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Texturing Silicon Nanowires for Highly Localized Optical Modulation of Cellular Dynamics

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Abstract

Engineered silicon-based materials can display photoelectric and photo-thermal responses under light illumination, which may lead to further innovations at the silicon–biology interfaces. Silicon nanowires have small radial dimensions, promising as highly localized cellular modulators, however the single crystalline form typically has limited photothermal efficacy due to the poor light absorption and fast heat dissipation. In this work, we report strategies to improve the photothermal response from silicon nanowires by introducing nanoscale textures on the surface and in the bulk. We next demonstrate high-resolution extracellular modulation of calcium dynamics in a number of mammalian cells including glial cells, neurons, and cancer cells. The new materials may be broadly used in probing and modulating electrical and chemical signals at the subcellular length scale, which is currently a challenge in the field of electrophysiology or cellular engineering.

Graphical Abstract

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Author Contributions

Y.F., Y.J. and B.T. designed the experiments. Y.F. and Y.J. performed all the experiments. H.A.L., J.Y., X.G. and F.S. help performing the characterizations. Y.F., Y.J., H.A.L., D.W., and B.T. prepared the manuscript and received comments and edits from all authors.

ASSOCIATED CONTENT

Supporting Information

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Additional experimental details and TEM images of silicon nanowires, SEM images and confocal images for additional cells (PDF) Intracellular calcium wave propagation (green, calcium; blue, Si nanowire) within a glial cell following a photostimulation at a Si nanowire/cell interface (AVI)

The authors declare no competing financial interest.

Keywords

Silicon nanowire; vapor–liquid–solid growth; metal-assisted chemical etching; porous materials; biointerface; photothermal; membrane depolarization; calcium imaging; wireless cellular modulation

Modulating cellular dynamics can yield either direct or indirect outcome. For example, recent studies suggest the opportunity of using the control of nervous system as a way to enhance the body's natural defenses against infection and disease.¹ In the past, researchers have interrogated the CNS using bulky electrodes,^{2,3} which have low spatial resolution and are not suitable for long-term probing due to their large-scale dimensions and mechanical mismatches with the targeted tissues.⁴ More recently, genetically encoded molecular actuators, such as channelrhodopsin⁵ and halorhodopsin,⁶ have been used for light-gated modulation of neural activity; but their use *in vivo* is limited because genetic manipulation is required to express these opsins. On the other hand, silicon nanomaterials have emerged as promising materials for the development of next generation biomedical devices because of their unique mechanical⁷ and electronic⁸ properties and are biocompatible.⁹ In particular, silicon nanowires (SiNWs) and silicon nanomembranes have been designed as field-effect transistors^{10,11} and photoelectrochemical¹² devices for the monitoring and modulation of neural activities and they can be configured into high density arrays^{13,14} or function as free-standing devices.^{12,15}

The composition^{16,17} and morphology^{10,15,18} of SiNWs synthesized through gold (Au) nanocluster-catalyzed vapor-liquid-solid (VLS) growth can be precisely controlled through doping⁸ and modulation of other synthesis conditions, such as temperature¹⁹ and pressure.²⁰ Given the important role that surface topography plays in dictating the biointerfaces, rational design of new meso- and nanoscale features over SiNWs could significantly expand the current toolbox of Si-based bio-materials.²¹

Here, we explore textured porous SiNWs for highly localized photothermal modulation of cellular activities. SiNWs have small radial dimensions, which is promising for highly localized cellular control. However, the single crystalline form typically has limited photothermal efficacy due to the poor light absorption and fast heat dissipation. Recently, through spontaneous instability at the Au–Si interface²² and pressure-dependent Au deposition and diffusion²⁰ on the Si surface, SiNWs with defined sidewall patterns have been prepared. Although SiNWs with increased surface area and roughness may experience enhanced interactions with cellular components,^{15,23,24} these structural features alone cannot modulate cell activities on demand. One potential strategy to achieve optical control of cellular dynamics with SiNWs is to further enhance the porosity or roughness throughout SiNW structures (i.e., not just at the sidewalls). Indeed, recent studies showed that mesoporous silicon particles (lateral dimension $\sim 2\text{--}5\ \mu\text{m}$) exhibit a strong photothermal property, which can be leveraged to elicit action potentials and other emergent output patterns in neurons.²⁴ In this current work, we present a new strategy to improve the photothermal effect in SiNWs by texturing them with inclined channels from periodic Au deposits and demonstrate that this new material is effective in remotely modulating calcium dynamics in a number of mammalian cells (Figure 1a).

