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TARGETED PROTEIN DEGRADATION BY SMALL MOLECULES: Applications in Biology and Medicine

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ABSTRACT -
Targeted Protein Degradation by Small Molecules is a promising approach for developing new therapeutics that can selectively eliminate disease-causing proteins. This approach uses small molecules to redirect the cell's natural protein degradation machinery towards specific target proteins, which are marked for degradation by the small molecule. This has the potential to be a highly effective way to eliminate disease-causing proteins, as it allows for precise control over protein levels and can overcome some of the limitations of traditional small molecule inhibitors, such as off-target effects. Targeted Protein Degradation by Small Molecules is a rapidly evolving field with significant potential for the development of new therapeutics for a range of diseases, including cancer, neurodegenerative disorders, and viral infections. However, there are still many challenges to overcome, such as improving the selectivity and potency of small molecule degraders, understanding the mechanisms of action and potential side effects, and developing methods for delivery of these molecules to the relevant cells and tissues.

INTRODUCTION: THE LIMITS OF INHIBITORS AND GENETIC KNOCKDOWNS

Genetic knockdown and knockout models, on the other hand, make it possible to completely or partially eliminate the expression of a protein. This provides researchers with the opportunity to investigate the function of the protein in vivo (Russ &Lampel, 2015). However, these models can have pleiotropic effects, which means that the removal of one protein might alter the expression or function of a great number of other proteins. Because of this, it can be difficult to trace a particular phenotype to the absence of the POI. Additionally, a large number of proteins are necessary for the continued existence of a cell, and the loss of all of these proteins can be fatal. (Russ &Lampel, 2005).

A possible alternative to these strategies for disrupting protein function is the use of tiny molecules to carry out protein degradation in a targeted manner. This strategy involves the utilisation of small molecules in order to selectively degrade a target protein by recruiting cellular degradation machinery. Examples of such machinery include the ubiquitin-proteasome system and autophagy. This allows for more precise control over protein levels and can overcome the constraints of targeting proteins with tiny molecules. As a result, it offers various advantages over more traditional techniques of inhibiting protein production. In addition, this strategy may be utilised to target proteins even if they do not have well-defined binding sites or have dynamic structures that are challenging to target with small molecules. (Conde &Artzi, 2015, Clague, Heride, &Urbé, 2015)

Targeted protein breakdown by small molecules is still a relatively young subject, and despite its potential, there are still a lot of hurdles to overcome. These include creating strategies for transporting these compounds to the relevant cell and tissues (Clague, Heride, &Urbé, 2015). Improving the selectivity and effectiveness of small molecule degraders is another one of these areas of focus. This method, however, has the potential to revolutionise our capacity to investigate and control protein function in vivo, as well as to generate new therapies for a wide range of disorders, provided that further research and development take place.

A possible alternative to genetic knockdown approaches is the use of chemical knockdown procedures. Some examples of these technologies include targeted protein breakdown by tiny chemicals. These methods include the use of tiny molecules in order to selectively degrade a target protein. As a result, they offer a temporal control over protein levels, which is absent from genetic knockdown techniques. According to Deshaies and Joazeiro (2009), chemical knockdown techniques are ideal candidates for the development of therapeutics because they exhibit pharmacokinetic features that are comparable to those of typical small-molecule medicines.

To selectively remove a target protein, one strategy involves the use of small-molecule degraders. These degraders take use of the natural protein degradation machinery that is present in the cell. These

degraders are composed of a ligand that binds to the target protein and a chemical moiety that attracts the degradation machinery (Clague, Heride, &Urbé, 2015; Deshaies&Joazeiro, 2009). The ubiquitin-proteasome system and autophagy are two examples of the degradation machinery that may be recruited by these degraders (Clague, Heride, &Urbé, 2015). Because it allows for more precise control over protein levels and can target proteins that don't have well-defined binding sites, this method offers the potential to overcome some of the limitations of classic small-molecule inhibitors.

The use of small-molecule inhibitors of protein-protein interactions (PPIs) that are essential for the stability or function of the target protein is an additional strategy. According to Conde and Artzi (2015), these inhibitors trigger the breakdown or instability of the target protein by interfering with the relationship that exists between that protein and its binding partner. Because PPIs are important to the functioning of a wide variety of cellular functions, this strategy holds the potential to target a diverse collection of proteins that are all linked to illness.

