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CHRONIC MYELOGENOUS LEUKEMIA

Can PROTACs cure Leukemia?

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Little did I know when I was a first year graduate student at Caltech in Ray Deshaies' laboratory, that the possibility of targeting cancer-causing proteins could lead to a new approach to treat diseases. Until then, it was extremely difficult to inhibit protein-protein interactions or "undruggable targets" with small molecules [1, 2]. The concept that one could bring any protein to an E3 ligase for ubiquitination and subsequent degradation by the proteasome had not been considered. Both Ray and Craig Crews originally had the idea that if a heterobifunctional protein or bridging molecule called PROTAC (Proteolysis Targeting Chimeric molecule) could recruit an unrelated protein close enough to a E3 ligase, the protein could be ubiquitinated and degradation. The PROTAC consists at one end a moiety that targets the protein of interest (also known as the warhead), while the other end would be a peptide or molecule that would be recognized by a E3 ligase; both connected by a chemical linker. The advantages of PROTACs are that they (1) can target virtually any intracellular or transmembrane protein; (2) are catalytic; (3) bind to any unique part of a protein surface for selective inhibition; (4) target non-enzymatic structural and regulatory proteins; and (4) act as potential "magic bullets" for eliminating proteins within multi-subunit complexes.

As "proof of concept," we demonstrated that protein MetAP-2 could be targeted to the E3 ligase $SCF^{\beta\text{-}TRCP}$ resulting in ubiquitination and degradation through covalent interactions (Fig. 1A) [3]. This was the first evidence that PROTACs could target any protein for ubiquitination and degradation if recruited to an E3 ligase. Subsequent experiments demonstrated that the cancer-promoting proteins, estrogen, and androgen receptors in breast and prostate cancer, respectively, could be targeted for ubiquitin-dependent proteolysis through noncovalent protein-protein interactions [4]. In our studies and others, additional E3 ligases, including VHL and Cereblon were used to develop PROTACs. The next challenge was to prove that PROTACs could enter cells to degrade intracellular proteins, which was another hurdle that was necessary to advance this technology. Up to this point, the limitation of PROTACs was the use of peptides to target proteins to the E3 ligase, which limited its application despite the incorporation of protein transduction domains to facilitate cell entry. It was strongly believed that for translation to the clinic, the peptide component of PROTACs be replaced with small molecules [5]. Second, the ideal combination of the target for ubiquitination and the E3 ligase was not yet identified for a particular disease-causing protein. Ideal targets for PROTACs include overexpressed proteins, protein aggregates, undruggable proteins, scaffold proteins, and oncogenic fusion proteins (Fig. 1B) [1]. Since the original concept of PROTACs, the field of targeted protein degradation has been advanced by both academic institutions and industry to develop new approaches to target proteins for degradation for preclinical testing and clinical application [6–8]. These advances have led to new versions of PROTACs, including molecular glues and other types of degraders [1]. Several of these approaches are currently in clinical trials.

Cruz-Rodriguez et al. provide a comprehensive review of development of PROTACs to target BCR::ABL1 for treatment of Ph+ leukemia [9]. The different functional activities of BCR::ABL1 kinase are described, including kinase-independent cellular phenotypes. BCR::ABL1 has demonstrated scaffold functions that drive proliferation adhesion and chemotaxis that are only partially inhibited by imatinib. This suggests that suppressing the kinase activity alone is not sufficient to inhibit BCR::ABL1 activity in CML [10]. Therefore, targeting the BCR::ABL1 protein for degradation may have a greater effect or in fact, be an optimal approach, rather than simply inhibiting its kinase activity. Other examples of non-enzymatic functions in cancer-causing proteins, such as EGFR and BTK, suggest that non-enzyme related activities of these proteins may contribute to TKI resistance. PROTACs have been developed that target other domains of BCR::ABL1, including the ABL-1 SH3 interaction domain that binds ABL-1 binding protein. Another PROTAC that targets the Inhibitor of apoptosis proteins (IAP) was also shown to effectively decrease proliferation of BCR::ABL1 positive and negative CML cell lines. There are also varying degrees of potency of PROTACs to target BCR::ABL1, depending on the warhead, i.e., dasatinib, and the E3 ligase, either VHL, CRBN, and cIAP1. From the beginning, it was recognized that optimization of PROTACs would be an iterative process and dependent on the target, warhead, and E3 ligase. Identifying the ideal combination of these has been the challenge. Cruz-Rodriguez provide a nice table summarizing the current list of BCR::ABL1 degraders that have been developed [9]. The authors describe a recent advancement in PROTAC technology in which the first amino acid is basic or hydrophobic. This residue is recognized by the UBR1 family of E3 ligases. These Arg-PEG1-dasatinib degraders were highly potent in in vitro and in vivo models of CML and correlated with growth inhibition of CML cells at a concentration of less than 1 nM [11]. This demonstrates another step towards developing potent and effective PROTACs for future clinical application.

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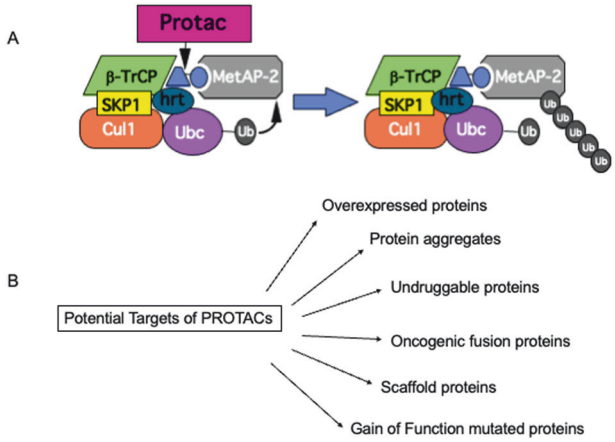

Fig. 1 Designing PROTACs. A The first PROTAC shown to target METAP-2 to the SCF ubiquitin ligase. **B** Potential targets of PROTAC.

CONCLUDING REMARKS

Recent advances suggest that BCR::ABL1 degrading PROTACs may be a better approach than simply targeting its kinase activity. The challenges remaining include optimization of cell permeability and specificity of target engagement. Additional studies demonstrating the efficacy and toxicity of PROTACs targeting BCR::ABL1 in CML mouse models are needed. The ability of BCR::ABL1 targeting PROTACs to impact treatment-free remission is yet to be determined. Ensuring specificity of the PROTACs will be essential to minimize toxicity and off-target effects. In addition, there are very few studies that demonstrate the effects of PROTACs on primary CML stem cells, which will be critical to prevent progression of disease. A comprehensive analysis of E3 ligase expression in primary CML cells both in chronic phase and blast crisis will potentially identify the ideal PROTACs for future clinical use. Mechanistic studies will provide advances in our understanding of the intracellular effects of PROTACs in degrading BCR::ABL1 and potentially other fusion proteins in leukemia. Despite the advances in PROTAC technology, additional efforts will be needed to optimize the design and efficacy of this approach for patients with CML.

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AUTHOR CONTRIBUTIONS

All contributions were from the single author.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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