To synthesize the textured SiNWs, we first used periodic pressure perturbations during the Au-catalyzed intrinsic SiNW (i-SiNW) growth to induce the Au deposition and diffusion at defined locations,²⁰ followed by the metal-assisted chemical etching (MACE).^{20,22,25–27} In a typical synthesis, i-SiNWs were first grown at 470 °C under a constant pressure of 40 Torr for 1 min by setting the flow rates of SiH₄ and H₂ as 2 and 60 standard cubic centimeters per minute (sccm), respectively. After forming the base segment, periodic switches between 5 s of evacuation and 25 s of pressure ramping were performed to modulate the growth chamber pressure during the subsequent nanowire growth. Upon chamber evacuation (Methods in Supporting Information), isolated Au nano-particles are precipitated from the alloy droplet²⁰ and get deposited on the Si surfaces. Later on, Au species can diffuse on Si sidewalls to form patchy domains on the i-SiNW sidewalls²⁰ (Figure 1b). Once the pressure ramps up, the Au diffusion ceases and the SiNW resumes its elongation. The pressure switching cycles were iterated for 10 min after the base segment growth to yield the pressure modulated i-SiNWs with periodical Au bands on the surfaces. In the subsequent MACE experiment, the as-grown i-SiNWs on the growth substrates were dipped into a hydrogen peroxide (H₂O₂) and hydrofluoric acid (HF) aqueous mixture solution to etch Si.

After MACE, inclined open porous channels were formed that extended from the original surface locations of Au nanoparticles, yielding SiNWs with three-dimensional porous interior (Figure 1c, etched for 30 s). Despite the Si removal, TEM images and selected area electron diffraction (SAED) patterns show that the nanowires are still highly crystalline with

the majority of SiNWs' growth direction following the (112) orientation (Figure S1). The depth of the textures and the corresponding SiNW porosity can be controlled by adjusting the etching duration (Figure S2). One unique aspect of this synthetic approach is that the locations of Au particles along SiNWs for MACE can be precisely programmed by the pressure modulation protocol.

To confirm the potential use of textured i-SiNWs for freestanding cellular modulation, we first assessed the physicochemical responses of these SiNWs to laser illumination in saline. We relieved SiNWs from the growth substrate through gentle sonication and drop-cast them in a phosphate buffered saline (PBS) solution. Using the patch-clamp system, we then positioned a micropipette electrode ($\sim 1 \text{ M}\Omega$) within a $\sim 2 \text{ }\mu\text{m}$ proximity of a single SiNW. While in the voltage-clamp mode, we monitored the current flowing through the pipet tip before, during, and after delivering short pulses (1 ms duration) of a 532 nm focused laser ($\sim 47.1 \text{ mW}$) (Figure 2a). On one hand, SiNWs could display photoelectric effect upon light illumination, where light-generated carriers accumulate at the Si interface and attract counterions in the solution to compensate the charge imbalance at the interface. The photoelectrically induced current is only a function of carrier dynamics at the Si surface so the amplitude of the current is independent of the pipet holding level. On the other hand, SiNWs could yield photothermal effect which elevates the local temperature of the electrolyte and increases the ion mobilities, yielding a reduced pipet resistance. In this photothermal scenario, even under the same holding potential, the amplitude of ionic current through the pipet tip will increase during the light illumination period, as governed by Ohm's law. Given the different dependence on the holding level of photoelectrically and photothermally induced currents, multiple recordings performed at different pipet holding levels can be used to decouple the light-induced thermal and electrical effects of SiNWs. At a given time point t during the light illumination period, the recorded current, $I_0 + I_{\text{light}}(t)$, excluding the photoelectrically induced current part $I_{\text{electric}}(t)$, and the pipet tip resistance $R(t)$ should follow the Ohm's law as long as the holding potential V_p is fixed, $V_p = I_0 \times R_0 = (I_0 + I_{\text{light}}(t) - I_{\text{electric}}(t)) \times R(t)$, where I_0 and R_0 are the holding current and pipet resistance in dark, respectively. Rearranging the equation gives the relationship between the light-induced current $I_{\text{light}}(t)$ and the holding current I_0 that

