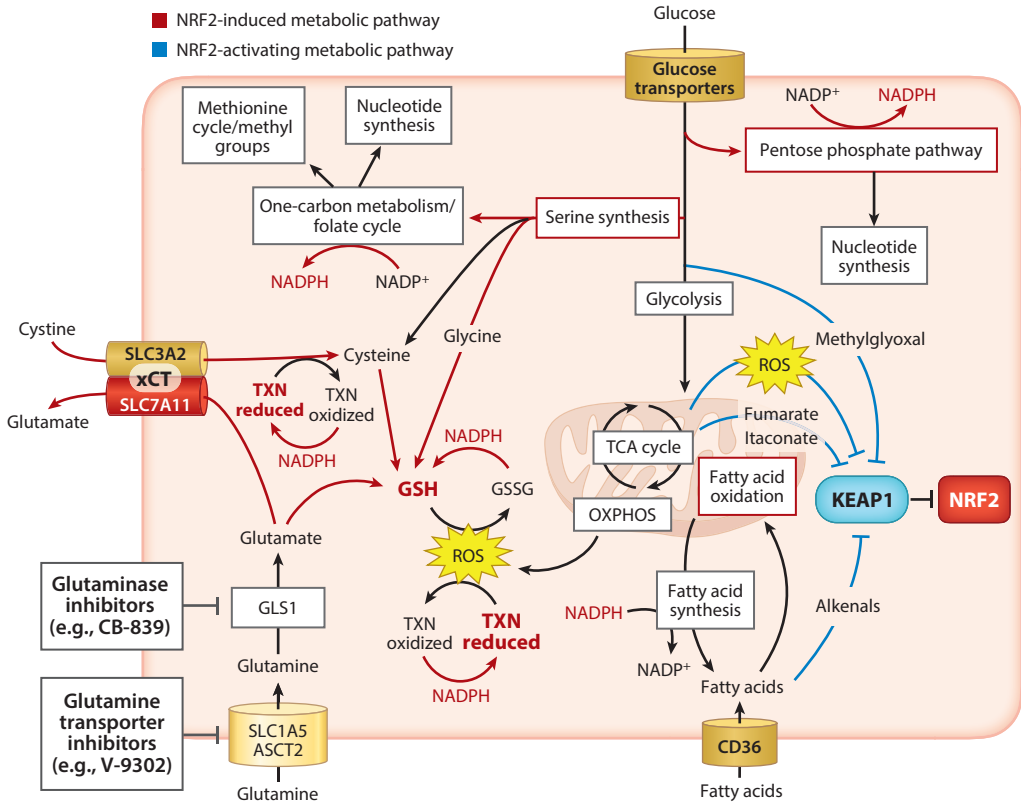

Figure 2

The interplay of the NRF2/KEAP1 pathway with cellular metabolism. NRF2 induces several metabolic pathways (*red*): Serine synthesis coupled to one-carbon metabolism can lead to NADPH regeneration, methyl group production, nucleotide synthesis, and the amino acids glycine and cysteine. The pentose phosphate pathway (PPP) regenerates NADPH and maintains nucleotide synthesis. Glutamine-derived glutamate along with glycine and cysteine form glutathione (GSH), the most abundant cellular antioxidant. Cysteine levels are maintained by cystine uptake in exchange for glutamate by the system x_c^- (xCT) antiporter, which consists of a heterodimer of SLC3A2 and SLC7A11, a bona fide NRF2 target. GSH and thioredoxin (TXN) scavenge reactive oxygen species (ROS) generated primarily from mitochondrial oxidative phosphorylation (OXPHOS) and form oxidized GSH (GSSG) and oxidized TXN, respectively. NADPH is essential for the reduction of both GSSG and oxidized TXN. Metabolic pathways that activate NRF2 (*blue*): Mitochondrial ROS, glycolysis-derived methylglyoxal, TCA (tricarboxylic acid) cycle–derived itaconate and fumarate, and polyunsaturated fatty acid alkenals can posttranslationally stabilize NRF2 (see **Table 1**).

PHYSIOLOGY AND DEVELOPMENT

Genetic rodent models have revealed the importance of the KEAP1/NRF2 pathway in development. Germline deletion of *Keap1* in mice leads to postnatal lethality due to esophageal hyperkeratinization through the effects of Nrf2; epistasis studies of esophageal *Nrf2* deletion in a *Keap1*-null background unmasks significant growth defects and disruption of both bone mineralization and renal homeostasis (Suzuki et al. 2017, Wakabayashi et al. 2003, Yoshida et al. 2018). Conditional tissue-specific deletions of *Keap1* have revealed more nuanced effects including lineage skewing in the hematopoietic compartment, resistance to adiposity and diet-induced obesity, and the expected resistance to drug toxicity and redox stressors (Blake et al. 2010, Murakami et al. 2014, Okawa et al. 2006). Notably, some of these phenotypes only manifest when *Keap1* is deleted during development and not during adulthood, which indicates that there are critical periods when Keap1/Nrf2

Table 1 Summary of the electrophilic molecules known to activate NRF2 by reacting with KEAP1 cysteine residues

Molecule	Source	Mechanistic implications
Fumarate/dimethylfumarate	Metabolism: TCA (tricarboxylic acid) cycle intermediate	Activation of NRF2 in response to block of TCA cycle
Nitric oxide	Metabolism: free radical produced by nitric oxide synthase (NOS)	NRF2-dependent increase in NADPH to support NOS activity
Alkenals	Metabolism: lipid peroxidation	NRF2 targets suppress lipid peroxidation
Methylglyoxal	Metabolism: glycolysis, lipid peroxidation, and threonine catabolism	NRF2-dependent detoxification of methylglyoxal
Itaconate	Metabolism: produced by the TCA cycle intermediate citrate	Metabolic activation of NRF2 in response to changes in TCA cycle
Sulforaphane (SFN)	Nutrition: natural product in vegetables	Dietary SFN may active the NRF2 pathway
Tertiary butylhydroquinone (tBHQ)	Nutrition: preservative in vegetable oils	Dietary tBHQ may active the NRF2 pathway
Zn^{2+}	Nutrition	Potentially required for NRF2 transcriptional activity
15-deoxy-$\Delta^{12,14}$-prostaglandin J2	Metabolism: prostaglandins derived from arachidonic acid	Cross talk between NRF2, G protein–coupled receptors, and peroxisome proliferator–activated receptor gamma. Regulation of glutathione-dependent processes
1,2-naphthoquinone	Environment: from natural and anthropogenic sources of naphthalene	NRF2-dependent detoxification of toxic pollutant
Cadmium chloride	Environment: industrial pollutant	NRF2-dependent detoxification of toxic pollutant
Methyl-mercury	Environment: from natural and anthropogenic sources of mercury	NRF2-dependent detoxification of toxic pollutant
Arsenic	Environment: from natural and anthropogenic sources	NRF2-dependent detoxification of toxic pollutant
Diethylmaleate	Environment: from anthropogenic sources	NRF2-dependent detoxification of toxic pollutant
Dexamethasone (DEX)	Drug: FDA-approved glucocorticoid agonist of glucocorticoid receptor	Anti-inflammatory use of DEX may also stimulate the NRF2 antioxidant program

