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Using human cathepsins as therapeutic degraders of pathological mucins

Stanford scientists have discovered that a subset of human cathepsins can degrade cancer-associated mucins. Targeted protein degradation of pathological mucins using these enzymes can be a platform technology for a new class of mucinopathy therapeutics for disorders such as cancer, infectious disease progression, autoimmune disease, and cystic fibrosis.

Mucins are densely glycosylated proteins that are known to be involved in tumor-progressive pathways. However, mucins are difficult to target using classical therapeutics (e.g. small molecules and antibodies) and remain canonically undruggable. Therapeutic interventions face the challenge that mucins contain no catalytic site to inhibit with a small molecular, nor a binding site that prevents function upon blockage with an antibody. Targeted protein degradation of pathological mucins has shown promise as a novel treatment for a variety of mucinopathies.

Here, a subset of human cathepsins has been demonstrated to degrade mucins within densely glycosylated mucin domains. Importantly, these cathepsins can degrade purified, recombinant, and cell-surface mucins. Consequently, directing the enzymatic activity of these cathepsins to pathological cells has the potential to degrade disease-relevant mucins and enhance the medical field by treating mucinopathies in patients.

Stage of Development:
Preclinical – in-vitro data
Continued research – engineer lead candidate to enhance mucin-selectivity, generate cell-type targeted cathepsin conjugate, demonstrate efficacy in reversing mucin-associated pathologies

Applications

- Development of therapeutics for mucin-associated cancers
- Other therapeutic applications such as treatment of gut dysbiosis, cystic fibrosis, and bacterial endocarditis

Advantages

- Bypass challenges associated with classical therapeutics by degrading undesirable mucins
- First-in-class approach of using human proteases to degrade disease relevant mucins
- Versatile platform that can be used with targeting molecules for the development of novel biologics to treat a myriad of diseases

Publications

- • Pedram, K., Laqtom, N. N., Shon, D. J., Di Spiezio, A., Riley, N. M., Saftig, P., ... & Bertozzi, C. R. (2022). Lysosomal cathepsin D mediates endogenous mucin glycodomain catabolism in mammals. Proceedings of the National Academy of Sciences, 19(39), e2117105119.

Innovators

- Carolyn Bertozzi
- Kayvon Pedram
- Gabrielle Tender
- Angel Kuo

Licensing Contact

Kimberly Griffin

Technology Licensing and Strategic Alliances Manager

Email