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Topical Review

Interactions between semiconductor nanowires and living cells

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Abstract

Semiconductor nanowires are increasingly used for biological applications and their small dimensions make them a promising tool for sensing and manipulating cells with minimal perturbation. In order to interface cells with nanowires in a controlled fashion, it is essential to understand the interactions between nanowires and living cells. The present paper reviews current progress in the understanding of these interactions, with knowledge gathered from studies where living cells were interfaced with vertical nanowire arrays. The effect of nanowires on cells is reported in terms of viability, cell–nanowire interface morphology, cell behavior, changes in gene expression as well as cellular stress markers. Unexplored issues and unanswered questions are discussed.

Keywords: nanowires, semiconductor, living cells, membrane, morphology, proliferation, motility

(Some figures may appear in colour only in the online journal)

1. Introduction

Nanowires are one-dimensional structures with a diameter below 100 nm and a length on the micrometer range. During the last decade, semiconductor nanowire arrays have been increasingly used for biological applications [1–3]. These include for instance biomolecule detection [4–7], biomolecule transport [8–10], mechanosensing [11–13], cell transfection [14, 15], cell recording [16–19], model nanoparticles in nanosafety studies [20–23], rare cell capture [24, 25], and cell guidance [26–28]. Although the development of nanowire applications is blooming, the interactions between living cells and nanowires are still poorly understood. Various parameters seem to influence the effects of nanowires on cells: cell type, nanowire array geometry, material, and even fabrication method [14, 26, 28–36]. However, in order to design nanowire arrays with specific functions, it is crucial to understand these interactions as well as the mechanism underlying them. Morphological effects are important to assess since they are the signatures of cytoskeleton rearrangements, which in turn, can activate signaling pathways and greatly affect cells. Nanowire-induced changes in cell motility are also important to evaluate, since they can relate to, either changes in chemical cues in the cellular environment, changes in the cellular sensing capabilities, or changes in the cytoskeleton dynamics. Effects on cell growth and proliferation are crucial to assess since possibly related to cytoskeleton rearrangements, cell internal machinery function and to cell cycle modifications. This paper reviews the interactions between vertical arrays of semiconductor nanowires and cells, with a special attention to giving the cell type, array geometry and material for each
mentioned study. The focus here is not on the various nanowire applications but on the nanowire–cell interface per se. Two main types of nanowire arrays are considered: epitaxial nanowire arrays, where individual nanowires are well defined and can even be patterned (figure 1(a)) and wet-etched silicon nanowire arrays (thereafter referred to as etched silicon nanowire arrays), which are much denser arrays, with sometimes coalescent nanowires (figure 1(b)). When relevant, studies of one-dimensional nanostructures (hollow nanowires or non-semiconductor nanowires) are also included. The effects of nanowires are considered in terms of cell viability, morphological effects, with global cell morphology, neurites and membrane conformation. The effects on cell behavior are reviewed in terms of attachment, guidance, motility and proliferation. The changes in the cell biochemistry are also examined. Finally, remaining important questions are discussed.

2. Cell viability

The viability of cells cultured on vertical nanowire arrays is not significantly affected by the presence of nanowires. On InAs nanowire arrays, more than 95% of HEK293 and F11 cells were found to be viable after 2 days of culture [37]. When varying the array density, the viability of HEK293 cells is slightly lower on the lowest density tested (corresponding to a 10 \( \mu \)m distance between nanowires) when compared to flat controls, whereas the cell viability on higher density substrates was similar to the one on control substrates [30]. On SiNW, the viability of primary immune cells was found to be similar to the one of controls [35]. Similarly, primary neurons were shown to survive to the same extent on GaP nanowire and flat substrates [38]. However, it is important to note that cell density and cell attachment are also important parameters in assessing the cell viability, as dead cells often detach from the substrates and therefore are not accounted for in live/dead assays.

