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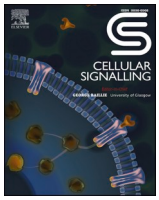

The mechanism of action and clinical value of PROTACs: A graphical review

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ABSTRACT

The use of small molecule drugs to inhibit active protein targets has revolutionised the treatment options for many diseases in the past 30 years. The greatly improved pharmacokinetic properties of modern drugs combined with enhanced cell permeability and oral bioavailability has made these molecules ideal for reaching protein targets of interest in cells and inhibiting disease-driven signalling pathways. However, these small molecule drugs have several limitations which have opened the doors for the development of a new class of compounds, known as proteolysis targeting chimeras (PROTACs). These next generation drugs actively and specifically degrade designated protein targets and hold the potential to greatly expand the druggable genome, including previously drug-resistant targets.

1. Introduction

PROTACs provide a new mechanism in that they dramatically reduce the cellular availability of a protein of interest (POI) with high selectivity yet greatly reduced side effects in comparison to traditional small molecule inhibitors [1]. The first PROTAC was developed in 2001 by Craig M. Crews and the field has rapidly developed in the last two decades since this breakthrough [2]. PROTACs have a bifunctional structure comprised of three elements – an E3 ubiquitin ligase ligand [3,4], a POI ligand and a linker region to connect the two ligands. The POI ligand selectively targets and 'hijacks' the protein of interest by binding to it and sequestering it to the joined E3 ligand. The E3 ligase ligand then recruits an E3 ubiquitin ligase from the cytosol to the PROTAC complex containing the bound protein of interest, and the linker region conjugates the POI and E3 ligase ligands together [5]. Therefore, the protein of interest and the E3 ligase are brought artificially close, permitting the polyubiquitination of the protein target and its subsequent destruction by the proteasome (Fig. 1). PROTACs can be used to destroy potentially any protein target, even proteins that are not naturally ubiquitinated. Literature suggests that the degradation of more than 50 different target proteins is possible with PROTAC technology. Current targets include protein kinases, nuclear receptors and transcription factors, with many more potential targets being developed [6]. The concepts covered in this graphical review are not exhaustive, and more in-depth reviews on PROTACs can be found elsewhere [7,8].

1.1. PROTAC mechanism of action

Traditional inhibitor compounds work in an occupancy-dependent manner, which involves binding to a binding pocket or active site of the protein target and causing a loss of function of the target as a result. However, as most enzyme inhibitors bind non-covalently e.g. reversibly to the protein target and can therefore become detached, they must be administered at relatively high concentrations to ensure that the active site of the target remains occupied by the inhibitor and the clinical benefits of this drug is maintained [1]. In contrast, PROTACs have an event-based mechanism of action. PROTACs only need to bind to their target for as long as it takes for the E3 ligase and POI to be recruited together and the POI degraded. In effect, they only have to interact briefly to induce proteolysis of the POI by the proteasome. After the target protein has been destroyed, PROTACs are able to detach and be recycled for the destruction of the next protein target. The PROTAC therefore not only survives the target protein ubiquitination and destruction events, but also maintains activity and is able to engage in multiple further cycles of target degradation [9]. Such an enzymatic, event-driven mechanism of action eliminates the need for a high level of

Abbreviations: PROTACs, proteolysis targeting chimeras; POI, protein of interest; CDK, cyclin-dependent kinase; VHL, Von Hippel-Lindau; CRBN, Cereblon; MDM2, mouse double minute 2; cIAP1, cellular inhibitor of apoptosis protein 1; AbTACs, antibody-based PROTACs; AUTACs, autophagy-targeting chimeras; LYTACs, lysosome-targeting chimeras.

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the drug to be administered, providing 'sub-stoichiometric' activity which helps to eliminate many of the problems associated with traditional medicinal compounds, a feature that will be discussed here.

1.2. PROTACs eradicate active protein targets

The novel PROTAC mode of action often results in the whole population of the diseased protein being effectively eradicated from the body, which offers many benefits [1]. Firstly, PROTACs are more effective at hitting populations of cells such as those at the core of a tumour which are more likely to survive conventional treatments. Secondly, by triggering target destruction rather than simply occupying an active site, PROTACs have been found less likely to induce an "escaping" mutation in the POI that may make small molecule binding less efficient [10]. As the target is exposed to the drug only long enough for an E3 ligase to be recruited and the ubiquitin-proteasome system to be activated, the duration of target exposure to the PROTAC drug is much shorter than with conventional compounds, reducing the likelihood of drug-resistant mutations developing in the target. The action of PROTACs also allows the drug to be administered at a much lower dosage [11] and this has the dual benefit of lowering the likelihood of resistance development and reducing the risk of adverse side effects occurring in patients.

