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Review article

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Bioinspired nanotopographical design of drug delivery systems

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Abstract

Effective drug delivery is important in the treatment of various biomedical conditions, ranging from autoimmune disorders to cancer and bacterial infections. Nanostructured systems can help to overcome challenges to efficient drug delivery such as poor drug distribution, inefficient penetration across biological barriers and off-target effects. The bioinspired nanotopography of drug carrier surfaces provides a physical cue to modulate their interaction with biological systems. In this Review, we discuss how naturally occurring nanotopographical systems can inspire the design of biomaterials for drug delivery. We highlight nanoscale surface modifications of drug carriers and fabrication strategies, followed by a discussion about nanotopographical biointerfaces to regulate biological functions. Key bioinspired nanotopographical functionalities include bio-adhesion, barrier remodelling, drug uptake and subcellular trafficking, cellular signalling and modulation, and antimicrobial interfaces. Finally, we provide an outlook on the future of nanotopographical applications in drug delivery, with a focus on key challenges and exciting opportunities from bench to bedside.

Sections

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Key points

- Three-dimensional nanotopography is ubiquitous in nature (for example, spiky pollen microparticles and nanopillars on cicada wings), impacting the biointerface of surfaces and biological components.
- Bioinspired nanotopography can be engineered for every major drug carrier class, including thin films, patches, implants, stents and discrete particle drug carriers.
- Bioinspired nanotopography can improve bio-adhesion, drug uptake and trafficking, epithelial barrier remodelling, cell signalling, and modulation and can be applied to implement antimicrobial effects.
- Nanotopographical drug carriers can be applied to treat a variety of diseases and conditions, including diabetes, cancer, cardiovascular disease, fractures, wounds and microbial infections, improving biomedical outcomes in preclinical studies compared to drug delivery approaches without nanotopography.
- Advances in nanotopographical fabrication, cell–material interface characterization, and in vitro and in vivo disease models will be key to promoting the clinical translation of nanotopographical platforms.

Introduction

The optimization of drug delivery strategies to treat medical conditions is often aimed at targeting therapeutics to specific sites in the body, such as tumours or infected tissues, and in reducing drug distribution in off-target tissues to minimize side effects. Using nanostructured materials is a promising strategy to improve drug delivery and targeting[1,2]. Many biological activities occur at the nanoscale, and thus engineered nanomaterials are advantageous for regulating biointerfaces and bioprocesses to improve therapeutic outcomes[3]. Nanoparticle drug carriers improve the stability and serum half-lives of drugs and maintain therapeutic drug concentrations[1–5]. Nanostructured thin films, patches and devices are used as wearable and implantable materials with engineered biointerfaces to reduce the foreign body response and inflammation and enable sustained drug release[1,6].

However, biological barriers, such as mucosal surfaces, epithelial junctions, cellular membranes and uptake pathways, can impede effective drug delivery[3]. Drug carriers can be designed to guide surface interactions with biological systems to overcome these barriers[3]. The engineering of nanomaterials for drug delivery has long focused on the choice of core material, surface chemistry, and morphological considerations such as shape and size[3,7–10]. However, optimizing these design parameters is often insufficient to enable drug carriers to interface with the complex three-dimensional (3D) topographical architectures of biological structures[11,12]. Therefore, nanotopographical materials with 3D surface nanostructures have been developed to engage with dynamic 3D biological nanoscale and microscale systems such as epithelial barriers, cell surface receptors and bacterial biofilms.

Nanotopographical designs started to be applied in biomedicine in the 1990s[6,13,14]. Initial investigations demonstrated that cells respond to 3D topographical nanostructures to regulate functions, such as cellular alignment, proliferation and differentiation, mostly through mechanotransduction and durotaxis pathways[14–16]. In the mid-2000s, nanotopography was applied to control and improve drug delivery processes such as drug loading and release kinetics[17–19].

Natural biological nanotopographies are employed for a range of functions, including nanoneedle injections of genomic material by viruses into their cellular targets, enhancing the bio-adhesion of nanostructured gecko feet and pollen microparticles, regulating transport across ciliated epithelial barriers, and preventing bacterial infection with antimicrobial nanopillars and nanospikes on insect wings[20–26]. These nanostructured biological systems have inspired bioengineers to design drug carriers with nanotopographical features to promote biological responses and improve drug delivery (Fig. 1); for example, drug and particle uptake has been facilitated using multivalent virus-inspired particles (Fig. 1a), drug carrier bio-adhesion has been improved using spiky pollen-mimetic particles (Fig. 1b), cellular reprogramming has been enabled using extracellular matrix (ECM)-mimetic, drug-loaded nanofibres, and antimicrobial functions have been increased with antibiotic-eluting, cicada-inspired nanoprotrusions[27–31] (Fig. 1c). Such bioinspired drug carriers have a range of applications, including cancer immunotherapy, gene editing, and treatment of vascular diseases and antibiotic-resistant infections[22,27,28,32]. Several commercialized products with nanotopographical features have recently undergone clinical trials, such as Nano+ (Lepu Medical), a sirolimus drug-eluting nanotopographical stent for the treatment of coronary artery disease (NCT02929030), and the SLActive (Straumann Group) dental implant for improved osseointegration (NCT00782171). Additionally, there are many commercialized products, such as the nanotube-functionalized NanoForticore spinal implant (Nanovis), for which preclinical investigations are still ongoing[33,34].