3. Morphological effects

3.1. Overall cell morphology (cell area, shape)

3.1.1. Cell area. The morphology of cell cultured on nanowires is often different from the one of cells on flat substrates. On arrays of etched silicon nanowires, the cells are less spread and more rounded compared to when on flat controls [31, 32, 39–41]. Possible explanations for this are the high surface energy of the material, the small surface area available for cell attachments and possibly the observed decrease of protein adsorption on silicon NW [41]. By varying the nanowire density, Qi et al. could not observe any obvious difference in the cell spreading properties and therefore concluded that the decrease in cell area on silicon NW is due to the presence of nanostructures rather than to a limited surface area available for cell attachment [33]. Note that a smaller cell surface does not imply a lower cell adhesion, as the size and density of focal adhesions can differ significantly between nanowire and flat substrates (see section 4.1). On epitaxial nanowires, the observations are less consensual. For instance, Bonde et al. measured larger cell areas on low density InAs NW arrays compared to flat controls, whereas no significant difference in cell area was observed on high density arrays [30]. San Martin et al. observed a reduced cell spreading on GaP nanowires [42]. Piret et al. also showed that glial cell spreading was of a lesser extend on GaP nanowires compared to flat substrates (figure 2) [39]. On ordered silicon NW, cell spreading and morphology depends on the nanowire stiffness and the array pitch [28].

3.1.2. Neurites. An important point in nanowire-induced morphological changes corresponds to the particular case of
neurite outgrowth (i.e. the cell projections from the body of neuronal cells). Several studies show that neurite outgrowth is extensive on epitaxial nanowires. In the first study of neurons cultured on nanowires, Hällström et al have shown that primary neurons thrive and extend multiple cell processes on GaP nanowires [38]. Berthing et al later showed that the neurite extension pathway in F11 cells was not affected when cultured on InAs nanowires [37]. Recently, Piret et al observed a significantly increased neurite outgrowth in mouse retinal neurons cultured on GaP nanowires compared to flat substrates [29] (figure 3). This effect was observed for nanowires over 1 µm in length. A possible preferential adsorption of neurotrophic molecules on nanowires may explain this effect, while mechanical effects were ruled out [29, 43].

On etched silicon nanowires, mouse retinal neurons do not extend any neurites as opposed to on GaP nanowire and flat substrates [34]. The neurotoxic effect was attributed to the presence of contaminants, such as hydrofluoric acid, entrapped in the porous nanowire array when etching the substrate. In contrast, Moxon et al measured a higher number of neurites per cell on silicon nanowires in PC12 cells. The discrepancies between these various observations can possibly be attributed to cell type, as primary neurons can be expected to be more sensitive to contaminants than immortalized cells.

3.2. Cell membrane conformation: do nanowires access the cytosol?

Whether or not the membrane of cells cultured on nanowire arrays is pierced by the nanowires is a very important criterion to determine what types of nanowires can be used as possible cell transfection system. Shalek et al pioneered silicon nanowire assisted delivery of biomolecules inside cells, including siRNA, proteins, and DNA, and reported over 95% of cells penetratred by nanowires [14]. The technique was then repeatedly used for delivering small molecules and siRNA inside cells (figure 4(a)), as well as for cell probing [44–47]. Importantly, the same group showed that various
Types of cells require different nanowire array geometries for successful transfection. For instance, non-adherent immune cells require longer, thinner and denser nanowires compared to adherent immune cells [35]. Using aluminum nanostraws, VanDesarl et al. also gained access to the cytosol of CHO and HeLa cells for sequential injections of biomolecules [15]. Later, the same group reported that although 95% of the CHO cells where penetrated by nanostraws, only 7% of the nanostraws interfacing a cell were actually gaining access to its cytosol [48]. When enhancing cell adhesion by preincubating the substrate with adhesion-promoting molecules, the proportion of penetrating nanostraws went up from 7% to 11%, showing that cell adhesion is an important factor in gaining access to the cytosol. The same group used a simple theoretical model to confirm that membrane penetration is more effective through an adhesion mechanism [49]. The observed low amount of successful cell penetration may partly explain why in the early work by Kim et al [50], only 1% of the cells were successfully transfected, since they used an average density of 2–3 nanowires per cell. In parallel, several studies were launched to assess the membrane morphology of cells cultured on high aspect-ratio-pillar arrays. Hanson et al. investigated the cell membrane–nanopillar interface using transmission electron microscopy [51]. Using \(1 \mu m\) spacing between nanopillars, they varied the diameter from 50 to 500 nm and the length from 0.5 to 2 \(\mu m\). In primary neurons, they showed that, for the variety of geometry tested, the cell membrane was always intact and wrapped itself around the nanopillars. At the same time, Berthing et al. came to the same conclusions for HEK293 cells using 2–11 \(\mu m\) long InAs nanowires, spaced 3–7 \(\mu m\) apart [52]. Their method consisted of labeling the cell membrane fluorescently and imaging the membrane fluorescence along the nanowires using confocal microscopy (figure 4(b)). Using a FIB-SEM slice and view method [53], Persson et al. showed that the nuclear membrane of immortalized fibroblasts folds and forms tubes in order to exclude the nanowires from the nucleus interior (figure 4(c)) [36]. Nuclear membrane folding around nanowires was also seen for HeLa and HEK293 cells [54]. Using a FIB-SEM slice and view method to investigate HL-1 cell membrane conformation on various gold nanostructures, Santoro et al. confirmed that the membrane was not pierced by any nanostructure. They also showed that a nanopillar is more likely to be engulfed by the membrane (i.e., the membrane following closely the contours of the pillar) when the pillar is located at the cell edge, rather than in the center of the cell [55].

