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COMMENTARY

Potential oncogenic risks of Keap1-targeting PROTACs: Caution warranted in drug design

KEY WORDS

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homoPROTAC;
Redox homeostasis;
Oncogenesis

The Kelch-like ECH-associated protein 1 (Keap1)−nuclear factor erythroid 2-related factor 2 (Nrf2) signaling axis plays a central role in maintaining redox homeostasis, and pharmacological activation of this pathway has long been considered a promising strategy against oxidative stress-related disorders[1]. Under basal conditions, Keap1 acts as an adaptor for the CUL3−Rbx1 E3 ubiquitin ligase complex, promoting proteasomal degradation of Nrf2 and preventing its constitutive activation[1]. Upon exposure to oxidative stress, critical cysteine residues of Keap1 are modified, disrupting Nrf2 ubiquitination and allowing Nrf2 accumulation, nuclear translocation, and binding to antioxidant response elements (AREs) with small Maf proteins[2]. The resulting induction of cytoprotective genes, including NQO1, HO-1, and enzymes involved in NADPH regeneration, strengthens the cellular antioxidant defense. This adaptive mechanism protects against reactive oxygen species (ROS), electrophilic damage, and mitochondrial dysfunction, and its dysregulation has been implicated in metabolic, neurodegenerative, and inflammatory diseases, as well as ischemia−reperfusion injury[1]. Given the pivotal role of the Keap1−Nrf2 axis in cellular survival pathways, recent years have seen intense interest in developing proteolysis-targeting chimeras (PROTACs) to selectively degrade Keap1 as a novel means to produce sustained Nrf2 activation, representing a promising therapeutic strategy for pathologies driven by oxidative stress[2-4]. Nevertheless, these earlier approaches have not fully utilized the homodimerization feature and intrinsic E3 ligase activity of Keap1, leaving opportunities to refine degradation strategies.

Recently, a pioneer study led by Chunlin Zhuang and colleagues, published in *Acta Pharma Sin B*, introduced the concept of homo-PROTAC^{KEAP1}, a self-targeted degrader that capitalizes on Keap1 homodimerization and its intrinsic E3 ligase activity to achieve chemical self-knockdown[5]. Guided by crystallographic analysis (PDB 9J70 and 9J7G), the team designed a series of bivalent molecules and identified compound **8** as a highly potent degrader forming a $(Keap1)_2$:$(PROTAC)_1$ complex. Biophysical and cellular analyses revealed cooperative ternary complex formation, dose- and time-dependent Keap1 degradation kinetics with DC50 values of approximately 1−3 μmol/L across multiple cell types and D_{max} approaching 90%−99% at 10 μmol/L within 24 h. Notably, higher concentrations revealed a hook effect, consistent with competitive formation of non-productive binary complexes, underscoring the importance of degrader stoichiometry and exposure control. This compound induced near-complete Keap1 degradation via the ubiquitin−proteasome pathway, robustly activated Nrf2 signaling, and alleviated oxidative stress and inflammation in both cellular and murine models of allergic rhinitis. This study provided the first structural and functional evidence for self-targeted proteolysis, establishing a new paradigm in redox-modulating drug design.

While these findings reveal an appealing therapeutic avenue, accumulating evidence raises the possibility that long-term or systemic inhibition of Keap1 could be associated with oncogenic risk, warranting careful consideration. Keap1 ensures the constitutive degradation of Nrf2 under basal conditions. Genetic or epigenetic loss of Keap1 disrupts this homeostatic regulation, resulting in persistent Nrf2 activation and metabolic reprogramming that can promote tumorigenic adaptation[1]. In multiple human cancers, including lung adenocarcinoma, hepatocellular carcinoma, and esophageal squamous carcinoma, somatic mutations or deletions of *Keap1* have been identified as recurrent driver events[6]. Furthermore, it is important to emphasize that the effects of Nrf2 on oncogenesis are highly context-dependent. Constitutive Nrf2 activation enhances antioxidant and detoxifying capacity, supports anabolic metabolism, and confers resistance to chemotherapy and radiotherapy,

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collectively favoring malignant progression and therapy evasion[7]. To be noted, emerging *in vivo* studies have demonstrated in specific experimental contexts that sustained Nrf2 activation can be sufficient to drive metabolic reprogramming, epithelial hyperproliferation, or malignant progression in multiple cancer models [8-11]. Importantly, genetic evidence further supports this concept, as *Keap1* loss results in persistent Nrf2 hyperactivation and accelerates tumor initiation and growth *in vivo*[12,13]. By contrast, physiological or transient Nrf2 activation in normal or premalignant tissues has been shown to enhance antioxidant defense and reduce carcinogen-induced damage, thereby exerting tumor-preventive effects [14,15]. These findings firmly establish Keap1 as a tumor suppressor, and its loss-of-function (LOF) represents a hallmark of redox-driven oncogenesis.