In this Review, we provide an overview of drug carriers and fabrication approaches used in the nanotopographical engineering of drug delivery systems. We discuss how bioinspired nanotopographical features interface with biological systems to improve drug delivery, including controlled cargo loading and release, bio-adhesion, barrier remodelling, drug uptake and subcellular trafficking, cellular reprogramming, immunomodulation, and antimicrobial activities. We emphasize the biomolecular mechanisms of nanotopographical engagement and their implications for drug delivery. Lastly, we provide an outlook on the future of the bioinspired nanotopographical design of drug delivery systems.

Nanotopographical drug carriers

Nanotopographical drug carriers have at least one design element on the nanoscale. However, the carrier itself can range in size from nanometres (in discrete nanoparticles) to millimetres and centimetres (in wearable patches or implantable stents)[1,5]. Drug carriers can be administered by different delivery routes, including parenteral injection, inhalation, ingestion and implantation. Ingestible materials can have a size of up to millimetres in diameter, whereas injectables and inhalable materials are typically below 10 μm in diameter[3,7]. Drug carriers can be composed of various materials, including hard materials, such as titanium and silica, and soft materials, such as synthetic and biological polymers, in addition to hybrid drug carriers composed of both soft and hard materials[5,35].

Drug carrier classes

Nanostructured thin films, fibrous mats and patches are among the most commonly employed nanotopographical drug-delivering materials. They are composed of a planar substrate with 3D nanotopographical structures such as pores, fibres, pillars or needles[1,5,36]. Films and patches

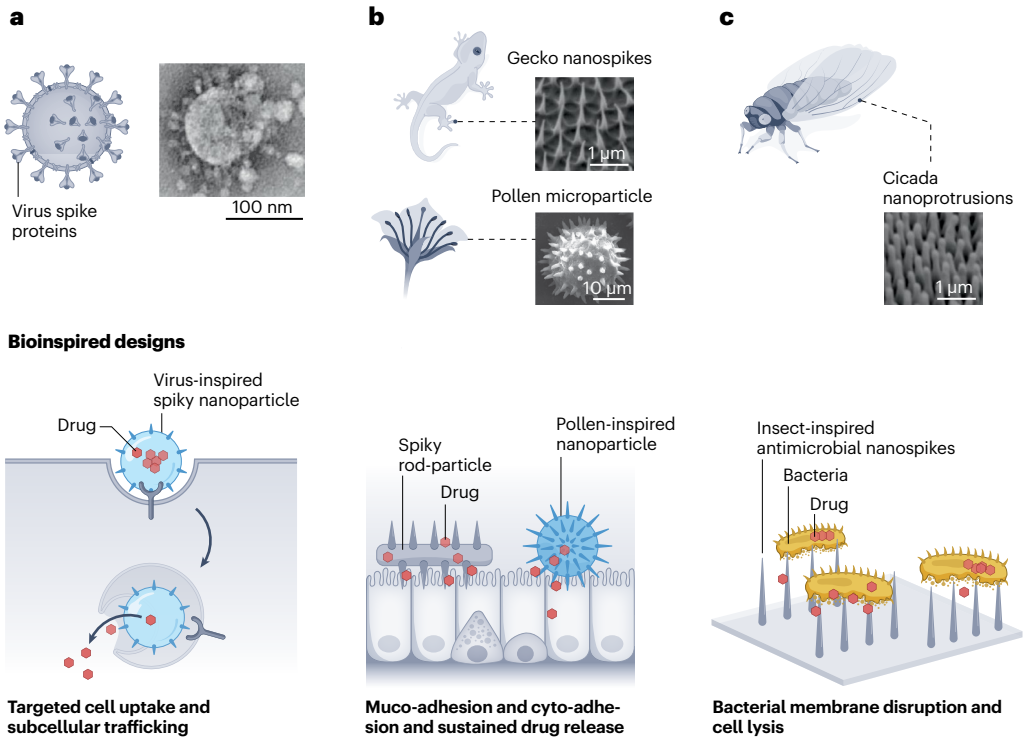

Fig. 1 | Bioinspired nanotopographical materials for drug delivery applications. Nature can serve as inspiration for the design of bioinspired drug carriers. **a**, Virus-inspired spiky particles can improve cell targeting and uptake. **b**, Pollen and gecko-inspired bio-adhesive particles and devices can prolong carrier retention and local drug release. **c**, Antimicrobial nanotopographical surfaces can prevent and treat antibiotic-resistant infections. Part **a** is adapted from (Centers for Disease Control and Prevention (CDC) / C.D. Humphrey; T. G. Ksiazek). Part **b** (Geko nanospikes) is adapted from ref. 22, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/) and part **b** (Pollen microparticle) is adapted from ref. 26, Springer Nature Limited. Part **c** is adapted from ref. 22, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

can be made of inorganic materials, such as silica, or soft materials such as polydimethylsiloxane and polycaprolactone (PCL)[37,38]. Films and patches can be used as wearable devices with gecko-inspired bio-adhesive nanotopographical features (Fig. 1b). They can also be applied as bandages for the treatment of infected wounds with insect wing-inspired antimicrobial nanospikes (Fig. 1c), and in the fabrication of drug-eluting contact lenses for ocular applications[3,31]. The nanotopographies of stents and implants are commonly shaped in the form of nanopillars or nanotubes using inorganic components such as titania (ref. 33). Titania nanotubes can direct osteogenic biointerfaces for orthopaedic applications, limit fibrosis for vascular implants, and control drug loading and release kinetics for drug-eluting stents[32,33].