**Approaches to facilitate cytosolic access.** Several strategies have been developed to facilitate the nanowire access to the cytosol, mainly electroporation, lipid coating, and chemical poration. Xie et al. developed nanorod electrodes for recording the action potential of HL-1 cells. They showed that the detected signal was extra-cellular, unless they applied a train of pulses, resulting in cell electroporation, after which the signal was intracellular for \(\approx 10\) min before the membrane sealed again [56]. Using HEK293 cells and gold-coated silicon nanowires as electrodes, Robinson et al. also observed that applying a short voltage pulse promoted nanowire penetration [18]. Electroporation was also used to gain transient access to the cytosol of CHO and HEK293 cells, in order to increase the efficacy of nanostraw-assisted biomolecule delivery systems. In that case, the electrophoretic effect during the electroporation pulse application enhanced the otherwise diffusion-driven delivery of biomolecules inside cells [57].

Forming lipid bilayers on the nanowires has been shown to enable cytosolic access, in a process where the bilayer fuses with the cell membrane upon insertion of the nanowires. Using kinked silicon field-effect-transistor nanowires as cellular...
probes, Tian et al showed that only the probes that had been coated with a phospholipid bilayer could measure the HL-1 potential intracellularly [58]. The lipid-modified nanowires can be inserted and retracted multiple times without any observable detrimental effects on the cells [59]. The same group repeatedly used lipid modification in other types of nanotube sensors and consistently found that it enabled spontaneous membrane penetration [16, 56, 60, 61]. This approach can possibly be used in vertical arrays since it has been shown that phospholipid bilayers could form on vertical nanowire arrays, for a broad variety of nanowire geometries, while following the contours of the array topography [62].

Finally, for nanotubes and nanostraws, chemical poration is another approach for gaining access to the cell interior. The method consists of delivering compounds that can dissolve locally the cell membrane and/or the cell cytoskeleton. Using saponin to dissolve locally the cell membrane, Peer et al successfully delivered small molecules as well as plasmids to HEK293 cells [63]. Using both dimethyl sulfoxide and Latrunculin A to dissolve the membrane and disrupt the cell actin network locally, Aalipour et al observed a transient small increase in the percentage of nanostraws penetrating the cells [64].

In summary, both electroporation and chemical poration can facilitate the access to the cytosol temporarily. However, electroporation requires the use of nanowire electrodes, the design of which can be cumbersome. Using chemical poration is easier to implement compared to electroporation. However, the drawback of this method is that the molecules used to dissolve the membrane and disrupt the cell cytoskeleton will end up in the cytosol and possibly affect the cells. Using lipids to facilitate cytosolic access has the advantage to enable the probing of the same cell multiple times. However, with this method, it is not clear whether the nanowire stays in cytosolic contact permanently or only transiently. Finally, an important piece of information missing in these studies is the survival time of cells penetrated by nanowires, which will be a determinant factor when choosing a method over another to gain access to the cytosol.