signaling is important. Consistently, many of these developmental phenotypes result from impaired or dysfunctional stem cell differentiation programs, which suggests that KEAP1/NRF2 regulates the cell fate decisions of multiple germ layer derivatives. This effect likely functions by modulating intracellular ROS levels; however, evidence from human embryonic stem cells has also implicated KEAP1/NRF2-dependent regulation of proteostasis and autophagy as a modulator of cellular differentiation and identity (Jang et al. 2014, Paul et al. 2014, Suzuki et al. 2017).

Although viable, aged *Nrf2*-null mice show disruption of central nervous system (CNS) myelination and signs of immune activation (Hubbs et al. 2007, Ma et al. 2006, Pi et al. 2010). This immunomodulatory effect is significant, as *Nrf2* deletion predisposes animals to develop lupus-like and other autoimmune diseases across organ systems (Ma et al. 2006, Yoh et al. 2001). Rare instances of human germline gain-of-function (GOF) mutations leading to constitutive NRF2 activation have been reported and have led to deficiencies in CNS myelination (Huppke et al. 2017). This particular disease presentation mirrors leukodystrophies observed in several forms of mitochondriopathies, which would be consistent with in vitro reports of altered mitochondrial bioenergetics and lipid metabolism in both untransformed and cancerous *Keap1*/*Nrf2*-mutant cells (Ludtmann et al. 2014, Sayin et al. 2017). This observation contrasts with the therapeutic model of using Nrf2 activators to ameliorate mitochondriopathies and may be reconciled by the fact

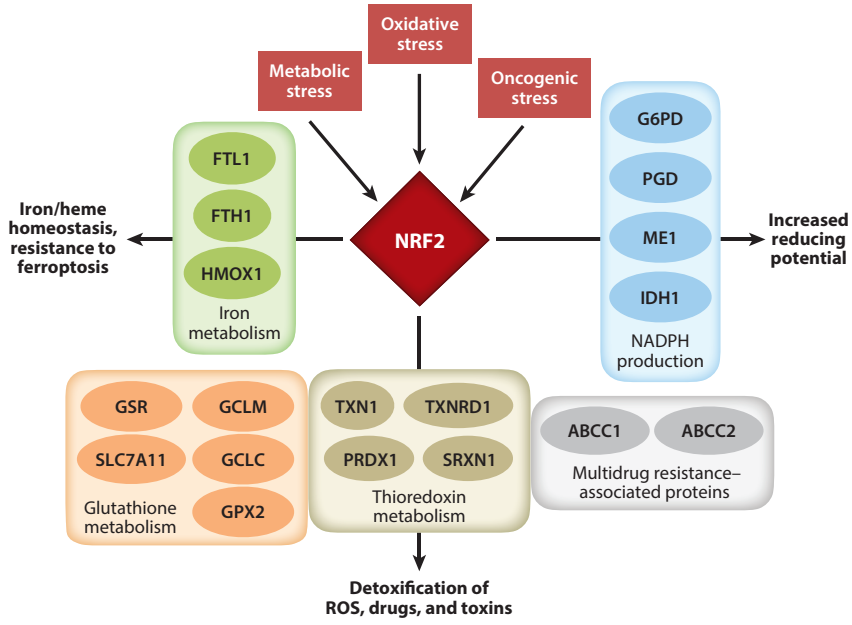

Figure 3

The major activating inputs and functional outputs of the NRF2 pathway. NRF2 is activated in response to oxidative stress, metabolic stress, and various oncogenic stress signals upstream. NRF2 is a pleiotropic transcription factor that induces the expression of a plethora of downstream target genes. Highlighted are some of the most well-studied functional outputs of the NRF2 pathway. Glutathione (GSR, GCLC, GCLM, GPX2, and SLC7A11), multidrug resistance–associated proteins (ABCC1 and ABCC2), and thioredoxin (TXN1, PRDX1, TXNRD1, and SRXN1) metabolism proteins mediate detoxification of ROS, drugs, and toxins (see **Table 1**). The glucose-dependent pentose phosphate pathway enzymes G6PD and PGD and the central carbon metabolism enzymes ME1 and IDH1 increase the reducing capacity of cells by regenerating NADPH. Heme degradation by HMOX1 and iron sequestration by FTL1 and FTH1 maintain heme and iron homeostasis, preventing iron accumulation and ferroptosis.

that chronic and unregulated Nrf2 activity may be unsustainable in terms of nutrient utilization (Hubbs et al. 2007, Sayin et al. 2017). These findings suggest that the acute and dynamic regulation of Nrf2 is essential for homeostasis and may reflect the consequences of disrupting natural circadian or redox oscillations that have been observed in Nrf2 activity (Hubbs et al. 2007, Huppke et al. 2017, Pekovic-Vaughan et al. 2014, Pi et al. 2010).

In the rare reports of human *NRF2*-activating germline mutations, no associated cancer syndromes have been reported, which is in line with *Keap1*-null animal models (Huppke et al. 2017). Human germline loss-of-function (LOF) mutations in *KEAP1* are also not associated with familial cancer syndromes; however, they do predispose individuals to develop multinodular goiters (Teshiba et al. 2013). It has been proposed that the redox stress experienced during the production of thyroid hormone selects for *KEAP1* loss of heterozygosity (LOH) and the development of thyroid masses (Teshiba et al. 2013). It is unclear whether a similar phenomenon occurs in the context of other high-output endocrine or exocrine organs such as the pancreas in these patients. The potential ER (endoplasmic reticulum) stress experienced by the pancreas may cause a similar phenotype, especially in light of the fact that NRF2 dysfunction has been implicated in pancreatic β cell exhaustion in several models of type II diabetes due to both directly activating protein quality control programs and interacting with other canonical ER stress response factors such as

ATF4 and HSF1 (Uruno et al. 2013). The KEAP1/NRF2 pathway exhibits significant pleiotropic effects extending beyond redox homeostasis, including effects in cellular differentiation, nutrient metabolism, and immune modulation; this ability to interact with a diverse array of pathways may explain why *KEAP1/NRF2* mutations are selected for in many cancers.