Microparticle and nanoparticle drug carriers can be composed of inorganic materials, such as silica, gold and silver; synthetic polymers, such as polystyrene and poly(lactic-co-glycolic acid) (PLGA); and biomaterials such as proteins, peptides and polysaccharides[1,5,39]. Nanotopographical surface features, such as spikes inspired by pollen and virus particles, can be fabricated on particle surfaces to improve functions such as bio-adhesion and cellular uptake (Fig. 1a,b)[3,21,40].

Nanotopography fabrication

Nanotopographical features consist of three main classes, that is, protrusions, depressions and heterogeneous surface roughness[14,16]. These classes can encompass an array of features, including bumps, needles, pillars, spikes, tubes, grooves, wrinkles and pores. Fabrication techniques are carefully chosen based on drug carrier type, material components and the desired nanotopography. Both top-down and bottom-up fabrication methods have been used, with top-down lithographic techniques, such as photolithography and colloidal lithography, being the most widely implemented[16,37,41,42]. Other widely used techniques include chemical etching to implement surface roughness, electrochemical anodization to fabricate titania nanotubes, electrospinning to produce nanofibre meshes, and polymer demixing and phase separation for porous or heterogeneous materials. In addition, colloidal self-assembly allows the creation of porous injectable scaffolds, chemical vapour deposition can be applied to build nanoscale features on prefabricated materials, and discrete particles can be fabricated by emulsion or self-assembly (Table 1)[16,18,38,43–47].

These techniques can be applied to create a variety of nanotopographical types and sizes, and are typically used to create a single nanotopography on a single material. However, lithographic techniques can be adapted to fabricate multiple topographies on a single substrate, for example, for high-throughput screening of nanotopographical features to elicit a desired biological response. This high-throughput approach is important to eventually achieve a rational design of nanotopographical drug carriers for specific biomedical applications as certain nanotopographical features may lead to distinct biological responses[16,33]. For example, a 2.2-cm^2 multi-architecture chip array can incorporate both microtopographical and nanotopographical features such as pillars and grooves[48]. These nanotopographical features can

Table 1 | Nanotopography fabrication of drug carriers

Technique	Drug carrier and material types	Nanotopography size and features	Strengths	Limitations	Refs.
Lithography (photolithography and electron beam, focused ion beam, dip pen, colloidal, soft, nanoimprint, micro or nano-moulding, and others)	Thin films, patches and implantable devices; polymers and biomaterials (PDMS, PMMA, PEG, PS, PP, PEEK, silk proteins)	5 nm to hundreds of micrometres; wells, grooves, bumps, channels, pillars, ridges, wrinkles, needles	Control over feature architecture and size scale, reproducibility	Specialized equipment and training, scale-up costs and limitations	16,37,42,45
Polymer demixing and porogen leaching	Thin films, patches and discrete particles; immiscible polymers (PCL-PEG, PS-PLA)	Hundreds of nanometres to hundreds of micrometres; pores, islands and ribbons	Ease of use, accessibility, low cost	Reproducibility, control over size scale	16,38
Electrospinning	Nanofibrous meshes, patches and wearables; polymers and biomaterials (PCL, PLGA, PS, chitosan, fibrinogen)	Widths of 5 nm to tens of micrometres, and macroscale lengths; porous nanofibre scaffolds (aligned or disordered)	High-throughput, relatively accessible equipment, reproducibility	Control over length size scale, limited feature types	16,36
Chemical and electrochemical etching	Stents, thin films, implants and particles; polymers (PCL, PLA) and Inorganic materials (titania, silica)	Tens of nanometres to hundreds of micrometres; tubes, pores, pillars and needles	High-throughput, wide accessibility, diverse substrate choice	Issues with feature control for chemical etching	37,46
Surface roughening and particle deposition	Thin films, patches, implants, stents and microparticles; most surfaces (polymeric and inorganic)	Tens of nanometres to hundreds of micrometres; textures such as bumps and wrinkles, and hydrophobic and hydrophilic patches	Ease of accessibility, low cost	Limited feature types and control over size scales	16
Particle fabrication (emulsions, precipitation, crystallization, self-assembly, hydrogelation, micromoulding and microfluidics)	Microparticles and nanoparticles, and porous self-assembling scaffolds; polymers and biomaterials (PS, PLGA, PCL, PEG, DNA, peptides and proteins), and inorganic materials (silica, gold, silver, and hydroxyapatite)	Tens of nanometres to hundreds of micrometres; particles with spikes, pores, grooves, deformations, patches and asymmetric Janus features	Diversity of materials, reproducibility, low cost, accessibility	Limited feature types that are typically governed by the core material	12,47