4. Effects of nanowires on cell behavior

4.1. Cell attachment (distribution, adhesion)

The information about cell attachment on silicon nanowires available in the literature is conflicting. Piret et al showed a very different retinal cell distribution on flat silicon substrates compared to silicon nanowire substrates, with cell clusters on flat substrates (figure 5(a)) and single, densely packed cells on silicon nanowires (figure 5(b)). Comparing the cell distribution after 3 days and 18 days of culture revealed that cells detach over time from the flat substrate but not from the nanowire substrate, suggesting a stronger cell adhesion on nanowires [34]. Qi et al did not find any striking differences in the density of cells on flat silicon substrates compared to silicon NW, for 4–48 h of cultures (figures 5(c) and (d)). However, when subjecting the substrates to a centrifugal force and counting the number detached cells, they found that HepG2 cells adhered more strongly to the nanowires, which was confirmed by performing RT-PCR of adhesion-specific genes, such as FAK and integrins [33]. In contrast, Brammer et al showed that the number of MC3T3-E1 osteoblastic cells on similar nanowire substrates was decreasing between 2 and 24 h culture, suggesting a poor cell adhesion [41]. Differences in cell type can possibly explain the different results. Indeed, Turner et al. used silicon grass, which can be considered as short etched silicon nanowires (≈ 0.2 μm) and selectively etched periodic bands on the substrate, resulting in a flatter topography in these areas [65]. They showed that primary cortical astrocytes adhered preferably on the nanograss regions, whereas immortalized astrocytes (LRM55 cells) attached mostly on the flatter regions, thereby stressing the importance of cell type in cell-nanostructure interactions.

In human mesenchymal stem cells, Kuo et al measured an increase in the expression of two adhesion complex molecules, pFAK and vinculin, on short (10–15 μm long nanowires) when compared to long nanowires (20–25 μm), which was explained by the osteogenic differentiation state on short nanowires, due to a less compliant surface on short nanowires, see section 5.

The results are more consensual on epitaxial nanowires, where the cell adhesion is increased on nanowires. Bonde et al subjected HEK293 cells to a rinsing assay and found that cell detachment was of lesser extent on nanowire substrates [30]. In that study, the area of focal adhesions was found to be bigger on nanowires than on controls. In agreement with the above, Piret et al showed that adhesion of retinal cells was stronger on GaP nanowires than on flat substrate [29].

Focal adhesions have been shown to be both preferentially associated with nanowires (primary superior cervical ganglion neurons on GaP NW) [26] and not (HEK293 cells on InAs NW) [30].

4.2. Cell guidance

Although chemical surface modifications in nanowire substrates have been used to pattern and guide cells (see for instance [66–69]), here the focus will be on pure topographical cues used to pattern and guide cells with nanowires (i.e. homogeneous surface chemistry). Axons from a mouse superior cervical ganglion have been shown to align along rows of vertical GaP nanowires (figure 6(a)) [26]. The nanowire spacing within a row was 0.4 μm and the rows were spaced 10 μm apart. The degree of guidance was substantially better than the one obtained when using grooves of similar height and the same cells [70]. This may be explained by an optimum spacing of nanowires within rows, close enough to prevent axons from crossing a row but far enough to fail in providing sufficient attachment points for an axon to climb gradually on top of a row, which contrasts with the case of groves. Using this concept, Hällström et al patterned the surface with short rows of nanowires arranged in a rectifier pattern (figure 6(b)) [27]. On this pattern, mouse superior ganglion axons coming from the right hand side (labeled in green in figure 6(b)) would be forced to grow towards the left, in tracks predetermined by the pattern, and axons coming from the left side (red in figure 6(b)) would grow towards the right in separate tracks. Note the dark
gaps between red and green tracks in figure 6(b), which shows that there are no axons on the nanowire area, confirming the fact that axons cannot climb on top of vertical nanowire rows. Denser arrays of nanowires can also guide cells, as shown in figure 6(c) for pluripotent C3H10T1/2 stem cells. In this case the cells are growing on top of the array and the guidance is seen only for an intermediate range of nanowire spacing. When guidance occurs, the cell processes always align along the axes where the nanowire pitch is minimum (red arrows in figure 6(c)).
Figure 6. Cell guidance using vertical nanowire arrays. (a) Left: schematic of axonal growth (green arrows) guided by parallel rows of nanowires (dark points). Right: fluorescence microscopy image of axons from a mouse superior ganglion (right hand side of the image) growing on a substrate with such rows of nanowires (right hand side of the white dashed line) and no nanowires (left hand side of the white dashed line). The axons align along the nanowire rows, adapted from [26]. (b) Sorting of axons using a nanowire rectifier pattern. The green axons are growing from right to left in predefined tracks and the red axons are growing from right to left in separate tracks, adapted from [27]. (c) C3H10T1/2 cells growing on top of a square arrays of silicon nanowires (pitch 2 \( \mu m \)). The cells align along the axes where the nanowire distance is minimum, adapted from [28].