SOMATIC MUTATIONAL LANDSCAPE OF THE KEAP1/NRF2 PATHWAY

Pan-cancer analyses have revealed frequent mutations of the KEAP1/NRF2 pathway in multiple cancer types (Kerins & Ooi 2018, Sanchez-Vega et al. 2018). These cancer genome sequencing studies have revealed that *KEAP1/NRF2* mutations disproportionately occur in non-small-cell lung carcinoma (NSCLC), uterine corpus endometrial carcinoma (UCEC), liver hepatocellular carcinoma (LIHC), bladder carcinoma, and various forms of squamous cell carcinoma (SCC) (such as head and neck, esophageal, and cervical) when compared to other solid cancers (Cancer Genome Atlas Res. Netw. 2012, 2014, 2017; Kerins & Ooi 2018; Konstantinopoulos et al. 2011; Ooi et al. 2011; Sanchez-Vega et al. 2018; Schulze et al. 2015; Singh et al. 2006). While somatic mutations in *KEAP1* occur throughout the protein, *NRF2* GOF mutations predominantly occur within DLG/ETGE motif hotspots, which mediate the interaction of NRF2 with KEAP1 (**Figure 1*a***) (Kerins & Ooi 2018, Singh et al. 2006). *KEAP1/NRF2/CUL3* mutations exhibit strong mutual exclusivity, which suggests that NRF2 hyperactivation is the primary selective pressure experienced by cancer cells (Kerins & Ooi 2018). This pressure appears to be primarily selective for ROS detoxification, as the acceleration of tumor progression has been reported in several well-powered clinical and translational studies of dietary antioxidant supplementation (Sayin et al. 2014). Alternate means of activating the KEAP1/NRF2 pathway, independent of their respective genetic or epigenetic mutational status, exist for some select cancers and appear to predominantly act through metabolic signaling pathways (discussed in the section below titled Metabolic Reprogramming) (Adam et al. 2011).

ROS production and signaling through oncogene induction is important for transformation and, when left unchecked, triggering senescence (Irani et al. 1997, Lee et al. 1999). Overcoming this barrier appears to be highly dependent on NRF2 activity, as the development of *Kras*- and *Braf*-driven pancreatic ductal adenocarcinoma (PDAC) and lung adenocarcinoma (LUAD) models is impaired following *Nrf2* deletion (DeNicola et al. 2011, Orru et al. 2018, Satoh et al. 2013). Similar results of inhibited progression have been reported in urethane-induced lung cancer models, which almost universally trigger activating *Kras* mutations (Bauer et al. 2011, Satoh et al. 2013, Westcott et al. 2015). In contrast, while other less specific carcinogen-induced cancer models show increased tumor incidence in *Nrf2*-null backgrounds, they also show enhanced tumor progression (see references in Bauer et al. 2011). These discordant findings may be explained by the selection for alternate oncogene pathway activation events that do not occur in genetically engineered mouse models (GEMMs), by non-cancer-cell-autonomous effects, or by driver mutation–specific and tissue-of-origin-specific dependencies of NRF2. This is supported genetically in preclinical models; whereas *Keap1* deletion in *Kras*-, *p53*-driven (KP) LUAD GEMMs leads to accelerated tumor progression (Romero et al. 2017), *Keap1* deletion in KP PDAC GEMMs results in a pancreatic atrophy that is *Nrf2* dosage dependent (Hamada et al. 2018). Notably, while NSCLC shows very high rates of *KEAP1* mutation, PDAC does not show selection for genetic inactivation of the KEAP1/NRF2 pathway and may instead depend on transcriptional or noncanonical regulation of NRF2 activity such as through autophagy (DeNicola et al. 2011, Ling et al. 2012).

The strong bias for *KEAP1/NRF2* mutations in certain cancers may indicate cooperative interaction with hallmark driver mutations or other features of tumor tissue of origin such as metabolite preferences (Mayers et al. 2016). Several lines of evidence support the model of somatic

mutation cooperativity, as several oncogene and tumor suppressor pathways feed into KEAP1/NRF2 signaling. These include direct activation of NRF2 by RAS/MAPK signaling (DeNicola et al. 2011), repression by wild-type p53 (Faraonio et al. 2006), and accumulation of NRF2 through the PI3K/AKT/GSK-3/β-TrCP pathway (Rada et al. 2011, Salazar et al. 2006). Indeed, the strongest co-occurrence signature detected in a pan-cancer analysis by The Cancer Genome Atlas was found between PI3K/AKT and NRF2 pathway mutations, with significant co-occurrence rates between *NRF2* and *PIK3CA*, between *KEAP1* and *STK11*, and between *CUL3* and *INPP4B* (Sanchez-Vega et al. 2018). This association between KEAP1/NRF2 and PI3K/AKT signaling is supported experimentally; NRF2 is stabilized in a KEAP1-independent fashion through the PI3K/AKT pathway, and the increased antioxidant production by NRF2 sustains autocrine EGFR/AKT signaling and increased protein translation capacity (Mitsuishi et al. 2012, Rada et al. 2011, Salazar et al. 2006). Such synergy appears to be highly relevant to tumorigenesis, as conditional loss of *Pten* and *Keap1*, but not loss of either alone, is sufficient for initiation and progression of LUAD in a GEMM (Best et al. 2018). A similar mechanistic understanding for other cases of apparent cooperativity such as *NRF2/CDKN2A* and *KEAP1/STK11* is currently lacking and may provide insight into the unique dependencies associated with specific tumor suppressors (discussed in the section below titled Metabolic Reprogramming) (Cancer Genome Atlas Res. Netw. et al. 2016).

