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Biomimetic nanowire coatings for next generation adhesive drug delivery systems

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Abstract

Without bioadhesive delivery devices, complex compounds are typically degraded or cleared from mucosal tissues by the mucus layer.^{1–3} While some chemically-modified, micro-structured surfaces have been studied in aqueous environments,^{4,5} adhesion due to geometry alone has not been investigated. Silicon nanowire-coated beads show significantly better adhesion than those with targeting agents under shear, and can increase the lift-off force 100-fold. We have shown that nanowire coatings, paired with epithelial physiology, significantly increase adhesion in mucosal conditions.

Keywords

Nanowire; nano-structure; bioadhesion; mucoadhesion; gecko-inspired; drug delivery; mucosa

Because of their easy accessibility, large surface area, and rich blood supply, mucous membranes (mucosae), such as intestinal, nasal, ocular, vaginal, and buccal tissues, are frequently targeted for therapeutic drug delivery.^{1,6} However, the mucosae present significant barriers to permeation, including a 1–450 μm motile mucous gel layer, tight junctions, and in some tissues, harsh enzymes and low pH.⁷ Delivery devices have been able to protect compounds from chemical degradation, but without adhesion to the underlying epithelium, the

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Supporting Information Available: Further descriptions of the methods used in this paper, as well as an interpretation of the Atomic Force Microscopy results in the context of these experiments, are available in the Supporting Information section. This material is available free of charge via the Internet at <http://pubs.acs.org>.

devices are cleared with the lumen contents or with the mucous layer in a matter of hours.^{1–3,8} A short transit time, in conjunction with chemical degradation, produce a relatively low concentration gradient at the cellular surface, and thus reduced compound absorption. Specific epithelial targeting agents, such as lectins, adhere to glycosaminoglycans on the cell surface; because these sugars are found in the mucous layer as well, competition between the mucous layer and cell surface for binding to mucoadhesives reduces the amount of direct device-cell binding to that of non-adhesive controls, particularly *in vivo*.^{9,10} Furthermore, mucoadhesives are constrained by the mucin turnover time (50–170 minutes¹¹), whereas devices which directly bind to cells are only constrained by the cell turnover time (2–3 days¹²). Thus, for robust mucosal adhesion, a device must penetrate the mucous layer and adhere directly to the epithelium.

One particularly promising class of adhesives is gecko-inspired (geometry-based) adhesives. Micro- and nano-structured surfaces naturally occur in a variety of insects and lizards, and have been shown to rely primarily on van der Waals forces for adhesion.^{13–18} While numerous experiments have shown biomimetic nanowires and nanotubes to adhere with forces ranging from 0.04 times^{19,20} to 30 times²¹ the adhesive strength of geckos (reported to be 500 kPa¹⁶) in dry environments,^{22,23} only two groups have looked at submicron structures in aqueous conditions (elements of diameter 0.4 μm for Lee *et al.*⁵ and 0.1 to 1 μm for Mahdavi *et al.*⁴). Despite using micro-structured surfaces, in a wet environment, chemical modification was necessary to bolster adhesion.

Under nanoadhesive conditions, as the number of adhesive elements per surface area increases (ie: diameter of individual elements decreases), the surface area to volume ratio increases and van der Waals adhesion is predicted to increase^{24,25}. Furthermore, because mucosal epithelia exhibit nano-structured microvilli, available surface area contact is considerably increased on the cell surface^{26–29}. Thus, by decreasing the diameter of the elements on the device surface to the nano-scale and targeting a microvilliated surface, it may be possible to generate strong bioadhesive forces due to geometric features alone.

To test the interaction of microvilli and nano-structures, a prototype device was created to couple the adhesive characteristics of nanowires with the drug delivery capacity of beads. A standard vapor liquid solid method for synthesizing silicon nanowires on flat wafer surfaces was modified to achieve growth of size-specific nanowires on the surface of 30–50 micron diameter glass beads (Figure 1).³⁰

A Caco-2 cell monolayer was used as an *in vitro* model of the intestinal mucosa because the cells display a microvilliated structure which closely corresponds to that found *in vivo*³¹. From scanning electron microscopy (Figure 1b), significant interdigitation of the nanowires and microvilli was visible at the cell-nano-structure interface, showing significant areas of contact between the cells and nanowires.

In order to characterize the effects of geometric and chemical modifications of the nanowires, three nanowire test geometries and a control group with no nanowires (See Table 1 in Supporting Information) were fabricated. A subset of the long nanowire group and the control group were chemically modified with tomato lectin, a well characterized mucoadhesive intestinal targeting molecule.^{10,32,33} Each test geometry had nanowires with an average diameter of 60 nanometers, but with varying lengths and numbers of adhesive elements per surface area (coating densities). Within each geometry, the quality of surface area nanowire coverage varied bead by bead (expressed as percent surface area covered).