4.3. Cell motility

Few studies have investigated the effects of nanowires on cell motility. Such a study requires the ability to image cells under culture condition. An alternative approach is to study cells with low motility, which allows for cell tracking without excessive perturbation by taking images only once a days outside the cell incubator. This approach was used by Xie et al [78] to study the mobility of neurons on fused silica nanowires over 5 days. The mobility of neurons was dramatically reduced on the nanowires (figure 7).

Using phase holographic microscopy, a label-free imaging technique which can be performed directly inside an incubator [71], Persson et al monitored the motility of L929 fibroblasts, which are highly motile cells for 20h [36]. They used 1.5, 4 and 7 \( \mu m \) long GaP nanowires, all at a density of 1 \( \mu m^{-2} \) on the surface and showed that the cell motility was dramatically reduced on nanowire substrates compared to flat controls. The longer the nanowires, the lower the cell motility with completely non-mobile cells on the 7 \( \mu m \) long nanowires.

Figure 7. Effect of nanowires on cell motility. (a) Movement traces of 4 free cells (blue) and nanowire-pinned cells (red). The bottom right plot zooms in the motility of pinned cells. (b) Analysis of cell movement for pinned and free cells, adapted from [78].

4.4. Cell proliferation

There is little data on the effects of nanowires on cell proliferation. Bonde et al measured a higher number of HEK293 cells positive for BrdU on InAs nanowire arrays, suggesting a higher proportion of proliferating cells on nanowires compared to when cultured on flat controls [30]. In contrast, Persson et al observed a lower rate of proliferation for fibroblasts on GaP nanowires [36]. This effect was more pronounced with long nanowires (figure 8(a)). In that study, multinuclear cells were more frequently observed on the nanowires, suggesting that cell division often could not be completed on these substrates (figure 8(b)). A possible explanation for the failed cell division is the entanglement of cells components on the long vertical nanowires.

5. Effects of nanowires on the cell biochemistry

Nanowires can impact significantly the cell biochemistry. Piret et al showed that primary retinal cells on etched silicon nanowires underexpress the cell markers \( \beta \)-tubulin-III, TRPV4, Brn3a, Chx10, PKC, recoverin and arrestin, compared to when cultured on flat substrates, which was attributed to residual contaminants trapped in the substrate [34]. Shalek et al performed RT-PCR on HeLa cells and fibroblasts cultured
Figure 8. Effect of nanowires on L929 fibroblast proliferation. (a) Cell density as a function of time for flat controls (polystyrene culture flasks and plain GaP), as well as nanowire substrates. Short NW refer to 1.5 µm long nanowires; medium NW to 4 µm long nanowires and long NW to 7 µm nanowires. (b) Fluorescence microscopy image of a L929 fibroblast cultured for 15 days on 7 µm long nanowires, showing multiple nuclei (blue). Scale bar 10 µm. Adapted from [36].