$$\Delta I_{\text{light}}(t) = \left(\frac{R_0}{R(t)} - 1 \right) \times I_0 + \Delta I_{\text{electric}}(t). \text{ From this equation, the photoelectric effect is}$$

explicitly manifested as the intercept of the $I_{\text{light}}(t) - I_0$ curve while the photothermal effect is implicitly embedded in the fitted slope as the pipet resistance is a function of temperature.²⁸ Individual photoresponses can then be extrapolated from all the measurements and compared between textured and smooth nanowires; the smooth SiNWs were synthesized under a similar condition as that of the textured ones except that neither pressure modulation nor etching were used (Figure 2b,c).

From the recorded ionic current dynamics from both textured and smooth SiNWs, the fitted intercept values of the $I_{\text{light}}(t) - I_0$ curves stay nearly zero throughout the entire illumination period, indicating minimal contributions from the photoelectric effect of i-SiNWs (Figure 2c, orange traces). Nevertheless, both SiNWs induce local temperature elevations upon laser illumination as derived from the fitted slope values of the $I_{\text{light}}(t) - I_0$

curves in conjunction with the temperature-resistance calibration (Figure 2c, black traces). On average, the textured i-SiNWs demonstrate larger photo-thermal responses ($\sim 2^\circ\text{C}$) than the smooth i-SiNWs ($\sim 0.2^\circ\text{C}$) over the 1 ms illumination (Figure 2b). Consistent with the prior work of mesoporous Si particles, the porosity in the textured SiNWs likely contributes to the enhanced thermal output due to reduced thermal conductivity, heat capacity, and enhanced light absorption.²⁴ Nevertheless, it should be noted that the laser power density used in the present study is still ~ 1 order of magnitude higher than that applied for the mesoporous Si particles in order to yield similar thermal response, because the size of a single textured SiNW (one-dimensional wire with ~ 200 nm in diameter) is significantly smaller than that of a mesoporous Si particle (three-dimensional quasi-spherical object with $\sim 2\text{--}5\ \mu\text{m}$ in diameter).

One important feature offered by SiNWs is that they can be readily dispersible in aqueous solution and can be administered to biological systems in a drug-like fashion. Additionally, the rough surfaces of the textured i-SiNWs may promote robust biointerfaces versus the smooth counterparts.^{20,24} Indeed, high-yield extracellular junctions can be observed between textured i-SiNWs and the filamentous membrane protrusions of satellite glia from a rat dorsal root ganglia (DRG) culture after a short coculture (Figures 2d and S3), frequently forming cross-bars. The ease of highly localized extracellular junction formation, along with the enhanced photothermal effect described above, suggest that textured i-SiNWs can be used for freestanding photothermal modulation of cellular dynamics through the artificial synapse-like interfaces.

Laser illumination of a textured i-SiNW in close contact with a glial cell protrusion elicits rapid calcium surges initiated right at the stimulation site, likely related to a series of coupled biophysical processes (Figures 3a and S4, Supplementary Movie 1). Briefly, the strong photothermal effect of the nanowire with porous channels upon illumination can rapidly elevate the local temperature and subsequently increase the capacitance of the interfacing cell membrane, which depolarizes of the membrane.²⁴ Calcium dynamics can then be triggered due to the existence of voltage-gated calcium channels on glial cell membranes.²⁹ Additionally, shock waves can also be initiated by the photothermal-acoustic effect that can activate mechano-sensitive ion channels of the cell.³⁰ The locally generated calcium concentration gradient can drive the propagation of the signal inside the cell by going through the cell body and then to other branches of protrusions (Figure 3a,b). Besides glial cells, SiNWs can also interface with DRG neurons for direct neuromodulations. Upon laser illumination of the Si/neuron junction, calcium dynamics can be evoked in a similar manner through either voltage³¹ or mechano-sensitive³² calcium channels expressed on the neuron membrane (Figure 3c,d).

