NRF2 Activation in Cancer: From DNA to Protein
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Abstract
The Cancer Genome Atlas catalogued alterations in the Kelch-like ECH-associated protein 1 and nuclear factor erythroid 2–related factor 2 (NRF2) signaling pathway in 6.3% of patient samples across 226 studies, with significant enrichment in lung and upper airway cancers. These alterations constitutively activate NRF2-dependent gene transcription to promote many of the cancer hallmarks, including cellular resistance to oxidative stress, xenobiotic efflux, proliferation, and metabolic reprogramming. Decades of research confirm that NRF2 activity strongly associates with poor patient prognosis and chemo- and radioresistance. Yet to date, FDA-approved drugs targeting NRF2 activity in cancer have not been realized. Here, we review various mechanisms that contribute to NRF2 activation in cancer, organized around the central dogma of molecular biology (i) at the DNA level with genomic and epigenetic alterations, (ii) at the RNA level including differential mRNA splicing and stability, and (iii) at the protein level comprising altered posttranslational modifications and protein–protein interactions. Ultimately, defining and understanding the mechanisms responsible for NRF2 activation in cancer may lead to novel targets for therapeutic intervention.

Introduction
Redox biology encompasses cell biological processes driven by reactive oxygen species (ROS; ref. 1). Uncontrolled redox reactions increase levels of oxidative stress and lead to the accumulation of ROS and reactive nitrogen species (RNS) within the cell. Elevated levels of ROS and RNS damage DNA, RNA, protein, and lipids (1, 2); therefore, regulation of redox levels within the cell is critical for cellular homeostasis and effective disease prevention (1, 3–11). The transcription factor nuclear factor erythroid 2–related factor 2 (NFE2L2, hereafter referred to as NRF2) is central for the cellular response to ROS and oxidative stress. Decades of research confirm that NRF2 activity improves cellular fitness under stress and is thus beneficial for normal cellular physiology. It is now increasingly clear that cancer cells subvert NRF2 activity to promote tumor growth and dissemination (reviewed in depth by Rojo de la Vega and colleagues; ref. 12).

In 2012 The Cancer Genome Atlas (TCGA) consortium reported whole-exome sequencing (WES) and RNA-sequencing (RNA-seq) of tumors from patients with lung squamous cell carcinoma (LUISC; 178 patients) and lung adenocarcinoma (LUAD; 183 patients; refs. 13, 14). In addition to known tumor suppressors (i.e., TP53) and oncogenes (i.e., KRAS), both studies revealed significant and mutually exclusive alterations to NRF2 (19% of LUISC; not significantly mutated in LUAD) and to its negative regulator Kelch-like ECH-associated protein 1 (KEAP1; 12% of both LUAD and LUISC; refs. 13, 14). Looking across all organ systems, 226 TCGA studies have catalogued genetic mutations and copy number alterations to the KEAP1–NRF2 signaling pathway, most notably lung (LUISC and LUAD; 31.4% and 24%, respectively), uterine (20.6%), head and neck (17.4%), esophageal (19.8%), bladder carcinomas (14.8%; refs. 13–19).

As reviewed in the following sections, nongenomic mechanisms of NRF2 activation are also common in cancer. Recently, a Pan-Can analysis of NRF2 transcriptional activity revealed 32 direct NRF2 cancer target genes (20). Evaluation of their composite expression across more than 9,000 TCGA samples demonstrated NRF2 hyperactivity in expected tumor types (e.g., LUISC and HNSCC), as well as in tumor types lacking strong genomic evidence of NRF2 pathway activity (e.g., liver/LIHC, kidney/KIRC, pancreas/PAAD, and stomach/STAD; ref. 20). Collectively, conservative estimations from mutation rates and projected cancer incidence suggest that more than 86,000 patients in the United States will be diagnosed with NRF2-mutant/hyperactive cancer in 2018 (15–19, 21). Of the 1,735,350 new cases of diagnosed cancer predicted by the American Cancer Society for the U.S. population in 2018, 5% or more of these cases are estimated to be NRF2 pathway mutant and hyperactive (21). These mutational rates likely underrepresent the true number of NRF2 hyperactive tumors, given the various nongenomic mechanisms of NRF2 activation discussed in this review.
KEAP1–NRF2 Signaling

A broad range of aberrant NRF2 activity levels can contribute to cellular pathology. Low levels of NRF2 activity lead to increased intracellular ROS, damage to cellular structures (e.g., DNA, mitochondria, proteins, and lipids), and apoptosis (1, 4, 7, 22). Consequently, cells with low levels of NRF2 and elevated ROS are at risk for neurodegeneration, cardiovascular disease, and chronic inflammation (4, 7, 8, 23–27). In contrast, high NRF2 activity leads to cellular resiliency in the face of various stressors, including ROS, genotoxic stress, and metabolic stress (3, 9, 25, 28). Thus, mutations and alterations that increase NRF2 activity contribute to cancer progression and the development of chemoresistance (29).