and penetrated by silicon nanowires to assess the mRNA expression of 'housekeeping' genes ACTB, B2M, GAPDH, GUSB and HPRT1. No significant differences in mRNA expression for these genes could be found for cells on nanowires compared to on flat controls [14]. SanMartin et al performed microarray analysis in cortical neural stem cells on 4 µm long GaP nanowire arrays [42]. They showed a small (1–2 fold) but statistically significant upregulation of Cd9 (related to adhesion), Rnd2 (related to actin cytoskeleton morphology), Kifap3 (related to microtubule processes), and Apoc1 (related to metabolism, on nanowires). They also observed an upregulation of the stress marker Hspa8 and the redox activity regulator Cybasc3. Persson et al also observed signs of stress in L929 fibroblasts cultured on GaP nanowire arrays [36]. They measured higher reactive oxygen species contents, as well as a higher mitochondrial metabolic activity in cells cultured on nanowires compared to flat controls. These effects were more pronounced on long nanowires (7 µm) than on short ones (1.5 and 4 µm).

**6. Remaining questions**

The issue of membrane conformation is still an open question since there are conflicting results in the literature on whether or not nanowires can spontaneously pierce the cell membrane. The mechanisms behind cell penetration by nanowires are not fully understood. It is not clear whether it initiated by cell sedimentation, adhesion or endocytosis [49, 72]. Coarse grained molecular dynamics simulations of nanorods endocytosis show that nanorods in contact with cells are rotated from their initial entry angle to an angle of ≈90° with the membrane plane in order to minimize the membrane elastic energy during internalization [73, 74]. It has also been shown experimentally that free floating nanowires in the cytosol were not exclusively internalized through endocytosis since many nanowires were not located in endosomes [75]. However, in the case of vertical nanowire arrays, endocytosis could possibly be the prevalent mechanism behind the observed membrane–nanowire interface. Indeed, for vertical nanowire arrays, the nanowire–membrane entry angle upon initial cell contact is 90°. Therefore, the nanowire size perceived by the cell is given by the nanowire diameter, which is in the right size range for receptor-mediated endocytosis (50–100 nm). These
results, as well as the fact that membrane is often coating the nanowires, suggest that the membrane–nanowire interface in cells cultured on vertical nanowire arrays is the result of uncompleted endocytosis.

It is also important to note that in most studies, it is the successful molecule delivery in the cytosol per se, rather than the membrane piercing itself that is assessed and interpreted as a proof of cell penetration. Indeed, an important factor that should be considered is the effect of membrane curvature on the trans-membrane pores and proteins, since high membrane curvature (such as the one imposed by nanowires) has been shown to influence the structure and function of these pores and can therefore affect the membrane permeability [76, 77]. A clear assessment of both membrane permeability and membrane conformation should enable a clear discernment between curvature induced membrane permeability and membrane penetration by the nanowires.

A remaining open question is the cell type-dependence of the nanowire effects. From the information gathered in this review, similar nanowire substrates can have different effects on different types of cells. However, it is difficult to point at the exact mechanism underlying the difference in effect. Cells with different mechanical properties, membrane receptors, motility, and proliferation rate, can be expected to behave differently on the same substrates. One can for instance speculate that nanowires have more detrimental effects on normally motile cells since nanowires reduce cell motility. Large scale testing of different types of cells on similar nanowire arrays would enable the prediction and design of a nanowire array function.

7. Conclusions and perspectives

The interface between semiconductor nanowires and living cells is very complex and crucial to understand in detail for the realization of biomedical applications based on nanowires. Cells cultured on vertical nanowire arrays are affected to different degrees by the nanowires, depending on the array geometry and cell type. Further studies are necessary to decipher the details of cell–nanowire interactions. Specifically, varying the nanowire length, spacing or diameter, and perform consistently the same assay on a given cell type may help understanding the effects of the array geometry. Moreover, investigating the effects nanowires on various cell type in a systematic fashion may bring new information on these interactions. Improving our knowledge on how living cells and nanowires interact is crucial to ensure minimal perturbation in cell sensing and manipulation.

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