Moving forward, highly localized modulations of both neuron and glial cell activities at subcellular resolution with programmed temporal patterns allow precise probing of natural neural-glial interactions as well as reinforcing intracellular and intercellular signaling networks for cellular engineering applications. In our work, the spatial resolution of extracellular modulation depends on the exact configuration of the junction. Indeed, the overlapped area between the nanowire, the cell, and the laser spot will determine the final resolution. If the nanowire is aligned with the cell protrusion or lies on top of the cell body,

the resolution would be the projected area of the nanowire under the laser spot, which is the nanowire diameter (~ 200 nm) times either the nanowire length (if the nanowire length is smaller than the laser spot size) or the laser spot size (if the nanowire length is larger than the laser spot size). On the other hand, when the nanowire and the cell protrusion form a cross-bar junction (Figure 2d, Figure 3), the resolution is the nanowire diameter (~ 200 nm) times the protrusion width (down to submicron scales). With a finely focused laser spot (down to the diffraction limit), one can generate highly localized heating of the nanowire right at the illumination spot. Therefore, even if the nanowire has a couple of microns in its length, the ultimate resolution will be determined by the laser spot size and the nanowire diameter. Furthermore, the photostimulation protocol adopted in this work is minimally invasive to cells. For example, the same cell can be stimulated repetitively to induce calcium elevations following each stimulus, suggesting that cellular functions are preserved after the calcium cycles (Figure S5). LIVE/DEAD assays (Figure S6) indicate that the cell cannot be killed unless a laser pulse of ~ 2.5 -fold of the threshold value for eliciting calcium dynamics was delivered, allowing a large dynamic range to manipulate cellular activities. At higher laser intensity, only the cell under stimulation instead of a large population of cells was killed, suggesting that the cell death was likely mediated through the apoptosis pathway.³³

Finally, we showed that textured nanowire-enabled and optically controlled cellular modulation can be extended to cell types directly involved in disease, such as cancer cells. We focused on U2OS, a human bone osteosarcoma epithelial cell line, and added a textured SiNW suspension to the cell culture in a druglike fashion. Focused laser pulses were delivered as described above onto individual nanowires interfacing with U2OS cell membranes. Our calcium imaging data shows that calcium dynamics can be elicited from the stimulation site immediately following the light illumination likely involving the contributions of voltage-sensitive³⁴ and/or mechano-sensitive³⁵ calcium channels (Figures 4a and S7). Rapid intracellular calcium wave propagation was then observed inside the cell under stimulation with a speed of ~ 15 $\mu\text{m/s}$ driven by the large calcium concentration gradient established through the local influx of extracellular calcium ions (Figure 4b). For nonexcitable cells, such as U2OS, action potentials cannot be fired and the cell membrane would just be depolarized more with a higher light intensity within a dynamic range. The cell membrane depolarization would lead to an elevated level of inositol 1,4,5-trisphosphate (IP_3 , lipid signaling molecule) in the cell under stimulation, which induces a calcium signal. Besides intracellular waves, calcium signals can also propagate to neighbor cells, likely due to the diffusion of IP_3 through gap junctions to adjacent cells, which has been reported in certain cancer cell lines.³⁶ Therefore, although the optical modulation method itself only input highly localized stimulus, this platform may still be adapted for large scale manipulation of cell populations or even small tissues. The fact that nonexcitable cancer cell cultures can be photostimulated demonstrates the broad applicability of the nanowire-enabled optical modulation to a variety of biological targets and suggests potential new areas for future bioelectric studies.

