Docket #: S22-345

Composition and Methods for Transglutaminase-2 Mediated Endocytosis

Stanford researchers in the Khosla lab have invented a new class of "molecular glues" that couple the enzymatic activity of a cell-surface enzyme, transglutaminase 2 (TG2), with the ability of the LDL receptor-related protein 1 (LRP-1) to promote receptor-mediated endocytosis and lysosomal transport of extracellular cargo. The novel TG2/LRP-1 pathway can be hijacked to deliver antigens, pharmacologic agents, or imaging tools into macrophages and dendritic cells or to promote lysosomal degradation of pathologically important extracellular or cell-surface proteins in a targeted manner.

A prototypical class of molecular glues are mimics of gluten peptides designed to selectively inactivate and degrade extracellular TG2 in the small intestine of celiac disease patients. TG2 is not only pathogenically important in celiac disease, but it also elicits auto-antibodies in patients with this autoimmune disorder. By inactivating catalytically active TG2 in the patient's small intestinal mucosa and also eliminating the protein from this environment, it is expected that both the T cell and B cell responses to dietary gluten will be controllable by this new generation of oral TG2 inhibitors. Some members of this class of molecular glues also have optically active probes attached to them and are therefore expected to have theranostic utility.

Stage of Development

in vitro and *in vivo*

Figure:

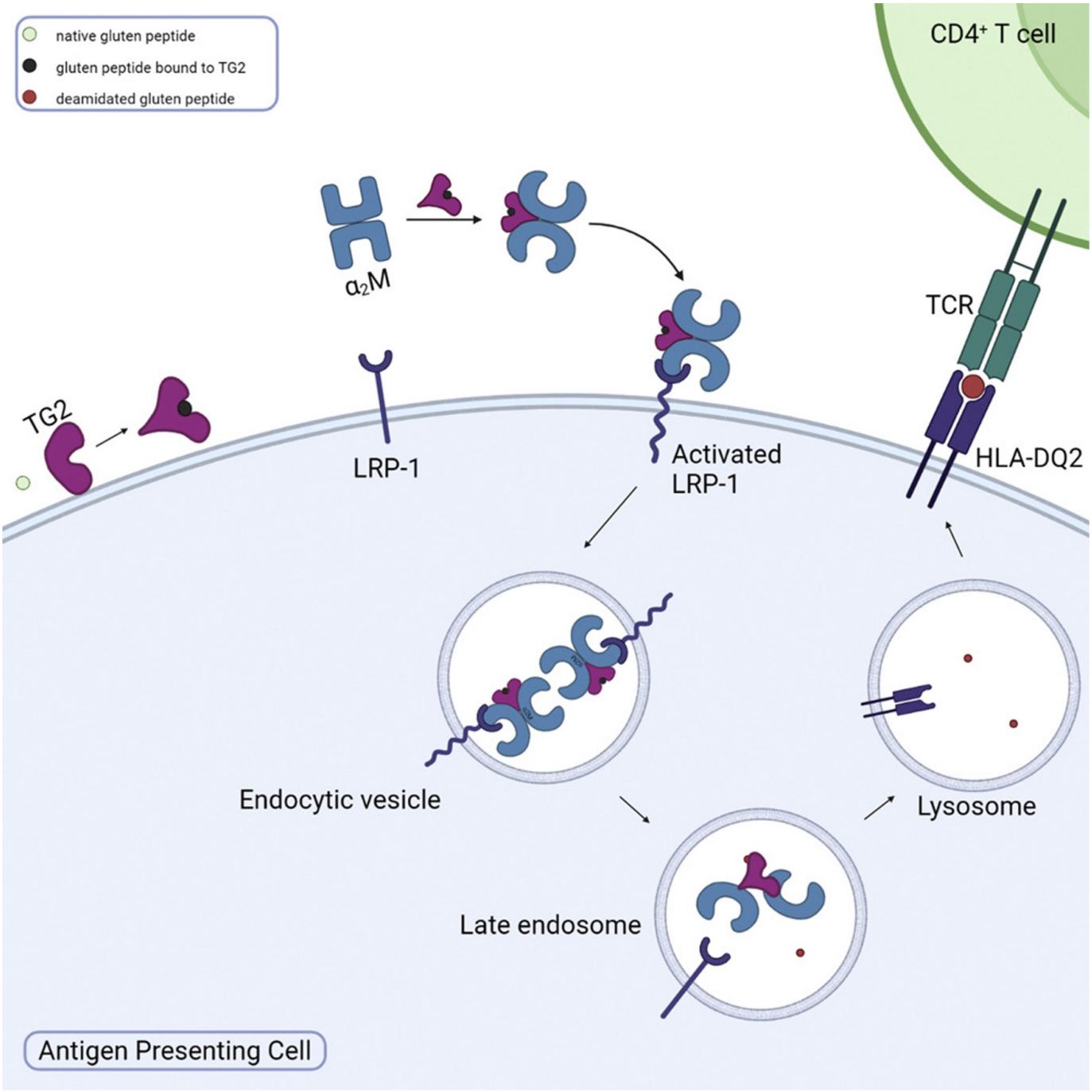

Figure description: Graphical Abstract (Figure Image Credit)

Applications

- TG2 inhibitors and degraders for celiac disease therapy
- Imaging probes for subclinical disease activity in celiac disease patients
- Antigen delivery into macrophages and dendritic cells

- Lysosome-targeting chimeras (LYTACs) for inactivating extracellular proteins and cell surface receptors

Advantages

- New class of TG2 inhibitors
- Bifunctional molecules capable of intracellular delivery of any agent that can be linked to a peptide

Publications

- Elise Loppinet, et. al. "LRP-1 links post-translational modifications to efficient presentation of celiac disease-specific T cell antigens." Cell Chemical Biology, 30(1), P55-68.E10 (2023).
- Elise Loppinet, et. al. "Targeted Lysosomal Degradation of Secreted and Cell Surface Proteins through the LRP-1 Pathway." J. Am. Chem. Soc. 145(34):18705-18710. (2023).

Patents

- Published Application: WO2024049543

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