Under basal conditions, cytosolic KEAP1 functions as an adapter for the E3 ubiquitin ligase Cullin-3 (CUL3) and constitutively targets NRF2 for ubiquitylation and degradation via the ubiquitin–proteasome system (30, 31). Upon exposure to oxidative stress or damage to cellular structures, KEAP1 is modified, leading to a conformational change in KEAP1 structure that prevents the degradation of NRF2 (4, 7, 9, 10, 30, 32–39). De novo synthesized NRF2 accumulates and translocates to the nucleus where it heterodimerizes with small muscle-specific fibrosarcoma (SMAF) proteins, MAFF, MAFC, and MAFK (40–42). NRF2–SMAF heterodimers bind to antioxidant response elements (ARE) in cell-type-specific responses to increase the transcription of a large number of genes. KEAP1–NRF2 signaling promotes the transcription of genes that govern various processes within the cell including: (i) antioxidant response, (ii) drug detoxification, (iii) cellular metabolism, and (iv) inflammation (4, 7–9, 12, 25, 27, 44). While great progress has been made, much remains to be learned of how NRF2 and its target genes contribute to cancer progression and therapeutic response.

NRF2 Activation in Cancer: Genomic Alterations to DNA

Alterations to NFE2L2, CUL3, and KEAP1 frequently occur at the genomic level, resulting in enhanced NRF2 protein expression and transcriptional activity (5, 6, 9, 25, 27, 31, 45–58). NFE2L2, located on a copy number–amplified region of chromosome 2q31.2, can be genetically modified through promoter demethylation, copy number amplifications (CNA), oncogene-induced transcription of NRF2 via cMYCERTZ, BRAFV600E, and KRASG12D, or by gain-of-function somatic mutations in the DLG or ETGE motifs required for KEAP1 association (Fig. 1A; refs. 13, 14, 31, 51, 54, 63). KEAP1 ubiquitylates NFE2L2, located on chromosome 19p13.2, can be functionally inactivated by promoter hypermethylation, homozygous deletion, or by KEAP1 LOF mutations (Fig. 1A; refs. 13, 31, 46, 58). KEAP1 promoter methylation appears in breast, colon, and lung carcinomas and is known to accelerate tumor progression (67, 68). Intriguingly, homozygous deletions of KEAP1 are rare, suggesting that normal and tumor cells rely on NRF2-dependent functions of KEAP1 (Fig. 1A; refs. 13, 16). In fact, KEAP1 ubiquitylates proteins involved in cell-cycle regulation such as MCM3, although the biological function of this interaction remains understudied (67, 70). KEAP1 mutations occur most frequently in LUSC and LUAD tumors (15, 16). Previous studies estimate that 75% of KEAP1 LUSC and 92% of KEAP1 LUAD somatic missense mutations abrogate KEAP1 protein function (31, 59).

Of these functional mutations, more than 50% presumably result in hypomorphic suppression of NRF2 transcriptional activity (31, 59). Differences in NRF2 transcriptional program between KEAP1 functionally inactive and hypomorphic classes of mutations may reveal differentially expressed genes with clinical importance.

NRF2 Activation in Cancer: Transcriptional Alterations to mRNA

Changes in NRF2 activity and stability of NFE2L2, CUL3, and KEAP1 can also lead to increased expression of NRF2 protein and its downstream targets. Cellular mRNA levels can be regulated by miRNAs, alternative splicing events, and by RNA-binding chaperones. miRNAs are short, noncoding RNAs that bind to the 3′-untranslated regions of mRNAs, resulting in changes to mRNA stability (71). Alternative splicing of mRNA can result in functionally inactive or unstable proteins. In addition, association of mRNAs with RNA-binding proteins or RNA chaperones can lead to altered transcript levels for a given gene (71). NRF2 transcript levels in cancer are regulated by miRNAs and alternative splicing of exon 2 or the combination of exons 2 and 3. To date, more than 20 miRNAs have been reported to impact NRF2 mRNA levels. For example, a miRNA library screen using the ARE reporter assay identified four miRNAs that regulate NRF2 mRNA levels (72). A summary of miRNAs regulating NFE2L2 mRNA (along with miRNA tables for CUL3 and KEAP1) is provided in Supplementary Table S2. Downregulation of mRNAs that