PCL, polycaprolactone; PDMS, polydimethylsiloxane; PEG, poly(ethylene glycol); PEEK, polyether ether ketone; PLA, poly(lactic acid); PLGA, poly(lactic-co-glycolic acid); PMMA, poly(methyl methacrylate); PP, polypropylene; PS, polystyrene.

be fabricated by nanoimprint lithography, followed by assembly into a 6 × 6 array. The multi-architecture chip was applied to study the influence of topographical features on neuronal differentiation, demonstrating that anisotropic gratings enhance neuronal differentiation, whereas isotropic pillars promote glial differentiation[48]. Similarly, the 'NanoTopoChip' platform enables the fabrication of over 1,200 different nanotopographies on a single 4-cm^2 polystyrene chip using UV projection and nanoimprint lithographies[49]. Using these chips and bioinformatic tools, the relationship between osteosarcoma cell morphology and surface nanotopography could be investigated. The study demonstrates how actin fibre assembly and cell spreading respond to nanostructured surfaces. These findings have implications for implantable device fabrication to reduce cell spreading and biofouling, and for tissue engineering surfaces to promote morphology-induced stem-cell differentiation[49]. Such high-throughput nanotopography screening platforms can be applied to study cellular reprogramming and differentiation[50,51] and to screen bioinspired topographies on polystyrene surfaces to develop new antimicrobial materials[52].

Cargo loading and release

Drug loading can be achieved during the initial fabrication process of the delivery system or post-fabrication using a layer-by-layer technique or physicochemical adsorption methods[3,39,53,54]. Nanotopographical features influence drug loading and release kinetics, especially in post-fabrication loading. Drug release profiles can range from burst release to sustained zero-order release kinetics. The required release pattern depends on the disease target, delivery site and cargo type, among other factors. Drug loading and release profiles need to be optimized for each case. However, general design parameters for drug carriers have been established focusing on the influence of material type, nanotopography, particle size and surface chemistry. Importantly, nanotopography, for example, nanoporous scaffolds, nanofibrous mats, nanostructured microneedles and nanotubes, impacts cargo loading and release kinetics[17,19,36,55–59].

A large surface area increases drug loading, and drug release can be prolonged by limiting drug diffusion by establishing confined spaces[59–61]. For example, IgG protein pellets loaded into nanoporous PCL thin films demonstrate sustained zero-order release of IgG for 6 months[60]. Electrospun cellulose acetate nanofibrous scaffolds achieve 70% loading efficiency and sustained zero-order release kinetics of ferulic acid as a model small-molecule drug over 48 h (ref. 62). Drug release kinetics can be further influenced by combining the nanotopographical and surface chemistry features of the delivery system, such as electrostatics and hydrophobicity, as well as the molecular weight of the cargo[60,63,64].

Nanotopographical features can also increase drug loading in colloidal particles; for example, silica nanoparticles with nanotopographical morphologies inspired by rambutans, raspberries and flowers can be loaded with DNA plasmids to improve cellular transfection[65]. Rambutan-mimicking particles with spiky features provide a large surface area for multivalent DNA binding, thus enabling high plasmid loading of 133 ng DNA per microgram of particles with transfection efficiencies of up to

88% in HEK-293 T cells (a stable clone derivative of the human embryonic kidney 293 cell line). Self-assembly of polymerized small interfering RNA (siRNA) into microsponges with nanotopographical pores also increases the loading capacity and allows controlled ratiometric encapsulation of multiple siRNA types into a single drug carrier[66]. Furthermore, these approaches can protect nucleic acids from nuclease-mediated degradation, improving the in vivo stability of nucleic acids.

Loading and release of multiple drugs or bioactive cargo into a single carrier is desirable for many biomedical applications[67,68]. Nanotopographical features can enable spatially separate loading and temporally independent release profiles of different cargos within the same drug carrier[69–72]. For example, an electrospun nanofibrous scaffold can be loaded with tenofovir and levonorgestrel for the prevention of infection by human immunodeficiency virus and pregnancy, respectively[69]. In this scaffold, drug release rates are controlled by either stacked or interwoven mixtures of single drug-loaded nanofibres in comparison to co-loading of both drugs in a homogenous mesh of nanofibres. Patchy nanoparticles, with separate patch and core components, can be prepared by triblock terpolymer self-assembly for multi-drug loading and release[70]. For example, cyanine 5 dye can be encapsulated in the core of these particles and the cancer drug doxorubicin can be loaded in the patches. Although independent release kinetics of cyanine 5 dye and doxorubicin have not been assessed in this case, such polymeric self-assembly approaches could be applied to match the physicochemical properties of the core and patch polymers to their respective cargos to enable independent loading and release.

Biofunctionalities for drug delivery

Various bioinspired nanotopographical functionalities can be applied to improve drug delivery. For each function, we highlight key material design criteria, biomolecular and physiological mechanisms of action, and important examples that demonstrate translational potential for drug delivery.