To isolate the effects of various factors within the mucosal environment which could lead to reduced adhesion, devices were incubated with cells while in the presence of either Hanks Balanced Salt Solution (HBSS), 2% w/v mucin, HBSS at pH 5.1 ± 1.0 (s.d.), or 0.03% trypsin

(Figure 2). In all solutions, nanowire-coated beads adhered to cells at a frequency 5 times greater than control beads. Additionally, except in the mucin solution, the tomato lectin-modified, nanowire-coated devices adhered as well or slightly better than the nanowire-coated beads, indicating that these solutions have no significant effect on the targeting capabilities of tomato lectin³⁴. The reduced adhesion of lectin modified, nanowire-coated devices in mucin suggests that unmodified nanowire-coated devices may have an advantage when exposed to mucus.

Lectin-modified and unmodified devices incubated on a Caco-2 monolayer were exposed to mucin flow to determine the effect of chemical modification on adhesion under shear stress (Fig 3a). Unmodified control beads and lectin-modified beads detached at the lowest shears, with median survival shears, the shear at which 50% of the devices had detached, of 2.35 dynes/cm² and 3.60 dynes/cm², respectively. Though lectin-modified nanowires decreased the level of bead detachment, unmodified nanowires showed the greatest retention (median survival shears of 5.70 dynes/cm² and 9.15 dynes/cm², respectively). Compared to unmodified nanowires, lectin modification enhanced detachment from cells under mucous flow, indicating that mucoadhesive chemistry may reduce overall mucosal tissue adhesion, compared to geometry-based adhesion. Because lectins bind to both cells and mucus, adding a mucin layer introduces competition between these elements for binding to the lectin-modified nanowires, which may explain the reduced adhesion.

Shear flow studies conducted on nanowires with varying geometric properties indicated strong device retention rates, above 90%, for all geometries in shear less than 4 dynes/cm², with the long nanowires providing the greatest adhesion at higher shears (median survival shear of 54.40 dynes/cm²). The median survival shears for the medium and short nanowires were 17.79 dynes/cm² and 9.54 dynes/cm², respectively. The median survival shear correlated to the length of nanowires, indicating a relationship between nanowire length and adhesion under shear flow.

An atomic force microscope (AFM) with devices affixed to cantilevers was used to quantitatively determine tensile adhesive forces. Typical curves from this system (Figure 4) indicated control beads produced an adhesion force of 1.80 ± 0.2 nN (s.e.m.) when contacting cells. When a nanowire-coated bead made contact with cells, forces upward of 100 nN were common (mean force: 172.0 ± 53.8 nN s.e.m.). In some cases, it was possible to visualize the apparent adhesion of single nanowires or small clusters of nanowires (see Supporting Information).

Using scanning electron microscopy after AFM experiments, length and surface area coverage of a given bead were quantified, to determine the relationship between nanowire geometry and maximal forces generated in the AFM experiments (Figure 5). At one extreme, short nanowires provided a smaller increase in surface area than longer nanowires, reducing available contact forces comparatively; at another extreme, long nanowires tended to fold over on themselves, creating a matted surface and reducing the overall available surface area compared to freestanding nanowires. Accordingly, within our AFM testing length range (0–3 μ m nanowire length), the data suggest that it is possible to optimize adhesion by growing nanowires between 1 and 2 μ m (Figure 5a). In addition to nanowire length, the quality of surface area coverage affected maximum forces achieved, with devices exhibiting reduced coverage, such as those that contain patches without nanowires, achieving lower maximum forces (Fig 5b). Based on surface area coverage and maximum force measurements, the force of adhesion of nanowire-coated devices was found to be 0.11 kPa; this estimation is a lower limit (see Supporting Information).

In addition to nanowire geometry and chemistry, we considered physiologically relevant variations in the geometry and chemistry of the underlying cell surface. Because much of the

documented dry nano-structure adhesion is due to van der Waals forces, which are dependent on the surface area in contact with the substrate, a nano-structured surface (such as a cell with microvilli or a nanowire-coated bead), would be expected to increase the adhesion over a flat surface. As expected, nanowire-coated beads brought into contact with flat polystyrene produced a mean force of adhesion of 1.30 ± 0.5 nN (s.e.m.); however, a nanowire-coated bead in contact with a nanowire substrate only increased the adhesion force to 9.3 ± 8.4 nN, still an order of magnitude less than the mean adhesion between nanowires and cells (Figure 5c). This minor increase suggests that forces beyond van der Waals forces may be responsible for a significant proportion of nanowire-cell adhesion.

