SYNTHETIC BIOLOGY

When pathogens come in handy

Bacterial proteins are used to rewire signaling pathways in yeast and mammalian cells.

Bacterial pathogens have evolved smart tricks to thrive in the cells they invade. For example, to dampen the immune response that a cell normally triggers upon bacterial infection, bugs have a collection of effector proteins that can directly act on the cell's signaling networks at different levels.

Although much research on bacterial pathogens is aimed at neutralizing the pathogens' infectious capabilities, other projects, such as those of Wendell Lim and his colleagues at the University of California, San Francisco, are focused on exploiting the proteins produced by these creatures in new and imaginative ways. In recent work, the group showed how certain bacterial proteins can be 'reinvented' as tools to engineer cells for therapeutic and biotechnological purposes.

Lim and his colleagues took two bug proteins, OspF and YopH, that are known to inhibit mitogen-activated protein kinases (MAPKs) in the cells that the bugs invade (as a way to dampen the cell's immune response) and used them to target the MAPK pathway in yeast and human primary T cells.

T cells can be readily isolated from patients' blood, genetically engineered *ex vivo* and then transferred back into the individual to treat cancer or chronic infection. However, the immune response mounted by T cells must be tightly controlled because too much activation could lead to undesired side effects.

Lim and colleagues decided to test whether their engineered bacterial pathogen effectors could be used to externally control the timing and level of T-cell activation. First, they built synthetic feedback loops to limit the amplitude of the T-cell

receptor response by making the expression of the effector proteins dependent on the activation of the targeted MAPK pathway. Second, they placed the effectors under doxycycline regulation, creating a mechanism to control when the effectors are turned on or off in time and allowing the T-cell response to be disabled at controlled intervals.

In the long run, the investigators hope that engineered mechanisms such as the ones they developed could be used to build 'safety switches' in T-cell adoptive immunotherapy trials. But the research also serves to show how old enemies can be turned into allies.

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RESEARCH PAPERS

Wei, P. *et al.* Bacterial virulence proteins as tools to rewire kinase pathways in yeast and immune cells. *Nature* **488**, 384–388 (2012).