Bio-adhesion

Naturally occurring nanotopographical materials often function to enhance adhesive properties through increased surface contact areas as is the case for pollen microparticles and spatula-shaped seta nanoarrays on gecko feet[21,73]. Bioinspired synthetic nanotopographical drug carriers with improved bio-adhesion can increase the residence times and half-lives of bioactive cargo and improve their therapeutic efficacies. This, in turn, can lower dosing and reduce off-target effects and side effects. For example, gecko-inspired nanotopographical bio-adhesives can be made from PLGA elastomeric films with dextran-coated nanopillar arrays[74]. Adhesive bilayer wraps to prevent abdominal adhesions can be engineered using electrospun dopamine-coated gelatin nanofibres with a poly(ethylene glycol) (PEG) hydrogel foam[75]. The nanofibrous mesh promotes abdominal tissue adhesion and ECM-mimetic cellular attachment through gelatin-mediated integrin engagement and nanostructured increases in cell–material surface contact areas. The PEG foam provides a spatially segregated, non-biofouling surface as well as mechanical properties of toughness and elongation for easy handling and application of the wrap. A hydrogel bio-adhesive to promote tendon healing following surgery can be made with spatially segregated adhesive chitosan and non-adhesive alginate sections. The hydrogel allows tendon gliding in live porcine patellar tendon, flexor tendon and Achilles tendon, as well as in human cadaveric wrists[76]. This asymmetric hydrogel can further be loaded with microparticle drug crystals of a corticosteroid for drug dissolution and sustained release.

Muco-adhesive nanotopographical materials can establish a biointerface between drug carriers and mucosal surfaces, for example, for ocular, pulmonary, oral and vaginal drug delivery[3,5,77]. For instance, a biodegradable and muco-adhesive poly(vinyl alcohol) and poly(vinyl pyrrolidone) nanofibrous mesh with embedded mucus-penetrating PEGylated nanoparticles was loaded with etravirine as an antiretroviral drug delivery system for vaginal application for human immunodeficiency virus prevention in mice[78]. Nanofibrous meshes provide sustained release of nanoparticles and a 30-fold improvement in vaginal residence of drug cargo after 3 days compared to mucus-penetrating nanoparticles alone.

Nanotopographical features can also be engineered on the surfaces of microparticles and nanoparticles to improve bio-adhesion. For example, the nanotopographical features of pollen microparticles, such as spikes, bumps and wrinkles, can be mimicked to improve cyto-adhesion[79]. Pollen-inspired particles with protruding nanotopographies improve bio-adhesive properties and biointerfaces (Fig. 2a)[9,80,81]. In addition, porous PCL microparticles mimicking Canola flower pollen grains increase binding to mucosal surfaces and cervical cancer cells through a high number of surface contact points[82]. However, controlling nanotopography together with other biointerfacial features, such as particle morphology and surface charge, will be needed to optimize the muco-adhesive and cyto-adhesive properties of pollen-inspired particles.

Nanostructured fibrous microparticles composed of PLGA and PEG can be applied as muco-adhesive drug carriers for ocular, oral and nasal drug delivery[83–86]. These microparticles improve in vivo muco-adhesion and retention through increased surface contact areas, compared to smooth microparticles, increasing the therapeutic efficacies of diverse cargos, including brimonidine for glaucoma and resveratrol for the treatment of nasal polyps. Nanostructured microparticles can also be designed with dendrite-mimetic nanofibrillar features through polymer precipitation in highly turbulent flow[87]. Dendritic particles can be fabricated from polymers, such as polystyrene, and display strong adhesive forces leading to tough hydrogel formation through increased dendritic contact points. These materials could potentially be applied as bio-adhesives[87].

Strong bio-adhesion can improve the half-lives and local retention of therapeutics. However, low bio-adhesion can also advance therapeutic outcomes by preventing biofouling and inflammatory responses. For example, nanotopographical thin films and surfaces inspired by lotus leaf topographies have anti-adhesive properties[88,89].

Barrier remodelling

Alternative delivery approaches to parenteral injection, for example, oral, dermal and inhalation routes, can increase patient compliance. However, biophysical barriers, consisting of epithelial cells with dynamic nanostructured tight junction complexes, which prevent pathogens, toxins and other foreign materials from entering the body[90], can hinder the delivery, tissue penetration, and absorption of hydrophilic and large-molecular-weight drugs such as antibodies, peptides and oligonucleotides[3,90]. Tight junctions, which are made of cross-linked complexes of transmembrane and membrane-associated proteins such as zonula occludens 1 (ZO1), regulate solute paracellular permeability and are sensitive to various external stimuli[91–93]. Particularly, ZO1 interacts both with transmembrane proteins and the cytoskeleton protein F-actin. ZO1 is recognized as a key mediator for tight junction mechanosensing through the formation of protein phase separation and tight junction turnover[94,95].