The pharmacological depletion of Keap1 by PROTACs may, under conditions of sustained or systemic exposure, phenocopy the pathological consequences of Keap1 LOF. Continuous or high-level Nrf2 activation could create a redox-permissive microenvironment that allows premalignant cells to tolerate oxidative or genotoxic stress, evade apoptosis, and accumulate oncogenic mutations. Moreover, the metabolic rewiring driven by sustained Nrf2 signaling, including enhanced glutathione synthesis, NADPH regeneration, and lipid biosynthesis, could further promote cell survival and growth. These mechanistic parallels raise potential safety concerns for chronic administration or broad tissue exposure of Keap1-degrading agents, particularly in populations with preexisting genomic instability or inflammatory conditions (Fig. 1). Meanwhile, PROTAC-mediated Keap1 degradation is pharmacologically distinct from genetic LOF. Unlike lifelong genetic ablation, PROTAC activity is dose- and exposure-dependent, can produce a graded degradation—response with potential hook effects, and is generally reversible through Keap1 re-synthesis after drug withdrawal[2]. These properties allow the possibility of intermittent, pharmacodynamically guided dosing that limits prolonged Nrf2 pathway activation[3]. In addition, pharmacological inhibition of the Keap1—Nrf2 interaction also differs mechanistically from proteolytic degradation of Keap1. Small-molecule inhibitors typically cause partial and reversible disruption of Nrf2 ubiquitination while preserving Keap1 protein and its Nrf2-independent functions[10], whereas PROTAC-mediated degradation eliminates Keap1 more broadly and may therefore reshape Nrf2 signaling dynamics in magnitude and duration[3]. Collectively, these differences underscore the need to evaluate Keap1 degraders independently and to define appropriate therapeutic windows, particularly in the setting of sustained or systemic Nrf2 activation.

Future research should incorporate rigorous long-term safety assessments of Keap1-targeting PROTACs in tumor-susceptible animal models or wild-type animals, accompanied by transcriptomic and metabolomic profiling to detect early signatures of neoplastic transformation. Rational drug design may mitigate these risks through tissue-selective delivery systems, reversible or conditionally controllable degradation mechanisms, and transient modulation strategies that avoid persistent Nrf2 hyperactivation. Alternatively, targeting downstream mediators of oxidative damage or modulating the Keap1—Nrf2 interface dynamically, rather than eliminating Keap1 entirely, could achieve therapeutic benefit with improved safety margins. Integrating these considerations into the design of next-generation redox modulators will be essential to balance efficacy and oncologic safety.

In summary, the emergence of homoPROTAC^{KEAP1} marks a remarkable conceptual advance in targeted protein degradation, demonstrating that Keap1 can be chemically programmed to degrade itself through its intrinsic E3 ligase activity. This work not only expands the molecular toolkit for redox-related therapeutics but also challenges existing paradigms of PROTAC design by exploiting homodimeric self-recognition as a degradative trigger.

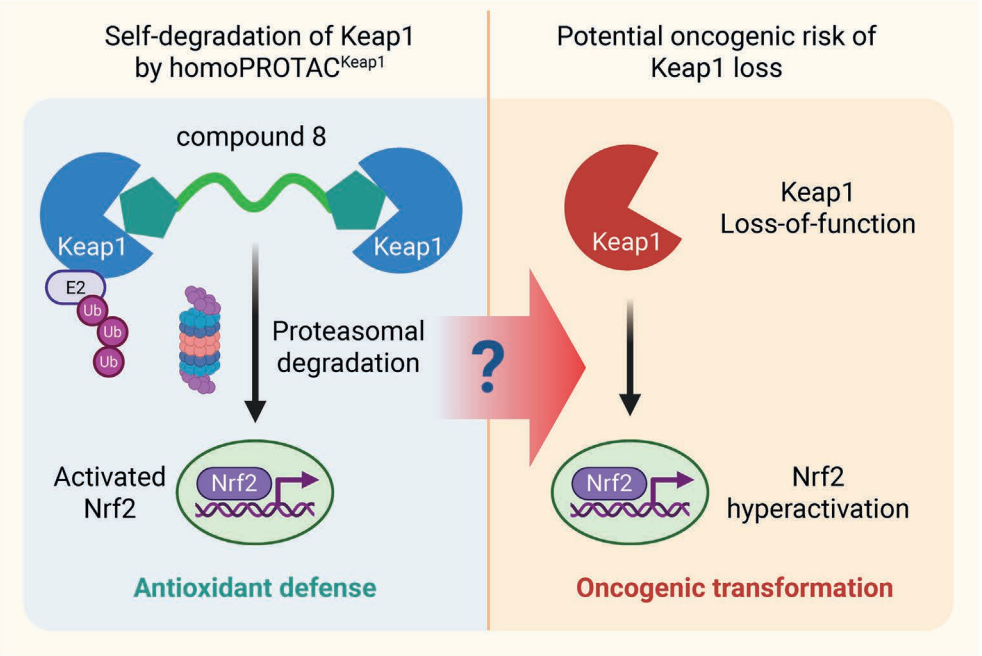

Figure 1 Schematic illustration of the dual implications of Keap1-targeting PROTACs. HomoPROTAC-mediated ternary complex formation promotes Keap1 self-ubiquitination and proteasomal degradation, leading to stabilization and activation of NRF2 and enhanced antioxidant gene expression (left). However, sustained or systemic Keap1 depletion may phenocopy loss-of-function events, resulting in persistent NRF2 hyperactivation, metabolic reprogramming, and a redox-permissive microenvironment that could potentially support tumor initiation or progression in susceptible contexts (right).

Yet, in light of the established tumor-suppressive role of Keap1, these findings also raise an important caveat: long-term or systemic depletion of Keap1 may mimic oncogenic loss-of-function events observed in human cancers. Therefore, the continued development of Keap1-targeting PROTACs should proceed with rigorous assessment of their chronic effects and oncologic safety. By integrating mechanism-based vigilance with chemical innovation, future research can harness the therapeutic promise of Keap1 degradation while ensuring that this powerful strategy remains both effective and safe.

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Author contributions

Zhe Zhao: Conceptualization, Writing−original draft. Wen Ma: Literature review, Writing−review & editing. Jincen Hao: Literature review, Writing−review & editing. Gaofei Hu: Writing−review & editing. Xinfeng Wang: Conceptualization, Supervision, Funding acquisition. All authors have materially contributed to the preparation of this Letter, critically revised the manuscript, and approved the final version for publication.

Conflicts of interest

The author declares no competing interests.

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