MOLECULAR ENGINEERING

Designing protein logic gates

De novo–designed protein logic gates allow post-translational regulation of protein function.

Cellular function can be controlled by regulating protein–protein association; however, naturally occurring proteins offer limited flexibility for incorporating desired function. Researchers from the group of David Baker at the University of Washington and their collaborators have designed proteins that can function as logic gates (AND, OR, NAND, NOR, XNOR and NOT) for programmable control of cellular function. The modular design is based on a set of de novo–designed heterodimers that differ in the buried hydrogen bond networks across the dimer interface. This detail in the design allows precise control of binding specificity and the free energy required to alter the ground state. The researchers constructed two-input or three-input gates controlled through competitive binding.

"Synthetic biology has traditionally been dominated by circuits built from nucleic acids; they offer great programmability but do not speak the same language as cellular pathways, which are predominantly protein-based. Our technology should now enable one to directly talk to cellular pathways, or construct new ones that are orthogonal to cell signaling pathways," says Zibo Chen, the primary author.

To demonstrate the practical utility of the designed logic gates, the researchers regulated a variety of protein units, such as split enzymes and transcriptional machinery in vitro, in yeast and in primary human T cells. Just as with logic gates, each setup requires the right combination of proteins to activate the downstream process: for example, in the case of an AND gate, both input proteins must be present, and for an OR gate either of the two can be present. Chen hopes to use these protein-based logic gates to perform more complex computation and develop them beyond simple logic operations in the future.

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