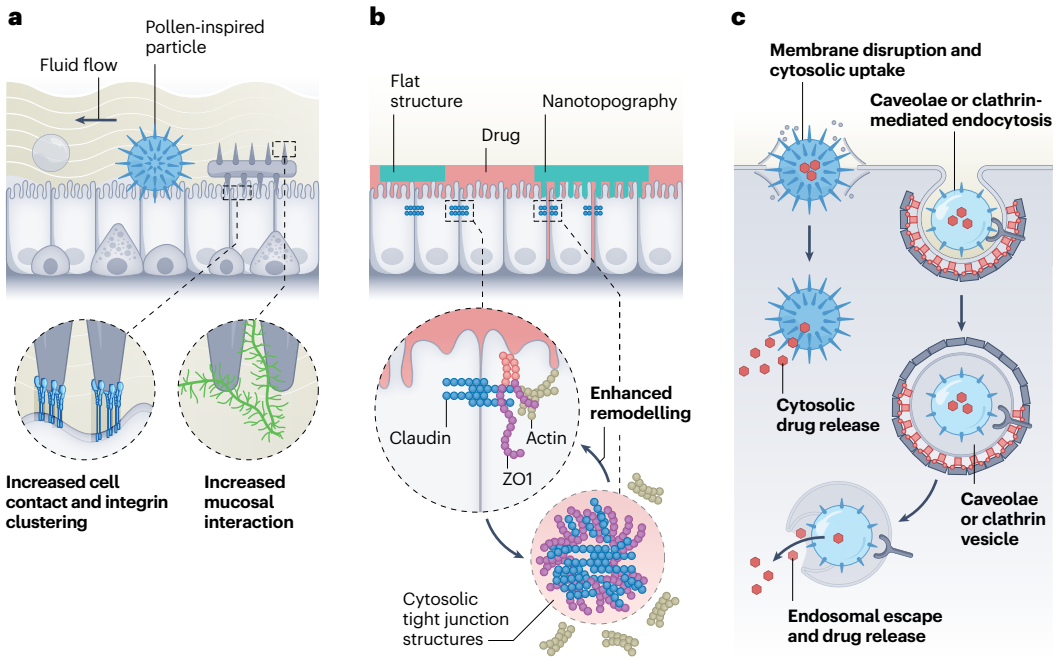

Fig. 2 | Nanotopographical biointerfaces to increase drug retention and uptake. a, Nanotopography can lead to enhanced interactions with cellular and mucosal barriers, reducing drug carrier flow rates and increasing residence times to prolong drug release at the site of action. By engineering the drug carrier aspect ratio and surface chemistry, further improvements in bio-adhesive properties can be achieved. **b**, Nanotopography modulates epithelial tight junctions and promotes drug penetration across epithelial barriers through integrin engagement and dynamic zonula occludens 1 (ZO1) remodelling. **c**, Nanotopographical features, such as protrusions and pillars, promote endolysosomal uptake of particles. Alternatively, nanoneedles on the surface of particles can cause membrane disruption and direct cytosolic uptake.

Inspired by the 3D nanostructures of tight junctions, nanotopographical surfaces and planar microparticles with protruding features have been designed to probe epithelial barriers, modulate tight junctions and increase transepithelial transport of biologics[14,93]. Importantly, tight junction modulation is reversible and does not lead to epithelial damage or dysfunction[14]. For example, microneedles with surfaces of nanotopographical pillars can improve the transdermal delivery of etanercept, an antibody therapeutic, in rat and rabbit models[96]. Nanotopography-mediated transepithelial delivery is dependent on integrin receptor binding and myosin light chain kinase (MLCK) phosphorylation[96]; however, key mechanisms and pathways remain unknown. To address this knowledge gap, nanotopographical thin films with nanopillars were applied for the delivery of fluorescently labelled IgG through epithelial monolayers[97]. Total internal reflection microscopy was then used to visualize and quantify the transportation routes of IgG with cell-level resolution in real time[97]. Here, nanotopographical thin films stimulated the paracellular transport of IgG by increasing the dynamic turnover of tight junction structures. This remodelling is mediated through cytosolic liquid complexes 1–5 µm in size, involving ZO1, claudin-family transmembrane tight junction proteins and cytoskeleton F-actin. The findings demonstrate a previously unknown mechanism of nanotopography-mediated tight junction signal transduction (Fig. 2b). This phenomenon agrees with reports showing the role of ZO1 protein phase separation in tight junction mechanosensing[94,95].

To enable clinical translation, these nanotopographical microneedles have been incorporated into the commercial patch device SOFUSA, allowing epithelial tight junction remodelling and, thus, tumour reduction in mouse models of mammary carcinoma by delivering anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA4) antibodies and transdermal lymphatic delivery of fluorescently labelled proteins in human volunteers[34,98]. Therefore, this technology may be useful for the delivery of immunomodulatory signals to treat cancer and autoimmune diseases.

Cellular uptake and subcellular trafficking

The biointerface between drug carriers and target cells directs cellular uptake and subcellular trafficking of cargos. However, targeted nanoparticle uptake can be challenging owing to non-specific uptake in off-target cells and nanoparticle entrapment in endosomes and lysosomes, which prevents drug delivery into the cytosol[3,99]. Viruses are one of nature's most efficient examples of nano-mediated cellular uptake and trafficking. Viruses use nanotopography in multiple ways to enable infection and gene delivery, induce multivalent interactions between protruding coat proteins and cell membranes to initiate cellular binding and uptake, and they can use nanoscale needles to inject genetic material directly into the cytosol of target cells[100]. Thus, virus-inspired nanomaterials can improve cellular uptake and subcellular trafficking.