In this article, we will explore approaches that can lower POI levels and include either temporal control or small molecule therapeutic properties. These chemical knockdown approaches provide alternate therapy options that extend outside the traditional druggable space while yet retaining pharmacokinetic features that are comparable to those of conventional small-molecule drugs.

SELECTIVE ESTROGEN RECEPTOR DOWNREGULATORS

Selective oestrogen receptor downregulators, also known as SERDs, are a family of drugs that have the potential to stimulate the degradation of their target protein. Because of this ability, selective oestrogen receptor downregulators are considered to be promising prospects for the treatment of breast cancer that is positive for oestrogen receptor alpha (ER). The first selective oestrogen receptor modulator, fulvestrant, was granted approval by the Food and Drug Administration of the United States in the year 2002; however, the drug's limited bioavailability and the necessity that it be injected intramuscularly once per month restrict its therapeutic value. New SERDs that have enhanced oral bioavailability have been created very recently. One example of this is ARN-810, which was developed by Seragon Pharmaceuticals and has demonstrated encouraging preclinical results in mice. Other businesses, such as AstraZeneca and Pfizer (Kieser, 2010), have also created molecules that have both a high level of potency and oral bioavailability. According to Liang, J. (2013), recent developments in the research and development of SERDs have opened the door to the possibility of enhanced therapy choices for ER+ breast cancer patients.

Although SERDs have been utilised for the induction of protein degradation for a significant amount of time, the mechanism by which they cause the degradation of the target protein, such as ER, is not completely known. It is hypothesised that when a SERD binds to its target protein, it promotes conformational changes that reveal hydrophobic patterns that are recognised by chaperones and cause protein degradation (Lai, 2015; Govek, 2015). This process is thought to be responsible for the breakdown of the protein. However, the specific structural changes that are generated by various SERDs are still not fully understood, which makes it challenging to rationally design novel compounds (Suzuki, 2011). According to several recent research, even relatively slight alterations to the structure of many SERDs can have a sizeable effect on how well they degrade their target molecules. High-throughput screening assays have been established in order to discover compounds that can swiftly assess intracellular levels of the target protein or disclose key hydrophobic surfaces, which will facilitate the development of new SERDs with increased efficacy (Callis, 2015).

IMMUNOMODULATORY DRUGS

According to Degorce (2015), the IMiDs, which include thalidomide, lenalidomide, pomalidomide, and CC-122, were initially found as sedatives but have subsequently been repurposed as powerful anticancer drugs. Lenalidomide is licenced for the treatment of relapsed multiple myeloma, myelodysplastic syndrome, and mantle cell lymphoma. Thalidomide, on the other hand, is only approved for newly diagnosed cases of multiple myeloma. Pomalidomide is also licenced for the treatment of relapsed multiple myeloma, and CC-122 is now being tested in Phase I clinical studies for the treatment of multiple myeloma, diffuse large B cell lymphoma, chronic lymphoblastic leukaemia, and a number of solid tumours (Zhao, 2015). It wasn't until recently that the mechanism of action of IMiD was deciphered. In 2016, cereblon was shown to be a primary target of the teratogenicity caused by thalidomide (Scott, 2016). The cytotoxic effect of IMiDs is caused by the reduction in the auto-ubiquitination of cereblon and the increase in the ubiquitination of the

transcription factors Ikaros and Aiolos. Lenalidomide was found to preferentially degrade a variety of proteins, including casein kinase 1 beta (CK1 beta), according to Miguel (2013).

Recent research has elucidated, from a biochemical point of view, how IMiDs recruit new substrates to cereblon, which is very helpful. The cereblon-IMiD complex and the ternary complex involving cereblon, lenalidomide, and CK1 have been crystallised, and these structures have revealed insights into the molecular interactions that underpin this mechanism (Miguel, 2013, Hagner, 2015).

