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COMMENTARY

A highly promising new avenue for targeting K-RAS: The small-molecule degrader XMU-MP-9

KEY WORDS

K-Ras mutants;
NEDD4-1;
Small-molecule degrader;
Bifunctional compound;
Ubiquitination;
Degradation

K-RAS mutations are among the most prevailing oncogenic drivers in human cancers, yet they have long been considered "undruggable" due to the absence of deep hydrophobic pockets on the protein surface and the high affinity of RAS for GTP. While recent advances have yielded covalent inhibitors targeting specific mutant K-RAS^{G12C} and non-covalent inhibitors for K-RAS^{G12D1,2}, many oncogenic K-RAS variants, such as K-RAS^{G12V}, remain difficult to target directly. In this context, the study by Zeng et al.[3] introduces a novel and compelling strategy: the small-molecule degrader XMU-MP-9, which exploits the natural E3 ubiquitin ligase Nedd4-1 for RAS proteins to ubiquitinate and degrade a broad spectrum of oncogenic K-RAS mutants.

The authors built on their prior discovery that Nedd4-1 is a physiological E3 ligase for wild-type RAS but is inefficient against GTP-bound oncogenic mutants due to conformational masking of the ubiquitination site[4]. Remarkably, they identified XMU-MP-9 through a high-throughput screen designed to find compounds that selectively inhibit the growth of NEDD4-1$^{+/+}$ over NEDD4-1$^{-/-}$ cells harboring K-RAS^{G12V} mutant. XMU-MP-9 emerged as a bifunctional compound that binds both the C2 domain of NEDD4-1 and an allosteric site on K-RAS, thereby stabilizing their interaction and inducing a conformational change that exposes lysine 128 (K128) on K-RAS for NEDD4-1 mediated ubiquitination. This leads to lysosomal degradation of K-RAS mutants, effectively suppressing downstream MAPK signaling and inhibiting cancer cell proliferation and tumor growth *in vivo*.

One of the most significant contributions of this work is the demonstration that XMU-MP-9 promotes degradation of multiple K-RAS mutants including G12V, G12D, G12C, G12S, G13D, and Q61H with similar potency in cancer cells, while sparing wild-type K-RAS in normal cells to a considerable extent. This broad-spectrum activity addresses a critical gap in the field, where mutant-selective inhibitors often fail to cover the full mutational landscape of K-RAS-driven cancers. Moreover, the compound's mechanism leverages a pre-existing physiological complex (NEDD4-1/K-RAS), differing from traditional PROTACs that recruit exogenous E3 ligases[5]. This may confer advantages in terms of specificity and reduced off-target effects.

This study also provides insightful mechanistic details. Through photoaffinity labeling and mutagenesis, the authors mapped the binding sites of XMU-MP-9 to an allosteric pocket near K128 on K-RAS and a cleft in the C2 domain of NEDD4-1. Mutations at these interfaces (*e.g.*, F78A in K-RAS or K127A/F129A in NEDD4-1) abrogated compound activity, confirming the specificity of the induced proximity. Importantly, the effect of XMU-MP-9 was shown to be dependent on NEDD4-1/K-RAS negative feedback regulation loop, and treatment with XMU-MP-9 significantly inhibited tumor growth in both immunodeficient and immunocompetent mouse models without evident toxicity.

However, challenges remain for the clinical translation of XMU-MP-9. The suboptimal pharmacokinetics, characterized by

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poor oral bioavailability and solubility, will require further medicinal chemistry optimization. Additionally, the lack of structural data for the ternary complex limits precise mechanistic understanding and rational design of improved derivatives. Nevertheless, XMU-MP-9 serves as a pioneering proof-of-concept for a new class of K-RAS-targeted therapeutics.

In conclusion, Zeng et al. have elegantly demonstrated how hijacking a natural regulatory axis, the NEDD4-1/K-RAS interaction, can be leveraged to degrade oncogenic K-RAS mutants. This work not only offers a promising candidate for therapeutic development but also opens a new paradigm for targeting "undruggable" oncoproteins through native E3 ligase engagement. With further optimization, such degraders could significantly expand the therapeutic arsenal against K-RAS-driven cancers.

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