Notably, many cancers enriched for *KEAP1/NRF2* mutations show strong associations with carcinogen exposure, which would indicate a selective pressure for the KEAP1/NRF2 xenobiotic detoxification program. Consistent with this model, accumulation of somatic mutations in *NRF2* and *CUL3* is found in noncancerous esophageal samples from humans (Martincorena et al. 2018). A similar field effect has been observed for *KEAP1/NRF2* mutations in deep sequencing of normal bronchial epithelial cells from early-stage NSCLC and in preneoplastic lesions of a carcinogen-induced model of LIHC (Kadara et al. 2019, Orru et al. 2018). Precancerous somatic mutations in the KEAP1/NRF2 pathway may provide a selective advantage not only to cells exposed to continuous environmental insults but also to cancer progression after subsequent transforming events (Martincorena et al. 2018, Satoh et al. 2013). This may explain why *KEAP1/NRF2* mutations have a clonal distribution within some patient tumor samples, similar to classic driver mutations; however it should be noted that this is not a universal feature of the KEAP1/NRF2 pathway mutation (Hao et al. 2016, Jamal-Hanjani et al. 2017). This fact, combined with evidence suggesting that *KEAP1/NRF2* mutations appear in tumors with no known driver, hints at a potential role of KEAP1 and NRF2 to act as oncogenes, at least in certain limited contexts, although this has yet to be experimentally demonstrated and would contradict data from animal models (Cancer Genome Atlas Res. Netw. 2014, Jordan et al. 2017).

Although specific cancers select for NRF2 activation, the prevalence of mutations within members of the KEAP1/NRF2 pathway shows unequal distribution between different cancer subtypes. NSCLC is a particularly illustrative example of this phenomenon, as LUAD shows significant enrichment in *KEAP1* LOF mutations, whereas lung SCC shows enrichment in *NRF2* GOF mutations (Solis et al. 2010). This biased distribution suggests that *KEAP1* and *NRF2* mutations each possess unique effects that are selected for in certain contexts. The point mutations within *KEAP1* impair targeting of not only NRF2 for degradation but also other substrates containing an ETGE motif, including PALB2, PGAM5, MCM3, IKKB, and others (Hast et al. 2013, Komatsu et al. 2010, Lee et al. 2009, Lo & Hannink 2008, Ma et al. 2012, Tamberg et al. 2018). KEAP1 substrates or binding partners can compete with or affect NRF2 degradation (Komatsu et al. 2010). Using this KEAP1 competitive binding as a model, *NRF2* GOF mutations may enhance degradation of other substrates, which are selected for in specific cancers or stages of tumor progression (Hast et al. 2013, Hayes & Dinkova-Kostova 2017). The evolution of KEAP1 regulation of NRF2

through its DLG/ETGE motif has been suggested to mimic MCM3 in order to coordinate DNA replication machinery with redox and nutrient status (Tamberg et al. 2018). Selective degradation of these proteins, many of which function in DNA repair pathways, may possess additional selection benefit to NRF2 hyperactivation, such as affecting genome stability or tumor evolution rate (Hanahan & Weinberg 2000). Intriguingly, hypermutant subtypes of UCEC show a high incidence of *NRF2* GOF mutations comparable to or exceeding that of SCC; however, it is unclear what significance this may have (Sanchez-Vega et al. 2018). Conversely, *KEAP1* LOF mutations may trigger the accumulation of non-NRF2 substrates that are beneficial in other contexts. Nevertheless, strong pharmacologic evidence suggests that modulation of redox homeostasis is the primary factor selecting for *KEAP1/NRF2* mutations and that other effects may play a lesser function (Alpha-Tocopherol Beta Carotene Cancer Prev. Study Group 1994, Klein et al. 2011, Sayin et al. 2014). It remains to be determined what role these factors play in relation to *KEAP1/NRF2* in both normal development and cancer, especially when specific genetic disruption of *KEAP1/NRF2* is uncommon, yet NRF2 activity remains critical for the tumorigenic process (Zhou et al. 2019).

The majority of cancer somatic mutations in *KEAP1* are missense or truncating mutations, with deletion events appearing in only a minority of cases (Berger et al. 2016; Hast et al. 2013, 2014; Kerins & Ooi 2018). This suggests that complete loss of *KEAP1* is selected against even when NRF2 hyperactivation imparts a survival advantage. A significant portion of *KEAP1* mutations exhibit dominant-negative effects of varying strength that can impair KEAP1 homodimerization (Berger et al. 2016, Suzuki et al. 2011), and *KEAP1* LOH is frequently observed in tumor samples (Berger et al. 2016, Singh et al. 2006, Suzuki et al. 2011). These features of *KEAP1* mutations bear a striking resemblance to the tumor suppressor gene *TP53* (Hingorani et al. 2005). If this parallel holds true, then this would suggest monoallelic *KEAP1* LOF followed by LOH is a fundamental aspect of the natural history of *KEAP1*-mutant tumors and that *KEAP1*-mutant or *KEAP1* LOH is not analogous to a *KEAP1*-nullizygous state. Interestingly, *Keap1* was originally named due to its homology to a *Drosophila* actin binding partner, and other BTB-Kelch domain proteins are also involved in actin regulation (Bomont et al. 2000, Itoh et al. 1999, Xue & Cooley 1993). The actin binding ability of KEAP1 is conserved in humans and appears to persist even when it bears somatic cancer mutations that otherwise impair substrate binding for ubiquitination; it has been suggested that through such cytoskeletal interactions, KEAP1 acts as a scaffold for protein complexes (Ito et al. 2015, Kang et al. 2004). Complete loss of *KEAP1* may alter cytoskeletal organization in a fashion that would be detrimental to aspects of cancer cell fitness such as invasion and metastasis potential (Ito et al. 2015). Adding this to the fact that many somatic *KEAP1* mutations nevertheless reduce KEAP1 stability (Hast et al. 2014), it is tempting to speculate that *KEAP1* mutations are selected against in SCCs (Kim et al. 2010) partly because of potential defects in cytoskeletal structure and keratinization in this particular subtype that may be better tolerated in LUAD.

METABOLIC REPROGRAMMING

Although classically thought of as a sensor of ROS or xenobiotic electrophilic stressors, KEAP1 also appears to act as a more general sensor of perturbations of cellular metabolism (Bollong et al. 2018, Chen et al. 2017, Mills et al. 2018). Disruption of lipid, amino acid, carbohydrate, and secondary metabolism all lead to an accumulation of electrophilic intermediates that activate the NRF2 pathway (**Table 1**) (Pae et al. 2006). Accordingly, KEAP1 is positioned as a key coordinator of the metabolic, redox, and environmental stress response of a cell, given that activation of geno- and cytoprotective pathways requires significant energy and metabolic substrate investment; the constitutive strain on carbon and sulfur substrates leads to a depletion of TCA cycle intermediates and a selection for the reorganization of cysteine metabolism (**Figure 2**) (Kang

et al. 2019, Sayin et al. 2017). Returning to reported germline disruptions of *NRF2* as examples of the metabolic stress caused by aberrant antioxidant production, *KEAP1/NRF2* mutations may affect not only intracellular but also systemic metabolite pools. Germline *NRF2* GOF mutations, some of which are identical to cancer somatic mutations, are associated with hypohomocysteinemia, increased glucose-6-phosphate dehydrogenase activity, growth defects, developmental delay, and immunodeficiency (Huppke et al. 2017). These symptoms appear to be due in part to the NRF2-dependent systemic depletion of limiting nutrients for the production of GSH (Huppke et al. 2017). A similar, although less profound, depletion of redox related metabolites was reported in a *Keap1*-null GEMM of LUAD (Best et al. 2018). Although these examples represent extreme instances of KEAP1/NRF2 hyperactivation, they do provide a basis for how tumor genotype might alter the tumor microenvironment (TME) (discussed in the section below titled Immunomodulation of *KEAP1/NRF2* Mutations). The profound changes in the cellular metabolic state triggered by *KEAP1/NRF2* mutations appear to be exploited in certain cancer subtypes and indispensable for tumorigenesis in some cases.