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decrease NRF2 mRNA in patient samples could also result in NRF2 stabilization; however, no studies have identified candidates (73). NRF2 transcripts are also alternatively spliced in patient samples (45). A 2017 analysis of RNA-seq transcript variants from patient samples with elevated NRF2 activity in the absence of KEAP1 or NFE2L2 mutations identified alternatively spliced transcripts of NRF2 lacking exon 2 or both exons 2 and 3. Exon 2 contains the DLG and ETGE motifs required for KEAP1 association; thus, KEAP1 is unable to ubiquitylate and degrade these alternatively spliced NRF2 variants (Fig. 1B; ref. 45). Currently, this alternative splicing event has only been detected in LUSC and head and neck squamous cell carcinomas (HNSCC); however, additional studies of other tumor types may identify additional instances of NFE2L2 alternative splicing (45).

Of the few reports describing miRNAs that regulate CUL3, only miR-101 and miR-455 have been shown to target CUL3 and activate NRF2 signaling (Fig. 1B; refs. 74, 75). However, whether the downregulation of miR-101 in other tumor types or miR-455

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**Figure 1.**

A. Schematic of genetic and epigenetic modifications to NFE2L2, CUL3, and KEAP1 DNA. Densities of copy number alterations across chromosome 2 (NFE2L2 and CUL3) and chromosome 19 (KEAP1) are shown for LUSC (light red) and HNSCC (dark red).

B. Schematic of alterations to NFE2L2, CUL3, and KEAP1 mRNA. NFE2L2 mRNA is regulated by more than 20 miRNAs and by alternative splicing. Two alternative splicing events for NFE2L2 have been detected in two different NRF2 isoforms in LUSC and HNSCC. CUL3 and KEAP1 are regulated by two and four miRNAs, respectively. Association of CUL3 and KEAP1 mRNA with RBM47 results in decreased mRNA transcripts.
found in colorectal cancers results in elevated NRF2 activity remains unclear.

A number of miRNAs impacting KEAP1 have been reported, including miR-200a, miR-7, miR-432, and miR-141 (Fig. 1B; ref. 76). Of these miRNAs, only miR-200a definitively activates NRF2 signaling in breast cancer cells; consequently, a careful examination of miRNAs regulating KEAP1 expression in patient tumors merits further examination. RNA-binding proteins also regulate KEAP1 mRNA stability. For example, the RNA-binding motif 47 (RBM47) protein associates with both KEAP1 and CUL3 mRNA (77, 78). RBM47 association with KEAP1 mRNA results in increased protein expression levels in the A549 L14D-mutant KEAP1 cancer cell line, suggesting that tumors may downregulate RBM47 to decrease KEAP1 transcript levels (77). RBM47 is downregulated in breast cancer where it suppresses breast cancer progression and metastasis (78). Given the many functions of NRF2 in cancer progression, it is possible that RBM47 loss promotes breast cancer progression in part through NRF2 activation (77, 78). Further studies of the family of RBM proteins in cancer may reveal proteins regulators that control the levels of NRF2, CUL3, or KEAP1 mRNA.

### NRF2 Activation in Cancer: Posttranslational Modifications and Alterations to the KEAP1–NRF2 Protein Interaction Networks

