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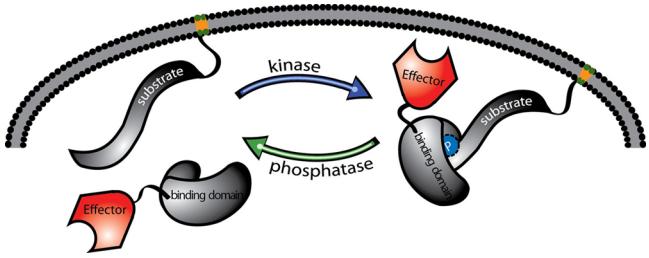
DESIGNER MOLECULAR SWITCHES

Molecular switches are systems that convert incoming signals, such as small molecule binding events, to output responses, such as modulation of enzymatic activity. Delineation of naturally occurring molecular switches has paved the way for engineering switches to purposefully manipulate specific cellular events. In this vein, Sample *et al.* (DOI: 10.1021/cb300393w) now describe the design and activity of an engineered kinase-inducible switch that enables control over the levels of a phospholipid in live cells.

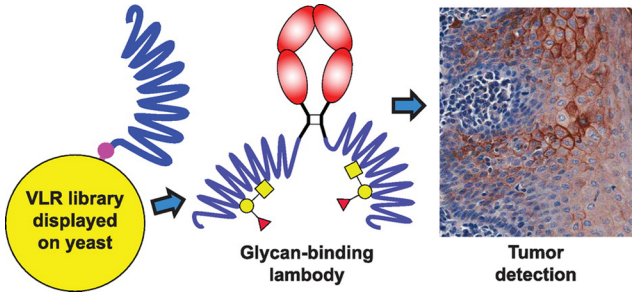


The switch consists of a protein construct comprising a phosphoamino acid binding domain coupled to a lipid phosphatase, as well as a peptide substrate for protein kinase A that is tethered to the cell membrane. Activation of protein kinase A leads to phosphorylation of its membrane-associated substrate, which then lures the phosphoamino acid binding domain to the cell membrane, dragging the phosphatase along with it. There, the phosphatase can act on its substrate, the membrane associated phospholipid phosphatidylinositol 4,5-bisphosphate, depleting its levels. Conversely, inhibition of PKA leads to replenishment of the phospholipid. Notably, this clever strategy can be expanded to enable perturbation of other cellular activities as well.

A SWEET SPOT FOR "LAMBODIES"

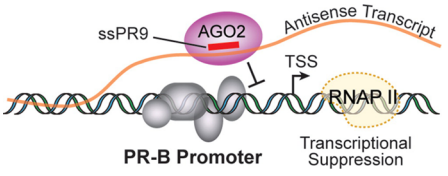
Glycans, oligomeric carbohydrate structures that decorate the surface of many proteins and lipids, modulate myriad biological events and contribute to various pathological processes. Agents that bind glycans have a variety of clinical applications, but most are either not very specific for their target carbohydrates or do not bind them very tightly. Despite substantial efforts, no general methods for generating effective carbohydrate binding proteins exist, which has limited their development both as exploratory tools and as prognostic, diagnostic, or therapeutic agents. Now, Hong *et al.* (DOI: 10.1021/cb300399s) report a strategy for the creation of "lambodies", monoclonal antibodies that bind glycans with high specificity and affinity, derived from the lamprey, the jawless fish-like vertebrate.

The authors identified the lambodies by screening a library of lamprey variable lymphocyte receptors displayed on the surface of yeast for their ability to bind various glycans. They discovered lambodies to numerous therapeutically relevant antigens, including some implicated in cancer, AIDS, and inflammation. The lambodies bound the glycans with remarkable affinity and selectivity, demonstrating the utility of this approach for generating novel glycan binding agents.



SINGLE-HANDEDLY SILENCING TRANSCRIPTION

RNA interference (RNAi), a process in which RNA molecules inhibit gene expression, has emerged as an enormously powerful tool to study biological processes and also has promising therapeutic applications. RNAi agents are commonly double-stranded RNA molecules that prevent translation of mRNA, but they can also inhibit gene expression at the transcriptional level. Notably, however, the use of single-stranded silencing RNA (ss-siRNA) can be technically simpler, more economical, and side-steps some obstacles faced by double-stranded RNAs during therapeutic development. Toward the continued advancement of ss-siRNA as gene silencing agents, Matsui *et al.* (DOI: 10.1021/cb300490j) now report the creation of a ss-siRNA that targets transcription of the progesterone receptor.



The authors designed a chemically modified ss-siRNA targeting a long noncoding RNA in the promoter region of the progesterone receptor. They determined that the ss-siRNA functioned through the normal RNAi pathway and effectively inhibited gene transcription. This demonstration that ss-siRNAs can be used as transcriptional regulators greatly expands their potential applications.

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