Virus-inspired topographical nanoneedles can improve cytosolic uptake of drug cargo either through direct membrane penetration and cytosolic injection of cargo, for example, nanostraw technologies[101,102], or through the promotion of cellular endolysosomal uptake mechanisms. Polymeric nanostraws can be fabricated as an array of hollow nanotubes connected to a drug reservoir for the delivery of bioactive cargos, such as plasmids and small drug molecules, into

cells. Upon seeding of Chinese hamster ovary cells on top of nanostraw surfaces, the nanostraws can penetrate through the cell membrane and allow cytosolic delivery of bioactive cargos[102]. The formation of adhesion complexes involving paxillin, actin, vinculin and integrin α5 was observed to correspond with nanostraw penetration. However, further studies are needed to elucidate the exact mechanism of action of nanostraw penetration. Coupling nanostraw arrays with low-voltage electroporation increases transfection in multiple cell types, including HEK-293T cells, stem cells and human fibroblasts, with various gene-editing agents, including mRNA, DNA and Cas9 ribonucleoproteins[103]. Alternatively, nanoneedles can promote cellular endolysosomal uptake mechanisms for the delivery of nucleic acids such as the use of siRNA, proteins and quantum dots[104]. Here, clathrin pits and caveolae are formed around the nanoneedle–cell biointerface and, thus, cargo can be delivered into endolysosomal compartments[105]. However, only 60% of nanoneedle-delivered siRNA is internalized through endolysosomal uptake and, therefore, other mechanisms of cellular uptake must occur, for example, through direct cytosolic penetration. Displaying nanoneedles on microparticles may better mimic the nanoneedle injectors of natural viruses, which may allow intravenous or inhalation administration.

Virus-inspired spiky particles can increase cellular uptake by mimicking the multivalent interactions between virus coat proteins and cellular surface receptors (Fig. 2c). These nanotopographical features influence biointerfaces, including protein corona formation, cell membrane interactions, cellular uptake and endolysosomal escape. The protein corona, which is formed following particle injection, can promote particle uptake and clearance by macrophages, alter biodistribution profiles, and impair cell binding of targeting moieties[3,106]. Therefore, protein corona formation should be limited, for instance, by implementing antifouling polymers, such as PEG, and zwitterionic ligands such as phosphorylcholine[106]. Alternatively, nanotopography can be exploited to alter protein corona formation; for example, glycosylated polymeric nanoparticles with patchy morphologies promote the localization of glycopolymer bundles on particle surfaces[107], thereby preventing non-specific protein adsorption and allowing specific lectin–glycan interactions and, thus, cell-specific uptake. By contrast, spherical non-patchy particles of the same material composition show non-specific protein corona formation and cellular uptake.

Virus-inspired particles are typically fabricated from inorganic materials, such as silica, using epitaxial growth strategies to form spikes, pillars or tubes on their surfaces[28,108,109]. For example, virus-inspired mesoporous silica nanoparticles with nanotube protrusions increase cellular uptake in HeLa cells compared to non-porous or mesoporous silica nanoparticles without nanotube protrusions[28]. Interestingly, these virus-inspired nanoparticles are predominantly taken up by cells through caveolae-mediated endocytosis and macropinocytosis rather than through clathrin-mediated pathways, by which the smooth particles are typically endocytosed. Furthermore, these nanoparticles can be functionalized with doxorubicin to target and kill cancer cells, demonstrating enhanced HeLa cell killing compared to non-nanotopographical mesoporous silica nanoparticles[28]. Virus-inspired spiky titania microparticles can be functionalized with positively charged polyethyleneimine polymers for siRNA delivery[109]. The spiky particles facilitate membrane penetration and cytosolic particle uptake, leading to high siRNA transfection compared to smooth and rough particles, which are taken up by endolysosomal mechanisms. Importantly, high cellular uptake of virus-inspired spiky titania microparticles is related to functionalization with positively charged polyethylenimine[109], highlighting the importance of surface chemistry.

Nanotopographical particles can also be synthesized from soft materials by polymeric self-assembly[107,110]. Similarly, nanotemplate-mediated fabrication allows the engineering of PCL cylinder-shaped high-aspect-ratio particles with phage-inspired multivalent spindles at the particle tip that can initiate cancer cell binding[111]. In addition to protruding features (such as spikes and needles), depressions (such as grooves and wrinkles) can also increase cell contact areas to increase cellular drug uptake[112–114]. Refined techniques will be needed to thoroughly characterize particle surfaces and decouple variables such as surface chemistry and roughness. For example, super-resolution microscopy with DNA-based point accumulation for imaging in nanoscale topography enables nanoscale mapping of functional sites on microparticles and nanoparticles[115,116].