In this work, we found that textured i-SiNWs show enhanced photothermal response to laser illumination compared to smooth nanowires. These textured nanostructures can establish synapse-like interfaces with cell membranes and can be used to elicit calcium wave propagations both intracellularly and intercellularly. The modulation mechanism mediated

by this device platform relies on photothermally³⁷ induced membrane capacitance change, a biophysical mechanism that can be generally applied to a variety of cell types including nonexcitable cells. Additionally, with the high spatial resolution of the wireless cellular modulation textured SiNWs provide a means for further exploration of biophysical processes across multiple spatiotemporal scales, such as intercellular communications, cell motility, intracellular transport, and disease progression. Moreover, Si-based materials have a bandgap (~1.1 eV) which allows light absorption over a broad range that includes one near-infrared (NIR) window. Therefore, instead of being limited by visible light stimulation, textured Si may be further adapted for NIR light-based in vivo stimulation. Overall, our results present textured SiNWs as a new platform for nongenetic optically controlled modulations of cellular signaling dynamics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Textured Si nanowires by Au-catalyzed chemical etching allows highly localized optical modulation of cellular dynamics. (a) Photostimulation of extracellular junctions between textured SiNWs and various types of cells can elicit local calcium dynamics and subsequent intracellular and intercellular propagations. (b) A structural model illustrating Au bands on the i-SiNW surface after iterated pressure modulations during the nanowire growth. (c) TEM images highlighting the open networks of porous channels after the Au-catalyzed etching of i-SiNW. The dashed blue box on the left represents the region for a zoom-in view on the right.

Figure 2.

Textured nanowires show a strong photothermal response to light and can interface with cell membranes. (a) A schematic diagram of the experimental setup for the photoresponse measurement of Si nanowires. 532 nm laser pulses are delivered onto the Si nanowires immersed in a PBS solution. (b) Textured Si nanowires (red) show significantly larger photothermal effects compared to smooth nanowires (blue) under illumination with 532 nm laser for 1 ms ($n = 8$). (c) Representative traces of local temperature dynamics (yellow) and photocurrents (gray) after laser illumination (532 nm, 47.1 mW for 1 ms) of smooth (blue dashed box) and textured (red dashed box) Si nanowires. (d) SEM images of a typical glial cell/textured nanowire interface showing a strong interaction between Si and the cell membrane (marked by the green arrow). The yellow dashed box in upper panel marks the region for a zoom-in view in the lower panel.

Figure 3.

Calcium dynamics can be elicited in DRG cultures with textured Si nanowires. (a) Confocal microscope time series images (green, calcium; blue, Si nanowires) showing an intracellular calcium wave propagation. The glial cell calcium was locally elevated right after the illumination of a textured Si nanowire. The black star marks the illumination site. A 1 ms laser pulse (592 nm, ~22.3 mW) was delivered right before the 2.754 s time point. (b) Quantitative analysis of calcium fluorescence intensities over time from four regions of interest show calcium dynamics at different locations marked in (a) black, the stimulation site; red, glial cell body; blue, upper branch protrusion; pink, lower branch protrusion. (c) Confocal microscope time series images of a neuron interfacing with a textured nanowire and (d) the corresponding quantitative analysis of the calcium fluorescence intensity over time showing the stimulation effect of the neuron. A 1 ms laser pulse (592 nm, ~22.3 mW) was delivered right before the 2.754 s time point.

Figure 4.

Extracellular stimulation of calcium dynamics can be extended to other cell lines. (a) Confocal microscope time series images of a U2OS cell culture being photostimulated by a textured Si nanowire (green, calcium; blue, Si nanowires). Intracellular calcium elevation was triggered at the stimulation site and caused subsequent intercellular calcium wave propagations to neighbor cells. A 1 ms laser pulse (592 nm, ~22.3 mW) was delivered right before the 2.748 s time point. The white star marks the illumination site. (b) A kymograph taken along the cell body shows the evolution of intracellular calcium gradient. (c)

Quantitative analysis of the fluorescence intensities over time show the stimulation effect of the cell under stimulation and two neighboring cells: black, the cell under stimulation; red and blue, neighbor cells.

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