Discovery of protein degraders targeting a multi-functional protein

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Abstract

Proteolysis targeting chimeras (PROTACs), which induce selective degradation of their target protein in cells or in vivo, are of interest as novel drug modalities. Unlike conventional enzyme inhibitors and receptor antagonists that inhibit a specific protein function, PROTACs reduce the protein through degradation, inhibiting all of its functions. This characteristic of PROTACs inspired us to apply this technique to multi-functional enzymes that possess both catalytic and scaffolding functions. So far, we have identified several PROTACs, including one for protein lysine deacetylase HDAC8, and demonstrated its advantages over conventional enzyme inhibitors.

Background & Results

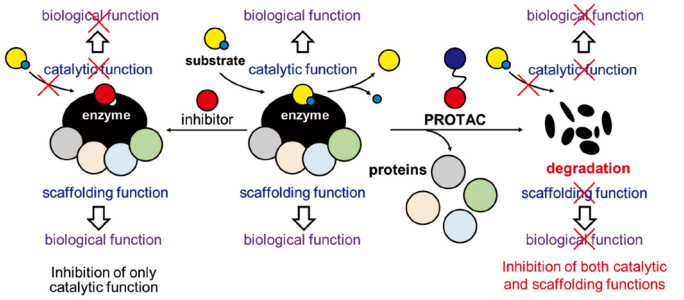
HDAC8 catalyzes protein deacetylation such as acetylated SMC3. Additionally, HDAC8 serves a scaffolding function, interacting with some transcriptional factors such as STAT3 and CREB. Furthermore, dysregulation and overexpression of HDAC8 are associated with the growth of T-cell leukemia. In other words, HDAC8 PROTACs are of interest as therapeutic agents for T-cell leukemia because they can inhibit both catalytic and scaffolding functions of HDAC8. Therefore, we endeavored to identify HDAC8 PROTACs.

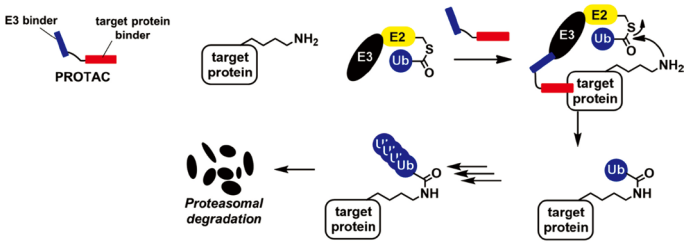
PROTACs are designed by linking a binder of a target protein to a binder of ubiquitin ligase (E3) and induce degradation of the protein via the ubiquitin-proteasome system. Thus, we designed and synthesized HDAC8 PROTAC candidates based on compound **1**, which binds to HDAC8 to inhibit its catalytic function, and thalidomide derivative **2**, which is one of the E3 binders.

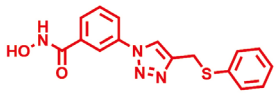
We evaluated the HDAC8 degradation activity of the candidates in T-cell leukemia Jurkat cells. As a result, we found that compound **3** reduced the level of HDAC8 in does- and time-dependent manner. We also confirmed that a proteasome inhibitor disrupted the reducing activity of **3**, which indicated that **3** induced the degradation of HDAC8 dependently on the ubiquitin-proteasome system. Additionally, we found that **3** inhibited the growth of Jurkat cells more strongly than conventional HDAC8 inhibitor **1**, which only inhibits the catalytic function (**1**: GI_{50} = 7.1 μM, **3**: GI_{50} = 0.78 μM). These results suggest that the inhibition of both catalytic and scaffolding functions by the HDAC8 PROTAC is more effective for the treatment of T-cell leukemia than only catalytic inhibition by the conventional inhibitor.

Significance of the research and Future perspective

PROTACs are adaptable to various proteins and have garnered significant attention as molecules that expand the druggability of proteins. In fact, several PROTACs targeting disease-related proteins have been reported and studies on their application have been conducted for drug development. Currently, more than ten PROTACs are in clinical stages as potential therapeutic agents for diseases such as cancer. Some of them may receive pharmaceutical approval.







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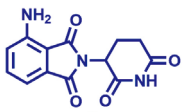

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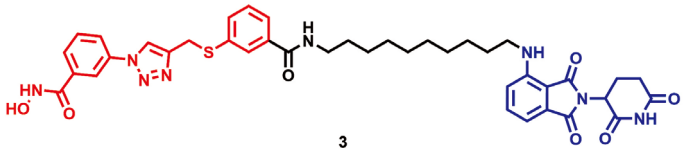

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Patent Japanese Patent Application No.2023-143583

Treatise Chotitumnavee, Jiranan; Itoh, Yukihiro; Suzuki, Takayoshi et al. Selective degradation of histone deacetylase 8 mediated by a proteolysis targeting chimera (PROTAC). Chem. Commun. 2022, 58, 4635-4638. doi: 10.1039/d2cc00272h
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URL

Keyword target protein degradation, PROTAC, HDAC8, enzyme