1.3. PROTACs offer enhanced selectivity and specificity

One of the main focuses of drug development is the constant improvement of the specificity and selectivity of drugs. This is critical in preventing unwanted side effects due to "off-target" interactions which often occur with conventional drugs when administered at high doses [1]. In the cell there are many other potential binding partners for a drug other than the desired target, including other proteins, DNA, lipids, sugars, metabolites and other small molecules. All of these molecules can potentially interact with an administered drug and reduce its effect in inhibiting the desired target, and these unwanted interactions can also result in the occurrence of dangerous and damaging side effects [12]. In relation to the bifunctional structure of PROTACs, both the POI ligand and the E3 ligase ligand can be optimised in order to increase the target selectivity. For example, this strategy has been used to develop an effective cyclin-dependent kinase 9 (CDK9) -degrading PROTAC, which can be used to effectively treat cancers in which the activity of this protein is shown to be enhanced. The CDK9 PROTAC was also shown to not affect other cellular processes that rely on the function of different CDK isoforms [13]. The production of these highly specific and selective PROTACs is possible through an extended screening process, involving trial and error when conjugating different POI ligands to different E3 ligase ligands until an effective combination is discovered [1]. Different linker compositions can also be used to build in enhanced specificity. Additionally, as more and more selective PROTAC combinations for specific targets are developed and the structural considerations better understood, the alteration of these combinations to bind to slightly different targets of the same type (e.g. CDK4 instead of CDK9) becomes much easier, quicker and more cost effective.

1.4. PROTACs have potential for overcoming drug resistance

Drug resistance has always been a major challenge with inhibitors. Although small molecules have revitalised treatment options for many difficult to treat diseases, varying degrees of resistance to their mode of action occurs over time, allowing disease symptoms to return [1]. This often stems from upregulation of the protein target via transcription and translation, hence PROTACs represent the next generation of therapeutic inhibitors that have been developed to overcome developed resistance, especially in cancer. The discovery of PROTACs that can bind to and degrade previously resistant protein targets has been highly successful and is attributed to the different molecular mechanism of action of these inhibitors compared to conventional drugs. For example, PROTACs have been successfully used to target oestrogen receptors in drug-resistant breast cancers and the Bruton's tyrosine kinase enzymes in drug-resistant lymphomas, showing the unrivalled potential of PROTACs for treating malignant and persistent tumours that have resisted previous therapies [14,15]. PROTACs have also been successfully developed to treat other drug-resistant diseases such as hepatitis C and have been shown to work even when the causative virus mutates its genes in an attempt to out-evolve these drugs. Such promising data suggests that PROTACs could be used in the future as an effective treatment for many rapidly evolving and drug resistant viral diseases [16].

1.5. PROTACs for broadening the druggable proteome

The final advantage of PROTACs is their potential to target the previously undruggable proteome. It is estimated that the druggable proteome contains over 5000 proteins, however only around 700 of these proteins are currently targeted by approved drugs [17]. Moreover, there are up to 30,000 protein-encoding genes in the human genome, and through the process of alternative splicing and post-translational modifications there are thousands of potential drug targets which are not currently exploited for treating human disease (Fig. 2) [18]. Many of