In this paper, nanowires were shown to significantly increase bead adhesion compared to uncoated control beads. Furthermore, devices with a nanowire coating adhered to cells as well as chemically targeted devices in common *in vitro* conditions, and better than chemically targeted devices when exposed to relevant physiological conditions such as a mucous layer and shear flow. Varying the length and surface area coverage of the nanowires further optimized adhesion. Mimicking the nano-scale microvilli with a nanowire surface (nanowire-nanowire adhesion) did not yield equivalent force to cell-nanowire adhesion, indicating that forces beyond van der Waals forces may be at work. While nanowires cannot move appreciably after contact, microvilli could rearrange themselves, creating more intimate contact, increasing surface area related forces, and possibly altering their shape to produce physical adhesion, similar to the interlocking interaction of Velcro.

Furthermore, because nanowire-coated devices have non-specific adhesive interactions, they may also adhere to other gastro-intestinal cells, such as those in the esophagus or stomach. To bypass these undesired regions, the devices may be encapsulated in an enteric capsule that only dissolves in the intestinal pH range.

Though a few nanoparticle delivery systems have been found to be immunogenic in certain situations³⁵, silicon nanowire-coated surfaces have been shown to elicit a less immunogenic response than that of bulk silicon³⁶. Additionally, because the nanowires are physically attached to the surface of a microsphere, they are unlikely to be ingested by cells, and thus unlikely to collect in other organs, such as the liver or spleen.

Nanowire-based, inorganic bioadhesives are attractive for mucosal drug delivery systems because they reduce interactions with therapeutic compounds and are robust even in degrading environments, such as the gastrointestinal system. Silicon is particularly interesting for biological applications because it is slowly degraded compared to mucosal turnover rates *in vivo*, has a variety of well-characterized nanowire fabrication techniques, and could be integrated into other silicon-based systems, such as microelectromechanical systems (MEMS) sensors or other smart systems^{37,38}. Furthermore, nano-structured adhesive surfaces may be useful in numerous clinical applications, such as soft tissue adhesives and engineered tissue implants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Nanowire-cell interactions. a, Scanning electron micrograph showing nanowire-coated microspheres with extensive nanowire coating. Arrow indicates an area of reduced nanowire coverage. Scale bar is 20 μm . b, Intestinal microvilli (top arrow) interdigitate with matted nanowires on the apical surface of the cells (bottom arrow). Scale bar is 500 nm. c, Caco-2 cells form a monolayer. Individual cells can be identified by their borders (arrows). Scale bar is 10 μm . d, Intestinal microvilli have nano-scale diameters, averaging 71.8 ± 10.5 nm. Scale bar is 1 μm . e, Two nanowire-coated microspheres sit on top of cells. Scale bar is 10 μm . f, Nanowires on the side of a microsphere interacting with microvilli on cells. Scale bar is 5 μm .

Figure 2.

Static Adhesion. Percent adhesion after incubation on cells in different solutions and subsequent washes with media. Hank's Balanced Salt Solution was used as a control. Two-way ANOVA shows significance in comparisons of the conditions, the devices, and between the conditions and devices. To compare data in the plot, error bars represent 95% confidence intervals. Multiple comparisons between the devices using a Bonferroni correction indicate significant differences between the Control beads and the Nanowire-coated beads ($p < 0.05$) and between the Control Beads and the Nanowire-coated, lectin-modified beads ($p < 0.05$). Multiple comparisons between the conditions using a Bonferroni correction indicate a significant difference between 2% Mucin and all other conditions.

Figure 3.

Device survival rates under shear flow with 95% confidence intervals shown in the respective shaded areas. a, Modified and unmodified device survival in 2% mucin flow (■ - nanowires, x – lectin- modified, nanowire-coated devices, ● – lectin-modified devices, + – control devices). The unmodified control beads survive at a significantly lower rate ($n = 4$, $p < 0.05$, as indicated by distinct 95% confidence intervals calculated using a Kaplan-Meier survival curve) than the nanowire coated beads for all shears, whereas the lectin modified beads and lectin-modified, nanowire-coated beads significantly differ from nanowire-coated beads above shears of 1.5 dyne/cm² and 3.5 dynes/cm², respectively. b, Survival of devices with varying nanowire

geometry in media (■ – long nanowires, ◆ – medium nanowires, ▲ – short nanowires). In this experiment, $n = 6$.

Figure 4.

Typical AFM adhesion force curves. a, Control beads with no nanowires show adhesive forces around 0.5–2 nN. b, Nanowire-coated beads with good coating show maximal adhesive forces upwards of 100 nN and can exhibit forces upwards of 100 times greater than control beads.

Figure 5.

Geometric effects on maximum force. a, Maximum force varies over a range of nanowire lengths indicating an optimal length of 1–2 μm in the range investigated. b, Maximum force increases linearly with surface area coverage – linear regression yields $r^2=0.91$. Based on this regression, the maximum adhesive force is calculated to be 0.11 kPa. c) Average maximum adhesive forces varying by device-substrate pairings. The Nanowire-Cells pairing is significantly different from the Nanowire-Flat and Control Beads-Cells pairings. Otherwise, differences are not significant. Error bars indicate standard error of the mean.