According to Ito (2015), the glutarimide moiety of IMiD binds to a hydrophobic cavity in cereblon, while the phthalimide ring is free to create interactions with the substrate. Together with residues found locally in cereblon, the phthalimide ring helps to provide a surface that can form a binding interaction with a tiny beta hairpin loop found on CK1. This hairpin is homologous to Ikaros in its structure, but not in its sequence; this gives mechanistic data on the selectivity of various IMiD drugs for their particular targets (Shaffer, 2018).

These discoveries may have significant ramifications for the research and development of novel treatments based on IMiDs. Researchers are able to create more effective compounds that selectively target certain substrates and minimise off-target effects if they understand the molecular interactions involved in IMiD-mediated substrate recruitment (Yang, 2018). This allows them to build compounds that preferentially target specific substrates. In general, the findings of these research give a comprehensive knowledge of the molecular pathways behind the action of IMiD compounds, which will assist in the development of novel therapeutics for a wide variety of disorders (Scheider, 2014).

PROTACS

PREVIOUS GENERATIONS OF PROTACS

In order to permit efficient ubiquitination and degradation of the target protein, the linker needs to be carefully engineered to optimise the distance and orientation between the substrate-binding and E3 ligase-binding moieties (Zengerle, 2017). This will allow for the most effective ubiquitination and destruction of the target protein.

The promise of the PROTAC technology has encouraged the further research and optimisation of these compounds, despite the hurdles that have been presented. Recent developments have included the use of more powerful E3 ligases, such as CRBN and DCAF15, as well as an enhanced linker design to boost both the potency and selectivity of the reaction. In addition, new methods for delivering PROTACs to target cells are now being investigated (Schneekloth, 2018). These methods include encapsulating PROTACs in nanoparticles and using cell-penetrating peptides.

In general, PROTACs are a promising new strategy for targeting protein breakdown; yet, there are still considerable obstacles to be overcome in order to optimise their potency, selectivity, and delivery. However, continuous study in this field offers a great deal of promise for expanding our understanding of the function of proteins and for creating novel treatments for a broad variety of disorders (Hines, 2020).

NEXT-GENERATION PROTACS

It is necessary to have high-affinity small-molecule E3 ligase ligands in order to construct effective PROTACs. A small-molecule VHL ligand with a Kd of 180 nM was created using a mix of in silico and fragment-based screening for the purpose of this investigation (Galdeano, 2018). The target for this research was the E3 ubiquitin ligase CRL2VHL. Synthesis was performed on three distinct classes of VHL-targeting PROTACs, with the goals of inhibiting BRD4, RIPK2, and ERR. The attachment site of the linker was chosen based on the surfaces of the ligands that were exposed to the solvent, and the ideal linker length and composition changed depending on the protein that was being targeted. Additionally, in order to target BRD4 for ubiquitination by the E3 ligase CRL4aCRBN, two additional ligands, ARV-825 and dBet1, were produced based on the IMiD phthalimide and paired with BRD4-selective inhibitors OTX-15 and JQ1, respectively. These ligands were generated using the IMiD phthalimide. According to Zengerle (2017), the disparities in the intracellular potencies of these two compounds may be attributable to the substantial differences in the linker compositions of the compounds.

ON CHOOSING PROTAC WARHEADS AND LINKERS

The process of developing efficient PROTACs is a complicated one that requires optimising the protein-targeting ligand, E3 ligase, and linker in order to get optimal results. Alterations to the linker might have an effect on the efficiency with which the substrate is degraded (Xie, 2017). This is because the choice of targeted ligand can have a significant impact on the PROTAC selectivity and

degradation activity. It is also possible for the E3 ligase that is being recruited to have a major impact on the PROTAC's capacity to degrade various substrates. Further research is required to build a more in-depth knowledge of the PROTAC design principles and to completely comprehend the processes that lie behind these discoveries (Xie, 2017).

HYDROPHOBIC TAGGING

The strategy of functionalizing a ligand for a protein of interest (POI) into a hydrophobic tag to mimic a partially unfolded state, thereby facilitating recognition by the cellular quality control system, has shown promise in the process of degrading endogenous proteins without the requirement of genetic engineering of fusion proteins. This strategy was developed to facilitate the degradation of endogenous proteins. According to Zengerle (2017), this strategy has been used effectively to degrade the pseudokinase Her3 as well as the androgen receptor (AR). It has also been reported that selective degradation may be induced by utilising a different approach that employs a big Boc3Arg motif that is attached to a POI ligand. However, recent research has demonstrated that the Boc3Arg motif can limit global translation by inhibiting the mammalian target of rapamycin complex 1 pathway. The connection between these findings and the alleged degradation that the ligand causes is not entirely evident at this time (Schneekloth, 2018).

