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Protease-Controlled Secretion and Display of Intercellular Signals

Researchers at Stanford have developed a generalized protease-responsive platform, called RELEASE, to control the secretion and display of proteins. RELEASE (Retained Endoplasmic Cleavable Secretion) is poised to enable local, programmable delivery of intercellular cues for a broad variety of fields such as neurobiology, cancer immunotherapy and cell transplantation. Across biomedicine, regulating the secretion and surface display of signaling proteins is crucial to program intercellular communication. Protein-based 'circuits' have advantages such as fast operation, compact delivery and robust performance compared to traditional synthetic circuits. However, these protein circuits have operated only inside the cell, and there remains an urgent need for a design that enables protein-level control of intercellular communication. To this end, the Stanford team created RELEASE, a modular design with engineered proteins retained in the endoplasmic reticulum and displayed/secreted in response to specific proteases. Their design allows functional regulation of multiple synthetic and natural proteins by synthetic protease circuits to realize diverse signal processing capabilities, including logic operation and threshold tuning. Linking RELEASE to additional sensing and processing circuits can achieve elevated protein secretion in response to "undruggable" oncogene KRAS mutants.

Stage of Development
As reported in *Nature Communications*, the researchers have shown that RELEASE is compatible with circuit-level functions, controls biologically relevant proteins, responds to oncogenic inputs, and supports plug-and-play capabilities.

Applications

- Improving cell therapies
- Cancer immunotherapy
- Neurobiology research

Advantages

- RELEASE enables novel therapeutic modalities in cancer immunotherapy.
- Protease circuit components can be encoded within single mRNA transcripts that do not pose the risk of insertional mutagenesis.
- RELEASE is compatible with pre-existing protein-based synthetic circuits that directly integrate with the signal transduction pathways of the host.

Publications

- Vlahos, Alexander E., et al. "Protease-controlled secretion and display of intercellular signals." *Nature communications* 13.1 (2022): 1-12.

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