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Sonogenetic Modulation of Cellular Activities Using an Engineered Auditory-Sensing Protein

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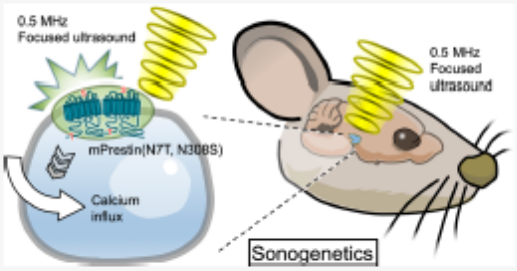
Supporting Information

ABSTRACT: Biomolecules that respond to different external stimuli enable the remote control of genetically modified cells. We report herein a sonogenetic approach that can manipulate target cell activities by focused ultrasound stimulation. This system requires an ultrasound-responsive protein derived from an engineered auditory-sensing protein prestin. Heterologous expression of mouse prestin containing two parallel amino acid substitutions, N7T and N308S, that frequently exist in prestins from echolocating species endowed transfected mammalian cells with the ability to sense ultrasound. An ultrasound pulse of low frequency and low pressure efficiently evoked cellular calcium responses after transfecting with prestin(N7T, N308S). Moreover, pulsed ultrasound can also noninvasively stimulate target neurons expressing prestin(N7T, N308S) in deep regions of mouse brains. Our study delineates how an engineered auditory-sensing protein can cause mammalian cells to sense ultrasound stimulation. Moreover, our sonogenetic tools will serve as new strategies for noninvasive therapy in deep tissues.



KEYWORDS: *Sonogenetics, focused ultrasound, mammalian cells, neuromodulation*

Approaches that can noninvasively stimulate target cells buried in the deep tissues are highly desirable for basic research and clinical therapy. Currently, different external stimuli including photons, chemicals, radio waves, and magnetic fields have been used to stimulate target cells implanted with stimulus-responsive proteins or nanoparticles.[1−4] However, these strategies suffer from several drawbacks including invasiveness, poor spatiotemporal precision, or low penetration depth, which greatly hinder their potential use in clinical therapy. To overcome these long-standing problems, we aim to use focused ultrasound (FUS) as a stimulus to remotely control cellular activities because it can noninvasively deliver acoustic energy to deep tissues while retaining spatiotemporal coherence.[5]

Ultrasound waves have frequencies greater than those of sound waves that can be heard by humans (>20 kHz). Low-frequency ultrasound waves (<3.5 MHz) are easily transmitted through tissues, including those of bones and brains.[6] Owing to its deep penetrability and spatiotemporal resolution (a few cubic millimeters), ultrasound-based neuromodulation has been tested on cultured neuronal cells and in brains of various model organisms.[6−11] As continuous ultrasound waves or pulsed ultrasound waves of high acoustic pressure are typically needed to activate neurons, neuronal cells are likely to be weakly sensitive to ultrasound stimulus.[8,12,13] To overcome this, gas-filled microbubbles (MBs) that vibrate upon ultrasound excitation have been used as ultrasound amplifiers to

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