Targeting cooperative nutrient scavenging in cancer with pharmacological inhibition of CNPD2

An innovative strategy to prevent cancer growth in amino-acid deprived conditions by disrupting cooperative nutrient scavenging from extracellular peptides.

Technology

Researchers at NYU have uncovered a crucial mechanism that allows cancer cells to work cooperatively to support proliferation in nutrient-deprived environments, as described in a recent publication in Nature (*Guzelsoy et al. 2025*). Specifically, they discovered that tumor cells can collectively digest extracellular oligopeptides to obtain essential amino acids. By screening inhibitors against major peptide protease families, the researchers identified bestatin (ubenimex) as an effective inhibitor of extracellular oligopeptide hydrolysis and resulting amino acid scavenging. Through subsequent CRISPR screening, CNDP2 (Carnosine Dipeptidase 2) enzyme was identified as the key mediator of extracellular oligopeptide hydrolysis. Loss of CNDP2 function was shown to inhibit tumor growth both *in vitro* and *in vivo*, establishing CNDP2 as a critical player in this nutrient-scavenging mechanism. They also showed that bestatin treatment significantly reduced tumor burden in orthotopic models of KEAP1-mutant lung cancer, demonstrating CNDP2 as a novel therapeutic target for cancer treatment. To improve the selectivity and efficacy of bestatin and other CNDP2 inhibitors while leaving intracellular processes unperturbed, the researchers modified its chemical structure. This modified version of bestatin demonstrated similar anti-CNDP2 effects but with additional desirable properties. Currently, the Carmona-Fontaine lab is working on improved iterations of this drug to further increase selectivity for CNDP2. The discovery that cancer cells cooperate to scavenge amino acids in nutrient-scarce environments opens an exciting new avenue for precision cancer therapy, as both cooperative nutrient scavenging and CNDP2 activity are dispensable in healthy cells. Thus, targeting CNDP2 offers a promising strategy to inhibit tumor growth and improve cancer treatment outcomes.

Background

The tumor microenvironment (TME) is characterized by nutrient scarcity, forcing cancer cells to compete for essential resources to survive. This competition drives cancer evolution and progression, making the TME a promising target for cancer treatment strategies. Conversely, cooperation amongst tumor cells has also been recognized as a factor in tumor evolution and growth, though it has been poorly understood and characterized until recently. Researchers from NYU have now successfully characterized a novel mechanism of cancer-cell cooperation in nutrient scavenging, paving the way for a promising new therapeutic intervention that targets the TME to disrupt tumor-cell populations.

Applications

Technology ID

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Category

Life Sciences/Research tools/Oncology

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- Potential for use as a front-line anti-cancer therapy or in combination with existing treatments.
- Development of alternative drugs or biologics targeting CNPD2 for cancer treatment.

Advantages

- **CNPD2 is a novel target for cancer therapy:** Opportunities for drug and biologic development.
- **Broadly applicable treatment strategy:** Cooperative nutrient-scavenging is not cell-type specific so treatment strategies should be applicable to many cancers
- **Novel modifications on a well-characterized inhibitor:** Bestatin is well-characterized and is already approved as a cancer adjuvant in Japan. It was also previously granted Orphan Designation in the U.S. for pulmonary arterial hypertension.
- **Potential for chemical modifications:** Specific modifications of bestatin demonstrated similar anti-tumor effects as unmodified, indicating that related structural modifications may also be well-tolerated.

Development Stage

The modifications to bestatin were a successful proof-of-principle that indicated key sites can be modified to improve this drug's selectivity and properties without reducing its inhibitory function. NYU is now seeking a commercial partner interested in further developing CNPD2 inhibitors to increase the specificity and pharmacokinetics of bestatin and related drugs.

Intellectual Property

NYU has filed a pending provisional patent application covering composition of matter and methods of treatment.

References

1. Guzelsoy et al. , https://pubmed.ncbi.nlm.nih.gov/39972131/