A cytoprotective effector of KEAP1/NRF2 is the autophagy pathway, which can facilitate clearance of reactive species–damaged macromolecules and organelles (Pajares et al. 2016). p62/SQSTM1 is a selective cytoplasmic aggregator of ubiquitinated proteins and organelles that directs substrates to the autophagosome for degradation and recycling. NRF2 directly targets *p62* transcription and triggers a positive feedback loop whereby accumulation of p62 triggers serine phosphorylation of an STGE motif that mimics ETGE motifs. This phosphorylation event enhances p62/KEAP1 binding, aggregation, and autophagic degradation, which results in NRF2 stabilization (Copple et al. 2010, Jain et al. 2010, Komatsu et al. 2010, Lau et al. 2010, Riley et al. 2010). However, this adaptive response can become pathological under circumstances of impaired autophagy, triggering the accumulation of cytoplasmic protein inclusions in a p62- and Nrf2-dependent manner (Taguchi et al. 2012, Umemura et al. 2016). This is relevant given that *p62* mutations are found in multiple forms of LIHC and that p62 is necessary for maximum expression of Nrf2 in preclinical models of liver injury. Hepatic preneoplastic lesions are dependent on enhanced Nrf2 activity to survive inflammatory liver injury and progress to LIHC; ectopic expression of an STGE-phosphomimic but not a phosphorylation-defective form of p62 is sufficient to enhance LIHC cell growth, suggesting that p62 effects are dependent on KEAP1 binding (Lahiri et al. 2016, Orru et al. 2018, Saito et al. 2016, Schulze et al. 2015, Umemura et al. 2016). LIHC genome sequencing efforts have not only identified an enrichment for *NRF2* and *CUL3* mutations but also implicated sonic hedgehog and WNT/β-catenin as signature signaling pathways of LIHC (Cancer Genome Atlas Res. Netw. 2017). Both pathways have been linked to autophagy inhibition in certain contexts, providing a plausible link between putative drivers and Nrf2-enhanced progression (Cancer Genome Atlas Res. Netw. 2017, Guichard et al. 2012, Schulze et al. 2015, Wang et al. 2013). The functional significance between these pathways merits further investigation.

Germline mutations of the tumor suppressor fumarate hydratase (*FH*) characterize the hereditary leiomyomatosis and renal cell carcinoma cancer syndrome, which leads to the formation of renal cysts and a predisposition to type 2 papillary renal cell carcinoma (pRCC) (Cancer Genome Atlas Res. Netw. et al. 2016). Inactivation of *FH* causes the accumulation of the TCA cycle intermediates fumarate and succinate, which react with cysteine residues within KEAP1, and leads to activation of NRF2 (Kinch et al. 2011, Ooi et al. 2011). In addition to stimulating antioxidant production, KEAP1/NRF2 activity in pRCC may act as an important compensatory metabolic adaptation to *FH* loss (Adam et al. 2011, Kinch et al. 2011, Ooi et al. 2011). The NRF2 core target gene heme oxygenase 1 (*HMOX1*) diverts TCA cycle intermediates into the production of heme and thus prevents their toxic accumulation (Adam et al. 2011, Frezza et al. 2011, Kinch et al. 2011, Ooi et al. 2011). This function appears to be important given that Hmox1 loss is

synthetic lethal in a model of *Fh1* deficiency (Frezza et al. 2011). Selection for NRF2 hyperactivation, through *NRF2* GOF or *CUL3* deletion, in clear cell renal cell carcinoma (ccRCC) has also been identified. Although this selective pressure is not as strong as *FH*-driven pRCC, KEAP1/NRF2 pathway mutants may represent an uncommon subtype within the highly heterogenous presentations of ccRCC (Cancer Genome Atlas Res. Netw. et al. 2016, Chen et al. 2016, Sato et al. 2013). In addition to the near universal loss of chromosome 3p (containing the tumor suppressor *VHL*) in ccRCC, chromosome 5q35 amplification is also a common truncal mutation event. Intriguingly, among the putative genes of importance identified in this region is *p62/SQSTM-1*. Tumors carrying this amplification appear to be mutually exclusive with cases of *KEAP1/NRF2/CUL3* mutations, and together they constitute over 10% of ccRCC cases at the time of writing according to cBioPortal (**https://www.cbioportal.org**), which suggests that *p62* amplification is not a passenger mutation (Li et al. 2013). However, unlike LIHC, in vitro models suggest that the oncogenic potential of p62 in ccRCC is *KEAP1/NRF2* independent, and so the significance of KEAP1/NRF2 pathway activation in ccRCC requires further investigation (Li et al. 2013, Mitchell et al. 2018). The cases of *p62/KEAP1* and *FH/KEAP1* provide examples of important noncanonical activation of the KEAP1/NRF2 pathway. Interactions such as these are of great interest, not only to understand basic KEAP1/NRF2 regulation, but also to identify cancers that use alternative means of engaging this pathway.

