Artificial receptors and signaling cascades in synthetic cells

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Artificial, synthetic cells are a fascinating research discipline. Cellularity is the foundation of life, and mimicking the design and the functions of cells is an intriguing possibility. It is fundamentally important and also has prospects for applications in e.g. biosensing, bioproduction, and biomedicine.

One of the most characteristics of cells in nature is their responsive behaviour. It is this attribute of life that makes cells interact, allows individual cells to assemble into multicellular organisms, and enables the cells to fight for habitat. Engineering responsive behaviour into synthetic cells is a grand challenge. This is because the molecular mechanisms of responsive behaviour in nature include transmembrane proteins for signalling, and intracellular signalling cascade to propagate the signal. These proteins are embedded into the homeostasis, which makes the prospect of reconstitution of receptors and cascades into synthetic cells receptors futile.

In our work, we approach the design of responsive synthetic cells through the engineering of artificial receptors and the design of artificial signalling cascades.

For transmembrane signalling, we design artificial receptors. These are small organic molecules, not proteins. Receptor molecule features an membrane anchor and an exofacial ligand for receptor activation. The mechanism of signal transduction is based on the chemistry of self-immolative linkers. Upon receptor activation, the decomposition of the self-immolative linker leads to the release of a secondary messenger molecule. The latter is released from the lipid bilayer, moves to the interior of the synthetic cell, and therein activates the proteins that comprise the downstream signalling cascade.

The design of signalling cascades requires that we engineer the tools to activate enzymatic activity on demand. We did so using the chemistry of thiols. “Thiol switching” is a nature-inspired approach to control enzymatic activity and reversible switch it, on demand. We applied this to proteases, kinases, and polymerases, thus building up a versatile toolbox to engineer responses in synthetic cells.

Most importantly, transmembrane signalling and enzyme activation could be coupled into signalling cascades that connect extracellular receptor activation and intracellular enzymatic responses. In so doing, we engineer synthetic cells with responsive behaviour. Responses of synthetic cells can be triggered by biochemical cues, mammalian cells, pathogens, and even inorganic surfaces.

Key references

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