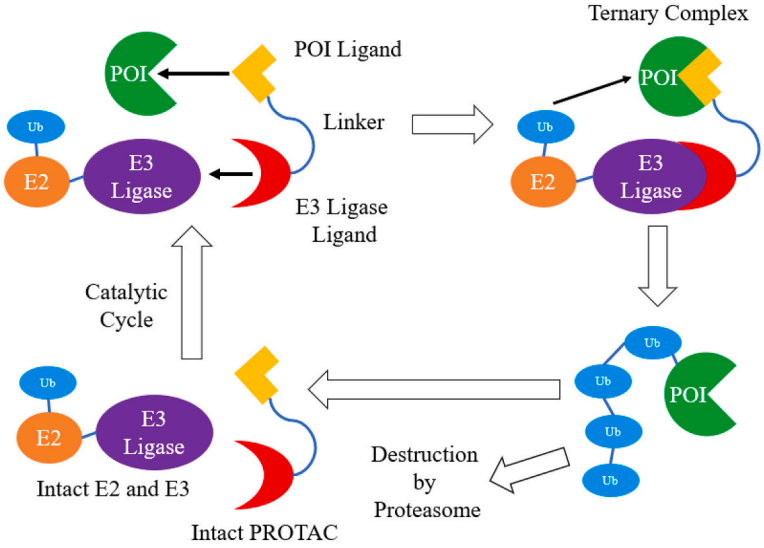

Fig. 1. Structure and function of PROTACs. As shown, a PROTAC is made up of a ligand for the protein of interest (yellow) and a ligand for an E3 ligase (red) connected by a linker, which allows the protein of interest (POI - green) to be brought in close proximity to an E3 ligase (purple). The target protein is then polyubiquitinated (Ub = ubiquitin - blue) by an E2 conjugating enzyme (orange) and degraded by the proteasome. The PROTAC is not destroyed in this process but instead can be reused in more cycles of the same reaction, similar to an enzyme (catalytic cycle). Figure adapted from Zeng et al. [1]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

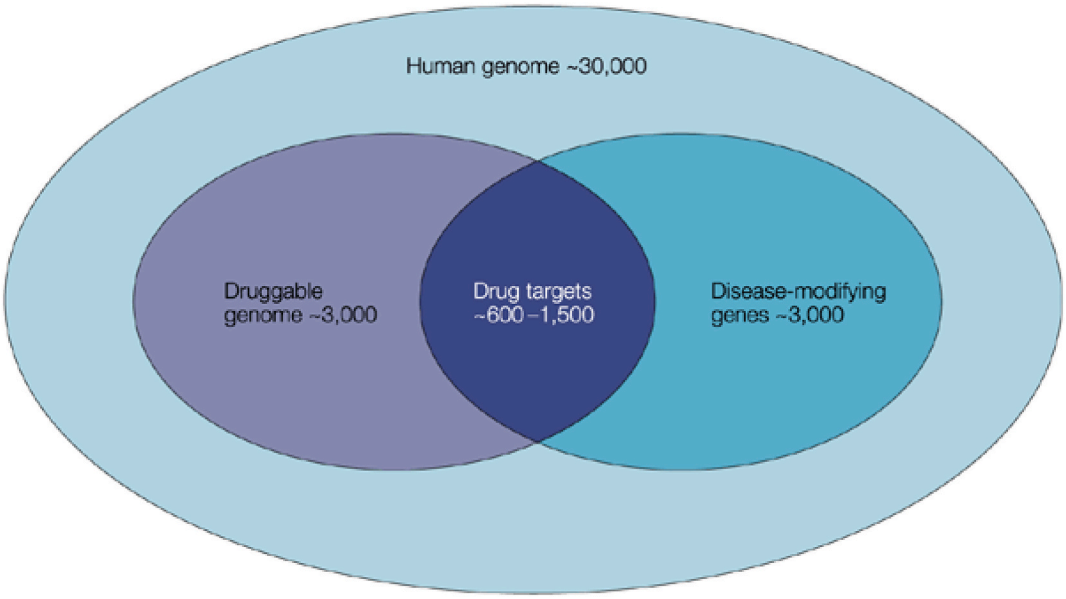

Fig. 2. Exploitable drug targets in the human genome. As shown in the outer ring, the human genome is comprised of around 30,000 protein encoding genes. The number of exploitable drug targets can be predicted from the number of genes linked to disease (disease-modifying genes) and the number of genes that are known to be possible to target using drugs (druggable genome). This indicates that there are approximately 1500 possible drug targets in the human genome, with only 700 currently being exploited by modern medicines. However, the use of novel therapeutic agents such as PROTACs could allow previously undruggable targets to be exploited, vastly increasing the druggable genome beyond its previously predicted limit. Figure sourced from Hopkins and Groom [18].