In addition to causing changes in central carbon and amino acid metabolism, NRF2 activation suppresses fatty acid synthesis and increases fatty acid oxidation, potentially in order to reduce the pool of oxidizable lipids when reactive species are present (Ludtmann et al. 2014, Zou et al. 2019). Lipid peroxidation is a highly toxic stress that can lead to the iron-dependent form of cell death known as ferroptosis. ccRCC is characterized by the accumulation of both glycogen and unsaturated lipid species, the latter of which appears to be significant, as ccRCC-derived cell lines are sensitized to ferroptosis upon inhibition of the NRF2 target gene glutathione peroxidase 4 (*GPX4*) (Zou et al. 2019). Intriguingly, NRF2 activation has also been reported to be enriched in the clear cell subtype of epithelial ovarian cancer and may indicate a general vulnerability of the clear cell cancer subtype to lipid oxidation, which selects for NRF2 activation (Konstantinopoulos et al. 2011, Zou et al. 2019). NRF2-mediated resistance to ferroptosis involves not only GPX4 but also HMOX1 and the ferritin light and heavy chains, which together work to clear free iron. NRF2-dependent regulation of cellular heme through HMOX1 exerts a signaling function by triggering the stabilization and accumulation of the prometastatic transcription factor BACH1 (Lignitto et al. 2019). The regulation of other metabolites by NRF2 such as the accumulation of GSH can affect the cysteine redox state proteins, which has a significant effect on translation machinery (Chio et al. 2016, Weerapana et al. 2010). Intriguingly, changes in global cysteine redox state also preferentially affect the iron sulfur cluster synthesis pathway (Weerapana et al. 2010). It would be of great interest to investigate how broadly *KEAP1/NRF2* mutations can affect the redox state of cysteine residues or other metabolic reactions sensitive to redox state (Liu et al. 2018), including subcellular compartment–specific effects, as well as what signaling functions this may have.

The relationship between the PI3K and NRF2 pathways provides strong support for cooperativity between somatic cancer mutations. It is unknown whether this model of compensatory metabolic signaling is applicable to specific cancer subtypes enriched for *KEAP1/NRF2* mutations such as pulmonary papillary adenocarcinoma or other strong genetic associations such as between *KEAP1* and *STK11* that have been reported in NSCLC (Li et al. 2011). Although it should be noted that *KEAP1* and *STK11* are located in close proximity on the short arm of chromosome 19 in humans, it is intriguing that both of these genes exert strong effects on metabolism and that *STK11* modulates downstream effectors of the *PI3K/AKT* pathway (Kaufman et al. 2014).

Previous reports have demonstrated enhanced sensitivity of *KRAS/STK11*-mutant NSCLC to inhibition of lysosomal maturation and disruption of autophagy that is due in part to changes in lipid accumulation (Bhatt et al. 2019, Kim et al. 2013). This is crucial in light of the fact that KEAP1 and NRF2 clearly modulate both of these pathways (Pajares et al. 2016). It is possible that *KEAP1* inactivation in the context of *STK11* mutation is a compensatory adaptation for this dependency on autophagy, and that this mirrors the dependency of *PIK3CA*-mutant tumors on increased antioxidant production. Understanding the functional significance of genetic interactions such as these would enable the rational development of strategies targeting vulnerabilities that define driver mutations, including in cases where KEAP1/NRF2 regulation remains intact (discussed below in the section titled Therapeutic Implications).

IMMUNOMODULATION OF *KEAP1/NRF2* MUTATIONS

The KEAP1/NRF2 pathway has long been appreciated as an immunomodulatory actor from studies of *Nrf2*-null animal models (Ma et al. 2006). This fact has been exploited therapeutically and is a focus of investigation for several inflammatory and autoimmune diseases (Ebihara et al. 2016; for a focused review see Cuadrado et al. 2019). Dimethyl fumarate is a clinically approved therapy for multiple sclerosis, and animal models have implicated NRF2 activation as the mechanism of action. This link is further bolstered by genetic polymorphisms within *KEAP1/NRF2* that reduce NRF2 signaling strength and show an enhanced positive association with chronic inflammatory diseases in the context of chronic smoking, indicating a gene-by-environment interaction (Korytina et al. 2019). KEAP1/NRF2 modulation of the immune compartment is highly context dependent and care must be taken when considering its potential immunomodulatory effects (Satoh et al. 2010, 2013). The importance of NRF2 and ROS signaling in the immune system per se has been discussed at length elsewhere. However, one particularly illustrative example of the importance of host-specific NRF2 activity is that bone marrow–specific *Nrf2* deletion enhances lung metastasis by creating an immunosuppressive microenvironment that supports engraftment of tumor cells (Satoh et al. 2010). Although effects such as this must be considered when employing NRF2-modulating therapeutics, in this section we primarily focus on cancer-cell-autonomous defects in the KEAP1/NRF2 pathway and how these mutations may alter immune evasion or the TME, given that this mutational configuration is expected in patients (**Figure 4*a***).

Large-scale and focused cancer genome sequencing efforts have revealed associations with *KEAP1* mutations and poor response to checkpoint blockade (Cristescu et al. 2018). This effect appears to occur through an altered T cell activation phenotype and to be potentially independent of mutational burden (Arbour et al. 2018, Best et al. 2018, Cristescu et al. 2018, Kadara et al. 2017). Although *KEAP1* mutations have been associated with upregulation of immune checkpoint markers (PD-L1) in preclinical studies (Best et al. 2018), this association does not appear in clinical studies (Brogden et al. 2018, Kadara et al. 2017), which suggests additional or alternate mechanisms of immune evasion. The immunomodulatory effects of *KEAP1* mutation also appear to be dependent on cancer type, as some *KEAP1*-mutant tumors actually display enhanced signatures of checkpoint blockade response (Cristescu et al. 2018). Nrf2 activity has been shown to potentiate natural killer response and tumor rejection via induction of *Il-17d* in a cancer-cell-autonomous fashion (Saddawi-Konefka et al. 2016). A crucial point about this finding is that these studies were conducted in sarcoma, melanoma, and B cell lymphoma mouse models, cancer types that show very low frequency of *Keap1/Nrf2* mutations (Kerins & Ooi 2018, Saddawi-Konefka et al. 2016). The induction of an antitumor response by Nrf2 in these specific tumor types is supported by the relatively low mutation rate of this pathway within these cancers, and it underscores the importance of considering tissue of origin and subtype when predicting and studying the effect of *KEAP1/NRF2* mutations.

