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REVIEW ON TARGETED PROTEIN DEGRADATION

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ABSTRACT
Proteolysis targeting chimeras and related molecules that induce targeted protein degradation by the ubiquitin-proteasome system represents a new therapeutic modality and are the focus of great interest , owing to potential advantages over traditional occupancy based inhibitors with respect to dosing ,side effects , drug resistance and modality under undraggable charges. Protein degradation plays a central role in many cellular functions. Misfolded and damaged protein are removed from the cell to avoid toxicity. The concentration of regulatory proteins are adjusted by degradation at the appropriate time. Both foreign and native proteins are digested into small peptides as a part of the adaptive immune response. In eukaryotic cells, and ATP dependent protease called the proteasome is responsible for much of this proteolysis. Targeted protein degradation has emerged as a transformative the reputic strategy that allows selective removal of disease causing proteins rather than simply inhibiting their function. TPD represents a paradigm shift in drug discovery and expected to revolutionize treatment for cancer neurodegradation, infectious diseases and drug resistance conditions.
KEYWORDS:-*Tpd ,Protac, Molecular Glue*

INTRODUCTION

The development of targeted therapeutics has historically relied on small molecule inhibitors designed to block activity of disease related proteins however, nearly 80-90 % of human proteome is considered undruggable using conventional inhibition based strategy due to lack of ligandable pockets or intrinsic structural features. Targeted proteins degradation has emerged as a new drug modality to overcome this limitation by eliminating proteins directly from cells.

This strategy uses by functional molecules or molecular Clues to recruit an E3 ubiquitin lyses to targete protein , leading to ubiquitination and subsequent degradation via the proteasome or lysosome .Since the method induced elimination rather than inhibition. TPD can targete scaffolding , transcript on factors and muted proteins lacking enzymatic activity, thus greatly expanding druggable proteins.

MECHANISM OF TARGATED PROTEIN DEGRADATION-

1) **The Ubiquitin Proteasome System**
   Cells regulate protein level through ubiquitination by E1 E2 and E3 enzymes marking proteins for 26s proteasome degradation.
2) **Proteolysis Targeting Chimeras**
   PROTAC;S are heterobifunctional small molecules with
- A ligand for the protein of interest
- A ligand for ubiquitin ligase
- A linker connecting them

DESIGN PRINCIPLES AND PHARMACOLOGICAL CONSIDERATIONS

1) **Selection of E3 ligase**- More than 600E3 ligase exists, but only a handful are druggable. Common ones are,
   - CRBN
   - VHL
   - MDM2
   - CIAP1

Tissue distribution and of –target substrate effects guide selections.

2) Linker optimization- Linker leangth , rigidity band polarity determines ternary coplex formation between POI-PROTAC-E3 ligase. Poor linker can impairs degradation even if both ligands bind strongly.

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3) Rules for PROTAC ADME and drug likeness-
PROTAC offen violate Lipinski" rule of 5" due to large molecular weight(700-1200 daltons)
Design strategy includes macrocyclization reducing polarity and improving conformational rigidity

TYPES OF TARGETED PROTEIN DEGRATERS

1) PROTACS (proteolysis targeting chimeras)-
- These are bifunctional molecules with , --
- target binding ligands
- E3 ligase ligand
- Linker

2) Molecular glues- small molecules that induces neomorphic interaction between E3 ligase and target proteins. e.g thalidomide analogs cc-90009
3) LYTACS-
Target extracellular and membrane proteins. These expand degradation beyond cytosolic proteins.
4) AUTACs ATTECs
These exploit autophagy. These useful for large complexes.

APPLICATIONS OF TARGETED PROTEIN DEGRADATION-

1) **Oncology**

cancer features overexpressed or mutant proteins ideal for degradation. Examples of oncology targets are,
- BRD4(epigenetic regulatiuon)
- BCL-XL(Apoptosis)
- EGFR Mutants
- AR and ER in prostate and breast cancer

2) **Neurodegenerative Diseases**

TPD approaches are being applied to,
- Taupathies
- Alpha synuclein in parkinsons
- Huntingtin protein

TPD-43 in ALS

3) **Immunoligy and Autoimmune Disorders**

Degradating immune regulators such as IRAK4, JAK kinase and BTK offers potent immunomodulation with potentially fewer side effects compared to inhibitors.
4) **Infectious Diseases**- Bacteria and viruses depends on essential host or pathogen proteins.
5) **Viral infections**- targeting viral proteins such as HIV integrase or SARS-cov2components.
6) **Rare genetic diseases-** TPD is also used in the treatment of rare genetic diseases.

DISCUSSION

Targeted protein degradation represents a paradigm shift from inhibition to elimination of pathogenic proteins. compared to traditional small molecules , TPD offers distinct advantages such as catalytic mechanism ability to target non enzymatic proteins and tackling drug reststance

CURRENT CHALLENGES IN TARGETED PROTEIN DEGRADATION

- In targeted protein degradation large molecular weight of PROTACs leads to poor oral bioavability.
- Off- target effects due to widespread E3 ligase expression.
- Limited understanding of linker chemistry and ternary complex formation.
- Difficulty in targeting proteins localized in inaccessible compartments.

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CONCLUSION

Targeted protein degradation has revolutionized drug discovery by offering a modality capable of eliminating disease relevant proteins once considered undrugagble PROTACs , molecular glues, LYTACs and autophagy based degraders have shown remarkable potential in preclinical and clinical studies across oncology neurodegenration and immunology.

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