Her3 Degradation

In the realm of induced protein degradation, a notable breakthrough would be the successful discovery of a covalent ligand to Her3 and the subsequent synthesis of a Her3 degrader molecule. Both of these accomplishments have been accomplished. Researchers have opened up a new doorway for the development of therapies for illnesses in which Her3 plays a role, such as some forms of cancer, by targeting Her3, a pseudokinase that is difficult to pharmacologically target using typical small-molecule techniques. By targeting Her3, they were able to overcome one of the challenges associated with pharmacologically targeting this pseudokinase. (Scott, 2016. Miguel, 2013).

A recent strategy that has showed promise in degrading Her3 and the androgen receptor (AR), another tough target for small-molecule medicines, is the use of a hydrophobic tag in order to stimulate protein degradation. This method was developed in the United Kingdom. However, as was said in the previous paragraph, there are still some issues to be answered about the processes that lie behind this method, notably in the instance of the Boc3Arg motif. This is because the Boc3Arg motif has been shown to play an important role in the regulation of gene expression. In spite of this, there has been a huge leap forward in the field of drug discovery thanks to the discovery of small-molecule degraders that can target proteins that were once considered "undruggable" (Miguel, 2013).

Androgen Receptor Degradation

The AR is an essential component in the progression of many hormone-responsive tumours, including prostate cancer. This is especially true of prostate cancer. Resistance to existing treatments such as aromatase inhibitors and AR antagonists ultimately develops, similar to the resistance shown with ER-targeting selective oestrogen receptor modulators (Schneekloth, 2018). This is the case even if current medicines such as aromatase inhibitors and AR antagonists have been successful in treating early stages of prostate cancer.

Researchers found the first selective androgen receptor downregulator (SARD) chemical by attaching the alkylfluoryl chain of fulvestrant to the dihydrotestosterone molecule. There have been reports of other substances that impede the production of AR, which leads to a reduction in AR expression (Zengerle, 2017).

Researchers used a similar technique in which they attached the adamantyl moiety to the AR agonist RU59063. They discovered that this addition transformed the agonist into a pure antagonist that was capable of degrading AR protein (with half-maximum degradation occurring at 1 M and maximal degradation occurring at 95%). According to Zengerle (2017), this SARD was also able to decrease the growth of a model castration-resistant prostate cancer cell line that was resistant to enzalutamide.

FUSION-BASED DEGRON TECHNOLOGIES

The acronym "PROteolysisTArgeting Chimaera" (or simply "PROTAC") describes a small molecule degrader that is one method of attack. PROTACs are molecules with heterobifunctional functions that attract an E3 ubiquitin ligase to a particular target protein. This leads to the ubiquitination of the target protein, which in turn causes the proteasome to degrade the target protein. According to Zengerle

(2017), PROTACs may be employed in this fashion to degrade a wide variety of target proteins without the necessity for a unique ligand for the protein of interest.

One such method involves the use of tiny compounds that, within the cell, can regulate the operation of the machinery responsible for the breakdown of proteins. It has been demonstrated that certain chemical compounds, such as lenalidomide and thalidomide, which are collectively referred to as "IMiDs" (immunomodulatory imide drugs), can hasten the breakdown of certain proteins, such as the transcription factors Ikaros and Aiolos, by recruiting them to the CRL4CRBN E3 ubiquitin ligase complex (Zengerle, 2017). Among these proteins are Ikaros and Aiolos.

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Auxin-Inducible Degron

It has been demonstrated that the auxin hormone system in plants acts as a molecular glue between CRL1Tir1 and auxin transcription factors. This molecular glue function has been used in order to degrade external substrates utilising the plant's natural protein degradation mechanism. In this approach, the auxin-binding domain (AID) is fused to the protein of interest (POI), which allows for the protein to be quickly degraded by employing the Tir1 FBox protein in conjunction with the tiny chemical IAA. Although genetic engineering is necessary for this approach, the fusion proteins and tiny molecules that are utilised are bioorthogonal and interface well with the machinery that is already present in the cell (Zengerle, 2017).

