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Commentary
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A Nano-robotic Device That Lands on Cell Membranes, Binds Targeted Mechanosensors, and Exerts Precise Piconewton-Scale Forces to Elicit Biochemical Responses

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Cells have a suite of mechanisms to detect their surroundings, including detection of mechanical forces exerted on the cell by the environment. Studying these mechanical detection mechanisms has been facilitated by techniques such as atomic force microscopy and optical tweezers. These methods have been tremendously successful but have a number of drawbacks including low throughput from serial operation, bulky and expensive instrumentation, and specialist personnel with extensive expertise.

We have produced a nano-robotic device termed the Nano-winch that is able to exert piconewton scale forces on cellular mechanoreceptors to elicit biological responses. The Nano-winch consists of a central piston connected by single-stranded DNA tethers to the top and bottom of an encircling sleeve, which itself is connected to two landing legs that allow the device to land on a cell membrane surface. The tip of the piston can be decorated with chemical moieties to attach it to targeted mechanosensors, then the piston slides freely through the sleeve to pull on the bound mechanosensor while simultaneously pushing on the cell membrane through the landing legs.

The Nano-winch was demonstrated in two applications. The first was the activation of integrins, highly mechanosensitive sensors that link cells to the extracellular matrix. Force exerted on integrins can mediate phosphorylation of the enzyme focal adhesion kinase. This phosphorylation event was monitored using a luminescence assay on MCF-7 cancer cells and only those exposed to Nano-winches decorated with the integrin ligand cyclic arginine-glycine-aspartic acid tripeptide on the tip of the piston elicited kinase phosphorylation.

The second demonstration was on the force-gated transport protein BtuB, a β-barrel channel occluded by a globular plug. Transport through BtuB across the outer membrane of *Escherichia coli* occurs in concert with inner membrane proteins that dislodge the plug domain sufficiently to open a channel. Purified BtuB was reconstituted into planar lipid bilayers and chemically attached to the tip of the Nano-winch. A force in the tens of piconewtons was exerted by addition of oligonucleotides complementary to the tethers at the top of the device forcing the piston upwards and creating detectable channel opening in the protein.

We hope that the Nano-winch and devices like it will open new investigatory approaches in mechanotransduction and mechanobiology more broadly. Such devices will serve as autonomous force generating nanorobots to greatly simplify higher-throughput investigations and answer problems that have been intractable thus far in cellular mechanosensors. Some limitations of the current Nano-winch design that need to be overcome include irreversibility of piston extension after addition of extension oligonucleotides and stabilization of the device against nucleases in culture media. Redesigns of future devices should include toehold-mediated displacement of extension tethers and chemical modification of the nanostructure to prevent nuclease driven degradation in cell media.

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