#### NRF2 at the protein level

NRF2 is a cap’n’collar basic leucine zipper transcription factor comprised of 605 (human; 597 murine) amino acids (Fig. 2A; refs. 79, 80). NRF2 contains seven NRF2-ECH homology (Neh) domains, each with distinct functions and posttranslational modifications (Fig. 2A). NRF2–sMAF heterodimerization is required for sMAF activation as sMAF proteins lack transactivation domains; therefore, sMAF homodimers act as functional repressors. Overexpression of sMAF proteins results in decreased NRF2 transcriptional activity; however, no studies have described differential gene expression or mutations of sMAF family proteins within tumors (81). Interestingly, a number of miRNAs targeting sMAF proteins are known to be altered in the TCGA Pan-Can dataset; however, whether these miRNAs promote NRF2 activation remains to be determined (82). The Neh2 domain is essential for KEAP1 cytosolic regulation of NRF2 and contains the two motifs required for KEAP1 association (the 29DLIC31 and 79ETGE32 motifs for human NRF2) as well as the seven lysine residues targeted by KEAP1-dependent ubiquitylation (4, 7, 9, 10, 23, 27, 48, 53, 83, 84). The Neh2 domain also contains serine 40 (S40) that is phosphorylated by protein kinase C (PKC; refs. 57, 85, 86). PKC phosphorylation at S40 results in NRF2 dissociation and nuclear localization of NRF2. Unexpectedly, NRF2 target gene expression is not significantly altered by PKC-dependent S40 phosphorylation of NRF2 (57, 85, 86). The Neh6 domain contains two beta-transducin repeat-containing E3 ubiquitin protein ligase (BTRC; hereafter BTRC) degron motifs: 343DSGIS347 and 382DSAPGS387 for human NRF2 (48, 83, 84). BTRC associates with the Skp1-Cullin 1 (CUL1) F-box–containing complex to form the ubiquitylation complex that targets NRF2 for proteasomal degradation within the nucleus of cells (48, 83, 84). Serine phosphorylation of the DSGIS motif by glycerogen synthase kinase 3-beta drives the NRF2–Neh6–BTRC association, resulting in NRF2 degradation (48, 83, 84). Whether BTRC alterations contribute to NRF2 activity in cancer has not been reported, but given the lack of NRF2 mutations in the DSGIS motif, it likely does not play a major role (15, 16). Dynamic changes to NRF2 phosphorylation, ubiquitylation, or interacting proteins alter NRF2 protein levels and subcellular localization; consequently, these events should be carefully examined in various tumor types to determine the functional impact on NRF2 transcriptional activity.

#### CUL3 at the protein level

Human and murine CUL3 is a 768 amino acid protein comprised of three domains: a low-complexity region, a CUL3IN domain, and a CUL3IN-neddylation domain (Fig. 2A; refs. 65, 66). Neddylation of CUL3 by the Ned-8 activating enzyme (NAE) is required for ubiquitylation activity, and small-molecule NAE inhibitors such as pevonedistat (MLN4924) result in stabilization of CUL3 substrates, including robust NRF2 transcriptional activation (87). Current clinical trials are testing the efficacy of MLN4924 in patients with hematologic malignancies. Whether NRF2 activation impacts the efficacy of MLN4924 treatment, either as a single agent or in combination with conventional chemotherapies, remains untested.

#### KEAP1 at the protein level

KEAP1 was identified in 1999 via a yeast two-hybrid (Y2H) screen utilizing the Neh2 domain of NRF2 as bait (88). Human and murine KEAP1 is comprised of 624 amino acids, 27 of which are cysteines (25 in mouse). KEAP1 contains a BTB domain, an intervening region (IVR, also known as the BACK domain), and a C-terminal double glycine region composed of six KELCH repeat domains (Fig. 2A; refs. 3, 7, 9, 89). Modifications to specific amino acid residues alter KEAP1 homodimerization, CUL3 or NRF2 association, or KEAP1 redox sensing via one or more of its reactive cysteines. Mutations that disrupt these essential functions of KEAP1 protein result in NRF2 stabilization and increased transcriptional activity in cancer. KEAP1 mutations span the entire coding sequence of KEAP1 as indicated by the mutation density of 149 mutations for KEAP1; however, additional studies examining classes of KEAP1 inactivating mutations demonstrated enrichment for KEAP1-inactivating and hypomorphic mutations at highly conserved and frequently mutated amino acid residues within the KEAP1 protein (Fig. 2A; refs. 31, 90). In general, predicting the effects of KEAP1 mutations found in tumors upon NRF2 signaling remains difficult and thus requires the use of biochemical and functional assays.