The use of this system in the investigation of biological concerns has been established by a number of research. These studies include the investigation of the creation of centrosomes in human cells and the function of calcineurin in the malarial parasite Plasmodium berghei. Using CRISPR/Cas9, the AID system was surgically implanted into the endogenous genomic locus of the gene of interest in the Caenorhabditis elegans model organism, therefore making conditional protein depletion possible. This has shown to be particularly helpful in the germ-line, which is a region that is understudied due to a lack of instruments that can conditionally degrade proteins. According to Zengerle (2017), the AID system makes it possible to do protein knockdown in a quick and effective manner, which more closely matches knockout phenotypes than knockdown phenotypes.

PROTAC-Recruiting Degrons

The study of the unfolded protein response (UPR) of the endoplasmic reticulum has benefited greatly from the utilisation of the modified bacterial dehalogenase HaloTag as a model system for induced protein breakdown. In cell culture and in living organisms, the hydrophobic tagging strategy utilising HaloTag was able to successfully cause the degradation of both cytosolic and transmembrane HaloTag fusion proteins. This method proved helpful in inducing the UPR by unfolding an endoplasmic reticulum–localized HaloTag fusion protein following the addition of a hydrophobic tag, which constituted just a tiny part of total protein within the endoplasmic reticulum. This was accomplished by adding a hydrophobic tag. This made it possible to explore more precise transcriptional modifications utilising the destabilised HaloTag in comparison to other globally acting agents, which are frequently utilised in research on the UPR (Russ and Lampel, 2015).

Additionally, the research facility has produced powerful PROTACs based on the HaloTag system. These PROTACs are able to degrade the more stable HaloTag7. While this is happening, the chloroalkane is concurrently forming a covalent link with the HaloTag receptor protein. These heterobifunctional molecules attach to an E3 ligase called VHL. After testing a number of various chemicals, researchers determined that HaloPROTAC3 was the most effective of the bunch. In addition, GeneCopoeia has made accessible 20,000 open reading frames for human genomes and 15,000 open reading frames for mouse genomes that have been fused to the HaloTag7 coding sequence (Russ &Lampel, 2015).

OUTLOOK

Comparison of the Technologies: What Tool Should One Use?

When selecting a protein degradation system, it is critical to take into account both the biological issue at hand and the characteristics of the molecule that should be used as the protein degrader. PROTACs are a potent protein degradation system that need a known ligand for the POI, but they can

be designed and manufactured as a modular molecule. This allows PROTACs to be used in a variety of applications. When the protein of interest (POI) is already constructed as a fusion to the HaloTag protein, small molecule-based protein degradation systems that use protein fusions like HaloPROTACs can be an effective and powerful tool for targeted protein breakdown. It has been established that AID is effective in vivo, and it degrades the POI in a very short amount of time. This makes it possible to answer more detailed questions about the passage of time. In the event that there is no known ligand for the POI, new screening methods can assist in the development of a ligand with a high affinity for the POI. This ligand can then be utilised to design and create a PROTAC or another protein degradation system.

FUTURE PROSPECTS FOR TARGETED PROTEIN DEGRADATION?

It is abundantly obvious that the area of small-molecule modulation of intracellular protein levels is undergoing tremendous development and expansion at the present time. The potential for new discoveries is substantial, particularly in light of recent developments, such as the approval of FDA-accepted IMiDs and the development of PROTAC-based clinical candidates. PROTACs are an intriguing method for studying the undruggable proteome because of their modular and powerful character. It is expected that the discovery of additional ligands for E3 ligases will broaden the spectrum of proteins that may be targeted for destruction. In addition, the use of innovative screening methods allows for the discovery of new ligands for proteins that were not able to be drugged in the past, hence substantially broadening the potential for targeted protein breakdown. In general, targeted protein degradation presents fascinating opportunities for the advancement of biological research as well as the pharmaceutical industry.

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