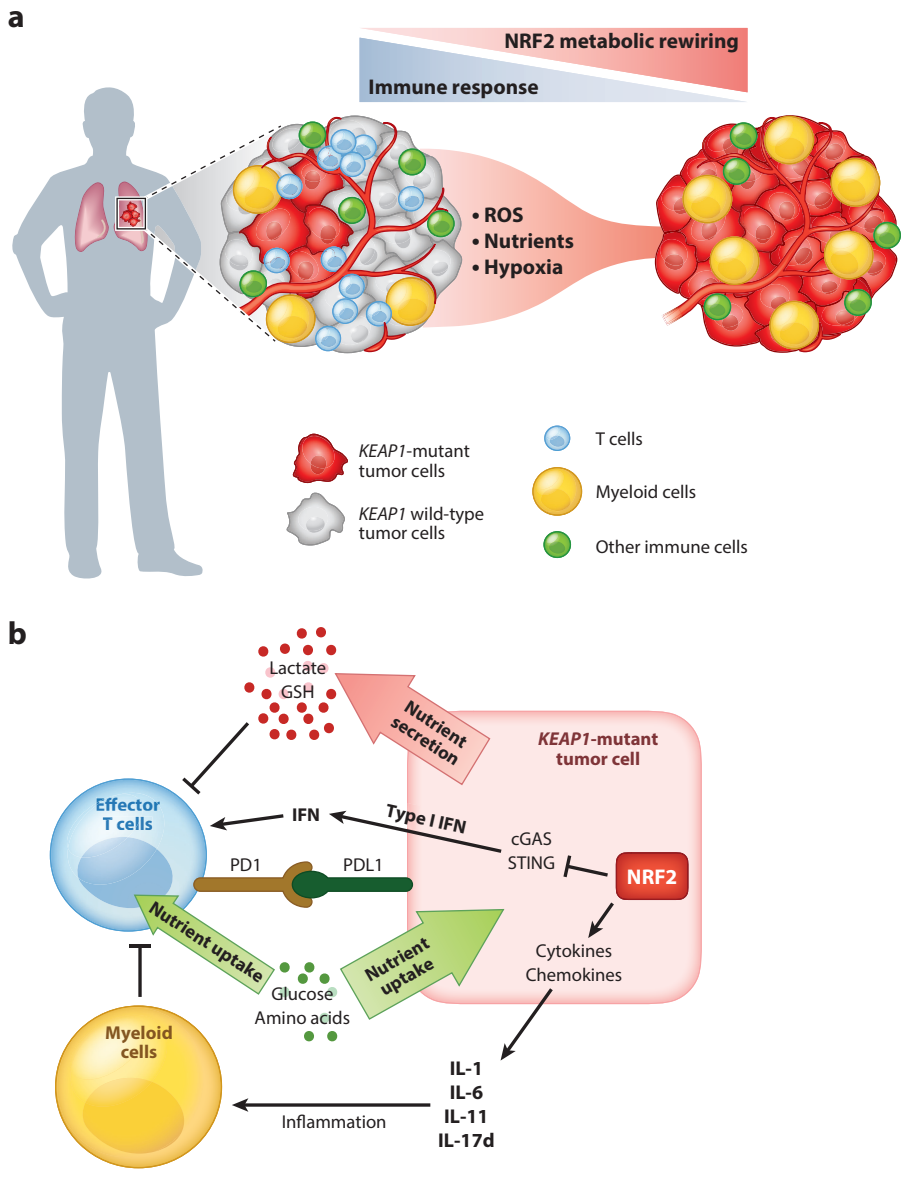

Figure 4

KEAP1/NRF2 modulation of antitumor immune responses. (*a*) Lung cancer patients with *KEAP1*-mutant tumors display signs of immune evasion with the exclusion of T cells. NRF2 activation by KEAP1 mutation may be selected for in lung cancer by enabling tumors to overcome metabolic bottlenecks [e.g., ROS (reactive oxygen species), hypoxia, nutrient availability] and suppress antitumor immune responses by altering the immune composition (e.g., T cells, myeloid cells, or other immune cell populations). Panel adapted with permission from Sayin et al. (2019). (*b*) Potential interactions of *KEAP1*-mutant cells with immune cell populations in the tumor microenvironment (TME). Metabolites secreted [e.g., lactate, GSH (glutathione)] or consumed (e.g., glucose, amino acids) by *KEAP1*-mutant tumors may alter the metabolic composition of the TME, therefore impacting the activity and function of effector T cells. In addition to a potential metabolism-dependent immune suppression, NRF2 transcriptionally regulates immunomodulatory pathways such as chemokines/cytokines (e.g., IL-1, -6, -11, -17d) and cGAS/STING-induced type I interferon (IFN).

Additional evidence has demonstrated direct modulation of cytokine expression by NRF2 or NRF2 target genes such as *STING* (Kitamura et al. 2017, Kobayashi et al. 2016, Olagnier et al. 2018). Many of these putative NRF2 targets belong to the IL-1 and IL-6 family of interleukins, which have been shown to modulate both the adaptive and innate arms of the immune system (**Figure 4*b***) (Kitamura et al. 2017, Nishina et al. 2017). As a model of the importance of NRF2-dependent cytokine production, *Il-11* expression is necessary for *Keap1*-null transformed embryonic fibroblasts to successfully establish tumors in an immunocompetent mouse model. This effect is dependent upon *Keap1*, *Nrf2*, and *Il-11*, thus providing direct experimental evidence for cytokine-mediated immunosuppression by *KEAP1/NRF2* mutation. Further characterization of other NRF2 target cytokines is warranted. Investigation into alterations of NF-κB signaling through KEAP1-dependent ubiquitination of IKKβ must also be considered, given that these effects have been reported to be independent of Nrf2 activity but can still potentially influence the cytokine production profile of cancer cells (Lee et al. 2009). A unique NF-κB- and NRF2-dependent cytokine profile may be an additional factor that explains the discrepancy between the mutational prevalence of *KEAP1* and of *NRF2* among cancers (Kitamura et al. 2017, Lee et al. 2009).