In addition to mutations, several studies have identified NRF2-competitive–binding proteins that prevent KEAP1 association with the DLG or ETGE of NRF2 resulting in impaired NRF2 ubiquitylation. The expression of these competitive binders in both in vitro and in vivo models of cancer contribute to NRF2 hyperactivity and confer protection from DNA-damaging agents in a NRF2-dependent manner (91–97). These competitive-binding partners include: (i) ETGE-containing proteins, dipetidyl peptidase 3 (DPDP3), partner and localizer of BRCA2 (PALB2), Wilms Tumor suppressor (WTX), minichromosome maintenance complex component 3 (MCM3), nuclear factor erythroid 2–related factor 1 (NFE2L1), and cyclin-dependent kinase 20 (CDK20); (ii) DOSTGE-containing protein p62/Sequestosome 1 (p62/SQSTM1); (iii) DLT-containing protein...
inhibitor of apoptosis stimulating protein of p53 (PPP1R13L; hereafter iASPP), which associates with the KRR motif of NRF2 required for KEAP1 association; and (iv) CDK inhibitor 1A (CDKN1A; hereafter p21), which contains a KRR motif analogous to the arginine triad motif of KEAP1 (Fig. 2B; refs. 69, 70, 91, 94–99). Proteomic analysis of the KEAP1 protein...
interaction network revealed that 42.8% (18/42 proteins) of high-confidence interactors contained either an ETGE, ESGE, or both motifs (91). Although not all of these interactors have been independently validated or examined in patient samples, overexpression of these proteins may result in increased NRF2 transcriptional activity and merit further examination. In addition to proteins containing ETGE or ESGE motifs, proteins containing a polyubiquitin-binding motif for KEAP1 and NRF2; a summary of all proteins containing KEAP1- and NRF2-binding motifs is provided in Supplementary Table S3 (100). Of 6,689 unique proteins containing KEAP1- and NRF2-binding motifs, only 532 are known to interact with NRF2, CUL3, or KEAP1 (Supplementary Table S3). Differential expression of these proteins in the absence of direct alterations to KEAP1, CUL3, or NFE2L2 may result in elevated NRF2 expression and transcriptional activity. In fact, increased DPP3 expression in LUSC and breast cancer results in increased expression of NRF2 target genes (91, 101).

Intriguingly, proteins that associate with KEAP1 impact KEAP1 stability without disrupting the KEAP1–NRF2 binding interface. For example, RNA-binding motif 45 (RBM45) is known to bind and stabilize KEAP1 protein in motor neurons with amyotrophic lateral sclerosis (102). Although changes in RBM45 expression in tumors have not been extensively studied, recent proteomic studies examining reactive cysteines in KEAP1-mutant non–small cell lung cancer cell lines revealed proteins that contain interacting motifs on KEAP1. In the absence of direct alterations to KEAP1, RBM45 and SNW domain containing protein 1 (SNW1) promotes NRF2-dependent transcription further establishing a role for RBM45 in KEAP1–NRF2 signaling in cancer cells (103).

Posttranslational modifications (PTM) that functionally inactivate KEAP1 also exist. KEAP1 ubiquitylation results in p62-dependent autophagic degradation of KEAP1 (104). KEAP1 phosphorylation also occurs, although the functional impact of these events is unclear (105). KEAP1 can also be metabolically modified as seen in papillary renal cell carcinoma, which is deficient for the tumor suppressor fumarate hydratase (106, 107). The loss of fumarate hydratase results in the formation of S-(2-succinyl) adducts (25C) on C151 and C288 that may increase NRF2 transcriptional activity by modifying KEAP1 structure (Fig. 2C; refs. 6, 51, 106). KEAP1 is also metabolically modified by S-glutathionylation (KEAP1-SSG), which inactivates KEAP1 repression of NRF2 and results in NRF2 nuclear localization (108, 109). In addition, it was recently reported that the mitochondrial metabolite itaconate activates NRF2-dependent transcription through alkylation of KEAP1 on C151, C257, C273, C288, and C297. Although a role for itaconate has been identified in peritoneal tumors, studies examining the interplay between itaconate, KEAP1, and NRF2 hyperactivation in cancer have not yet been reported (110, 111). Recently, Bollong and colleagues identified a new PTM for KEAP1, methylimidazolone crosslink between proximal cysteine and arginine residues (MICA; ref. 112). MICA occurs as a result of cysteine modification by methylglyoxal (MGO), a glycolytic metabolite, and promotes formation of a KEAP1-high molecular-weight dimer, resulting in increased NRF2 transcription (112). Additional studies in patient samples may identify novel KEAP1 PTMs from oncometabolites.

Clinical Applications of NRF2 in the Context of Cancer Prevention and Treatment

NRF2 activation in the context of cancer is often described as having a unique duality: NRF2 activation prior to tumor initiation or progression is chemopreventive whereas NRF2 activation for an established tumor enables increased proliferation and resistance to chemo- and radiotherapies. The tumor-promoting effects of NRF2 activation has been poetically described as “the dark side” of NRF2 (55). Therefore, clinical diagnostic testing for pathway activation, as well as the development of small-molecule inducers and inhibitors of NRF2 may prove beneficial for patient treatment depending on context and tumor development.