these proteins have been found to be undruggable as they do not have an effective binding site for a traditional small molecule on their surface. As PROTAC binding to the POI can be directed by a number of ligand types (e.g. peptides, chemical entities, etc.), this makes it possible for these drugs to be developed to degrade targets previously believed to be undruggable [1]. Additionally, unlike traditional small molecules, PROTACs require less binding affinity for their target proteins because they only bind transiently to the POI. Therefore, even low affinity POI ligands can be included in the PROTAC complex and the target can still be efficiently, effectively and selectively degraded [19]. Such a concept has been verified by the Von Hippel-Lindau (VHL) PROTAC1 drug, which targets the kinase p38α, as despite the POI ligand having low binding affinity, this PROTAC was found to be highly potent in degrading the target kinase [20]. The E3 ligase ligand has also been found to be unaffected in its ability to recruit and bind to an E3 ligase even with a low binding affinity, allowing both ligands of the PROTAC complex to be modified in their binding affinities in order to target previously undruggable proteins. For example, the Ras protein was previously considered to be an undruggable target despite being involved in the progression of many cancers as it has a lack of well-defined binding pockets on its surface. This made it impossible to develop effective compounds to bind to Ras, as they require a high affinity for their targets in order to work effectively [21]. Recently a PROTAC called XY-4088 has been developed and has been successfully shown to induce the degradation of K-Ras in vitro, but has not yet been proven to degrade K-Ras in vivo [22]. The further development of this PROTAC therefore shows huge promise for producing an effective K-Ras degrader that could be used to treat cancer, based on targeting a protein that was previously thought to be inaccessible to therapeutic agents. In addition, Homo-PROTACs can be designed to induce the degradation of E3 ligases involved in disease. These PROTACs are comprised of two linked E3 ligase ligands and can therefore induce the dimerisation of aberrant E3 ligases, leading to their self-destruction [23]. Since many E3 ligases have been associated with cancers such as glioblastoma [24] and prostate cancer [25], this technology could be used to selectively degrade these targets as a novel oncological treatment.

1.6. Limitations and the future of PROTACs

Despite the many advantages of PROTACs over conventional inhibitors, there still remain several areas for improvement. For example, drug resistance to PROTACs is not completely avoidable, despite the sub-stoichiometric dosage that is required for target elimination. It has been shown in VHL- and Cereblon (CRBN)-based PROTACs that resistance can be developed to these compounds in cancer cells following long term treatment [26]. However, the mechanism by which drug resistance was acquired was found to be different for PROTACs than for conventional inhibitors and involved mutations developing that caused the destruction of the E3 ligase recruited to the target-bound complex instead of mutations that prevented the PROTAC complex from binding to the POI or E3 ligase. It is therefore suggested that in the future, PROTAC resistance could be addressed by administering the PROTAC with an E3 ligase in order to increase the availability of this effector [1]. In addition, the development of PROTAC technology is also limited by the number of ligands which have been successfully developed to bind to E3 ligases. Despite there being more than 600 endogenous E3 ligases known in humans, less than 1% of these E3 ligases have had corresponding ligands identified or developed to bind to them [27]. So far only four classes of E3 ligase ligands have been developed – VHL and Cereblon as mentioned before, mouse double minute 2 homolog (MDM2) and cellular inhibitor of apoptosis protein 1 (cIAP1). Therefore the flexibility of PROTACs in destroying specific targets of interest is still limited by the ability to successfully recruit an E3 ligase to the complex, and the activity of these inhibitors in cells will depend upon the inherent abundance of different E3 ligases [1]. However, this limitation could also be ameliorated by supplying an E3 ligase alongside the PROTAC. To date, the majority of PROTACs also do not follow Lipinski's classic “rule-of five”, making them much less bioavailable and less capable of penetrating into cells than other small molecule inhibitors [28]. Therefore, despite being possible to administer at a low dose, this low dosage may not be able to reach the target in cells and therefore the pharmacological activity of PROTACs could be greatly reduced in vivo. The design of the PROTAC linker must also be optimised in order to prevent the functional domains of the PROTAC from being separated, as the linker chain is often at high risk of degradation by oxidative metabolism [1]. Finally,

despite having greatly reduced side effects in comparison to previous drugs, PROTACs are not exempt from producing side effects when administered to patients. However, several novel strategies are being used to minimise PROTAC-derived side effects. For example, photo-PROTACs allow the activity of the PROTAC to be reversibly controlled based on the isomerisation of the linker element in response to light [29], and antibody-based PROTACs (AbTACs) allow enhanced target selectivity to be achieved for the targeted degradation of cell surface proteins [30]. Besides PROTACs, many more targeted protein degradation technologies are also in development, such as autophagy-targeting chimeras (AUTACs) and lysosome-targeting chimeras (LYTACs), highlighting the breadth and potential of this field of drug discovery [31].

2. Conclusion

PROTACs provide new hope for the treatment of many different recalcitrant disease types. Due to the obvious advantages over conventional small molecule inhibitors as outlined in this review, these drugs have the potential to revolutionise the ability to selectively destroy even drug-resistant protein targets with greatly reduced side effects. In addition, PROTACs provide the potential to inhibit previously undruggable protein targets due to their novel mode of action. However, PROTACs still require extensive development to optimise their pharmacological properties in vivo, making the next 20 years very exciting for the field of PROTAC drug development.

Data availability

No data was used for the research described in the article.

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