Independent of direct tumor–immune cell signaling through either receptor or cytokine expression, changes in the metabolite availability within the TME can have substantial impacts on immune cell effector functions (Chang et al. 2015). These metabolites include factors such as glucose, lactate, inorganic ions, and other nutrients (Chang et al. 2015, Ho et al. 2015). *KEAP1*-mutant and *NRF2*-mutant cells show increased uptake and utilization of extracellular glucose and glutamine when compared to their wild-type counterparts in vitro (Romero et al. 2017). This increased dependency on exogenous nutrients to support their anabolic cell state may significantly compete with non–cancer cell populations and alter the constitution of the TME (**Figure 4*b***). Non-cell-autonomous effects of *KEAP1/NRF2* mutations may also extend to the enhanced production of antioxidants; a *trans* effect such as this has been demonstrated in several experimental models, albeit in noncancerous contexts (Schafer et al. 2010; Shih et al. 2003; Vargas et al. 2006, 2008). Nrf2 activation specifically in the suprabasal layer of the epidermis induces GSH secretion and recycling that protects adjacent basal keratinocytes from UVB-induced apoptosis (Schafer et al. 2010). A similar phenomenon has been reported in the CNS, where astrocyte GSH and GSH precursor secretion protects motor neurons from nitrosyl stress-induced apoptosis in a manner involving Nrf2 (Vargas et al. 2006). These studies, including a genome-wide screen for ferroptosis sensitizers, implicate multidrug resistance–associated protein 1 (*MRP-1*) as the key target of the KEAP1/NRF2 pathway for GSH secretion (Cao et al. 2019). Extracellular redox buffering from tumor cells carrying *KEAP1/NRF2* mutations may provide a selective advantage to subsets of tumor-infiltrating immune cells. This is a particularly attractive line of inquiry given that tumor immune cell populations have differential sensitivity to redox stressors and that their functionality can be dictated by redox imbalances (Cubillos-Ruiz et al. 2015, Maj et al. 2017). Extracellular conditioning phenomena such as these may provide a crucial bridge between immune cell and tumor cell redox homeostasis and metabolism. This may be especially important in unique contexts such as the high-oxygen environment of the lung, which coincidentally has the greatest enrichment in *KEAP1/NRF2* mutations among all cancer types (Kerins & Ooi 2018). Whether this is relevant to the noncancer actors of the TME remains to be demonstrated. Moreover, the generally high nutrient consumption of tumor cells must also be considered, which may confound or negate the effects of extracellular GSH metabolism that have been described in physiological settings.

THERAPEUTIC IMPLICATIONS

The activation of xenobiotic detoxification programs is a core function of the KEAP1/NRF2 pathway and plays an important role in dictating response to clinical therapies. Both radio- and

chemotherapy effectiveness has been reported to depend on *KEAP1/NRF2* mutation status, since many of the mechanisms of action of these therapies involve the production of ROS (Cao et al. 2019, Frank et al. 2018, Kadara et al. 2017, Krall et al. 2017, Singh et al. 2010). Targeted therapy response is also affected by *KEAP1/NRF2* mutations, as the increased expression of efflux transporters, which show affinity toward several kinase inhibitors, can dramatically alter drug sensitivity and confer drug resistance (Krall et al. 2017, Yu et al. 2018). The activation of cytoprotective pathways such as these may be one additional factor explaining why patients carrying *KEAP1/NRF2* mutations often have poor prognosis and therapy response (Kadara et al. 2017). Given this broad desensitization to both classic chemotherapies and targeted inhibitors, developing novel treatment strategies against the KEAP1/NRF2 pathway would be of outstanding clinical value (Jordan et al. 2017). Indeed, preclinical studies have shown that genetic and pharmacologic inhibition of Nrf2 sensitizes cells to cisplatin and radiation treatments, which creates the possibility of unlocking currently available therapies to which tumors might be otherwise resistant (Chian et al. 2014, Ren et al. 2011). Targeting crucial downstream factors of NRF2 activation may also be viable, as preclinical models have shown Nrf2 targets such as *Xct*, *Gclc*, *Gclm*, and *Txn* are important for tumor initiation and progression and are promising ROS vulnerabilities of oncogene addiction (Harris et al. 2015, Stafford et al. 2018). Independent of modifying response to therapy, KEAP1/NRF2 pathway mutations show parallels to previously described oncogene addictions; *KEAP1/NRF2*-mutant cancers exhibit a significant dependence on sustained, hyperactivated NRF2 activity (McDonald et al. 2017). This suggests that targeting NRF2 itself would be a viable therapeutic strategy. Several small-molecule inhibitors of NRF2 have been reported; however, their exact mechanisms of action remain unclear or are nonspecific (Cuadrado et al. 2019). Large-scale chemical and genetic screens have identified several novel candidates that can alter the KEAP1/NRF2/CUL3 interaction or specifically inhibit NRF2 transcriptional coactivators, which should exhibit increased specificity (Bar-Peled et al. 2017, Choi et al. 2017).

The high co-occurrence rate of *KEAP1/NRF2* mutations with other tumor suppressors and oncogenes may also create opportunities for novel therapies. As an example, like *STK11*, *SMARCA4* is located near *KEAP1* on chromosome 19p and is frequently co-mutated. Although the interaction between *SMARCA4*, a frequently mutated gene in cancer, and *KEAP1* remains to be fully clarified, this codeletion event appears to create a collateral lethality where cell lines with low *SMARCA4* expression are sensitive to *SMARCA2* knockdown (McDonald et al. 2017). Likewise, the strong synergies reported between somatic cancer mutations and *KEAP1/NRF2* mutations may create exploitable synthetic lethality events. Indeed, *KEAP1/NRF2*-mutant cells become particularly vulnerable to targeted inhibition of amino acid (Gwinn et al. 2018, Romero et al. 2017) and glycolytic pathways (Koppula et al. 2017, McMillan et al. 2018). This phenomenon can be exploited pharmacologically, as *KEAP1/NRF2*-mutant cancer is particularly sensitive to inhibition of glutamine metabolism using glutaminase inhibitors (CB-839) (Cardnell et al. 2015, Sayin et al. 2017), an effect that may be extended to other agents such as ASCT2 inhibitors (V-9302) (**Figure 2**) (Schulte et al. 2018). The dramatic alterations to cellular metabolism caused by *KEAP1/NRF2* mutations may create other novel metabolic dependencies that have yet to be characterized. Finally, the association of *KEAP1/NRF2* mutations with immune evasion in certain cancers makes it a particularly attractive target for checkpoint blockade–independent treatment approaches. This characteristic of *KEAP1/NRF2* mutations also makes understanding the detailed molecular mechanisms underlying this immunosuppressive effect of outstanding interest, as they have the potential to identify novel targets to potentiate current and developing immune-oncology therapies.

CONCLUSION

The appearance of molecular oxygen marked a dramatic change in Earth's environment and represented a significant new obstacle to the evolution of complex life (Holland 2006). Although the accumulation of atmospheric oxygen permitted the high-efficiency use of organic substrates, it also created the additional burden of ROS that threatened cellular homeostasis (Alberts et al. 2002). The KEAP1/NRF2 pathway is the major cellular antioxidant defense pathway in nearly all metazoans and has been proposed to have evolved, at least in part, in response to global oxygenation (Gacesa et al. 2016). Transformation appears to universally trigger a novel pathophysiological state of general redox and nutrient stress for which cancer cells must evolve mechanisms to buffer or circumvent. Given the profound role the KEAP1/NRF2 pathway plays in integrating the cellular stress response to meet these insults, understanding and targeting this pathway will be of great importance for the advancement of treatment and care for cancer patients.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank R. Romero, S.E. LeBoeuf, and V.I. Sayin for critical reading of this review.

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