Many studies suggest therapeutic applications for NRF2 inducers in the prevention of cancer as well as for the treatment of neurodegenerative disorders and chronic inflammation (3, 7, 9, 10, 23, 26, 28, 113–117). NRF2 small-molecule inducers are thought to inactivate KEAP1 function through degradation of KEAP1 protein, slowed KEAP1 conformational cycling, covalent modifications of KEAP1, or through dissociation of the KEAP1–NRF2 complex, resulting in NRF2 stabilization and transcriptional activity (7, 118, 119). tert-Butylhydroquinone decreases KEAP1 half-life by promoting autophagic degradation of KEAP1 (104). Sulforaphane decreases the rate of KEAP1 conformational cycling, perhaps slowing the rate of NRF2 ubiquitylation or degradation (104, 120). Mechanistically, many of the NRF2 small-molecule inducers modify reactive cysteines in KEAP1, resulting in its functional inactivation (35). Inducers have been broadly categorized into five classes based on the KEAP1 cysteine reactivity profile (7, 36, 118, 121). Class I inducers are KEAP1 C151-dependent; class II inducers are specific to the C288 residue in the IVR of KEAP1; class III molecules require KEAP1 C151, C273, and C288; class IV compounds activate NRF2 through other cysteine residues in KEAP1 and do not require C151, C273, and C288. Examples of class IV–reactive cysteines include C226 and C613, which are responsive to transition metal ions (i.e., As3+, Cd2+, Se4+, and Zn2+), and are capable of forming a disulfide bridge following exposure to hydrogen peroxide or hydrogen sulfide (122–124). C434 can also be targeted by class IV compounds, specifically 8-nitroguanosine 3’,5’-cyclic monophosphate (3). The primary mechanism of class V NRF2 inducers is disruption of the KEAP1–NRF2 interaction (7, 25, 118). Examples of class I–V inducers are provided in Supplementary Table S4. Although not assigned to a specific class, the NEDD8-activating enzyme inhibitor (NAE1; hereafter, MLN4924) and the CYP450 inhibitor oltipraz also induce NRF2 activation (107, 125–130). To date, the CYP450 inhibitor oltipraz and sulforaphane, an isothiocyanate derived from broccoli sprouts, are the only NRF2 inducers to reach phase I and II clinical trials for the prevention of cancer (107, 127, 128, 131, 132).

Multiple reports have established that hyperactivation of NRF2 is detrimental for survival in patients with cancer (5, 8, 9, 25, 47, 49, 52, 133–135). Therefore, developing NRF2-specific chemotherapeutics for the treatment of NRF2-hyperactive cancers has become a major goal (51, 136). NRF2 inhibitors function primarily through disruption of nuclear NRF2 transcriptional activity and have been historically
identified through high-throughput screening of NRF2-ARE transcriptional activity (137). Examples of these compounds include all-trans retinoic acid (ATRA), ARE expression modulator 1 (AEM1). ML385, 1-(2-Cyclohexylethoxy)aniline (IM3829), brusatol, and clobetasol propionate (CP; refs. 57, 121). ML385 disrupts NRF2–sMAF heterodimerization via direct association with the Neh1 domain of NRF2 (141). CP results in NRF2 nuclear degradation in a BTRC-dependent manner. Both of these small molecules highlight how molecular understanding of the mechanisms driving NRF2 regulation and activation can yield candidates for therapeutic intervention. Although both ML385 and CP were effective in preclinical studies using cellular-based assays and animal models of cancer, they remain untested in clinical trials for patients with NRF2-hyperactive tumors.

Conclusion

In summary, numerous studies have established multiple genomic, transcriptional, and proteomic mechanisms for NRF2 activation in cancer. Identification of these mechanisms has further defined NRF2 as an oncogene and KEAP1 as a tumor suppressor across tumor types. Increased mechanistic understanding of KEAP1–NRF2 signaling in cancer has not yet translated into targeted therapies or diagnostic testing for patients with NRF2-hyperactive tumors. Considering the many mechanisms of NRF2 pathway activation observed in cancer, it is maybe not surprising that a standardized diagnostic strategy is not available to identify patients with NRF2-hyperactive tumors.

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