Cellular signalling and modulation

Nanomaterials can be designed to improve the delivery of therapeutics that target biochemical pathways regulating cell signalling, for example, to modulate signalling in fibroblasts and osteoclasts for regenerative medicine or in immune cells for the treatment of autoimmune disorders and cancer[32,117–119]. Cells can sense and respond to biophysical cues in the ECM such as stiffness and substrate topography (Fig. 3a), which guides cell behaviour, differentiation and function[119]. The ECM biointerface is mediated through the mechanotransduction of forces through the nanotopographies of the ECM transmitted from cell–cell junctions and integrin-based cell adhesion[120,121]. Inspired by the nanotopographical ECM, nanoscale delivery systems can be designed that induce biophysical signalling in conjunction with soluble factor delivery to modulate cell behaviour and function.

Tissue regeneration and wound healing can be promoted with biomaterials that have ECM-mimicking 3D surface topographies and that incorporate soluble biochemical factors[47,119,122,123]. For example, a vertically oriented PLGA nanopatterned patch with 800 nm ridges can be fabricated by capillary force lithography. The patches promote human dermal fibroblast adhesion in vitro and can release fibroblast growth factor 2 (FGF2) to accelerate wound closure after 21 days in an athymic mouse model of full-thickness skin wounds[124]. Similarly, two-dimensional PLGA surfaces with 400 nm and 800 nm nanogrooves coated with 3,4-dihydroxy-l-phenylalanine for improved fibronectin and poly-L-lysine attachment can trigger human neural stem cell differentiation. These polymeric surfaces can guide cell alignment along the nanogrooves through focal adhesion formation and alignment with F-actin[125]. The addition of soluble nerve growth factor to the culture medium further increases the expression of the neuronal markers class III β-tubulin (Tuj1) and microtubule-associated protein 2 (MAP2)[125].

ECM-mimetic nanolattice structures with tetrakaidecahedral periodic geometry can be fabricated by two-photon lithography direct laser writing and then coated with titanium or tungsten[126]. These nanolattices are inspired by the osteoblast microenvironment to provide optimal conditions for cell growth at the bone–implant interface during early osteointegration of orthopaedic implants[126]. Substrates can be engineered to modulate mechanical stiffness independent of nanotopography, with a stiffness similar to cartilage (0.7 MPa). The ECM-mimetic nanolattice enhances osteoblast functional activity of human sarcoma osteogenic cells (SAOS-2), increases intracellular F-actin levels by 20% and promotes 40% greater secretion of calcium and phosphorus[126]. This approach of independently optimizing physicochemical

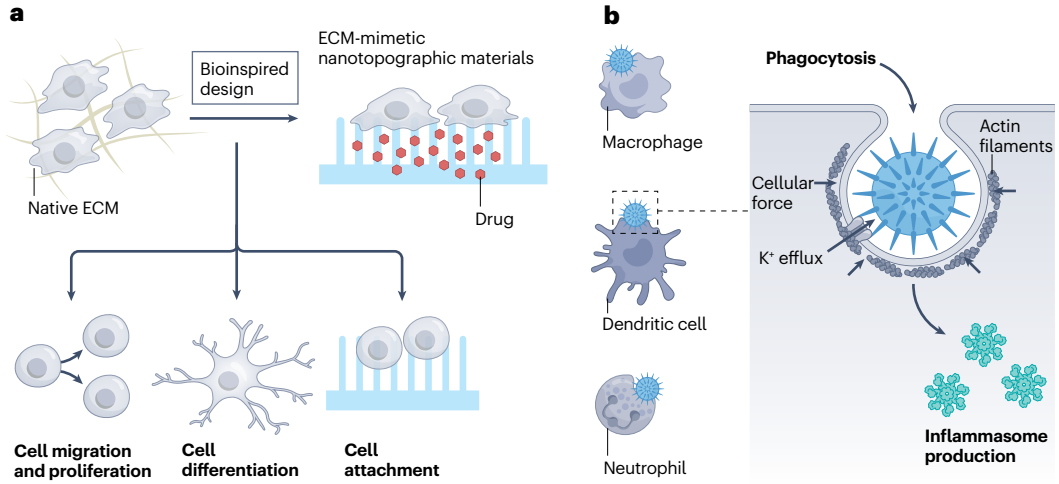

Fig. 3 | Nanotopography for cellular reprogramming and modulation. **a**, Nanoscale surface modification of materials inspired by the native extracellular matrix (ECM) can influence cell behaviour, differentiation and attachment through a combination of biophysical and biochemical cues. **b**, Discrete microparticles and nanoparticles with topographical features, such as spikes and pillars, enable immune activation of macrophages and dendritic cells during phagocytosis through mechanosensitive pathways and increase inflammasome production.

parameters and nanotopography could be applied to other scaffold types and may lead to enhanced tissue remodelling.

Immunomodulatory nanotopographical materials can be inspired by nanotopographical biointerfaces involved in the host immune defence[127]. For example, spiky microbe-inspired particles increase the activation of innate immune cells, such as dendritic cells and macrophages, to amplify adaptive immunity[27,128–131]. In another example, nanotopographical spiky titania microparticles cause mechanical stress in the cell membrane during phagocytosis in antigen-presenting cells. This leads to the activation of K^+ efflux, caspase 1, and the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome (Fig. 3b)[129]. These nanotopographical features activate the innate immune system only in the presence of certain biological stimulants, such as lipopolysaccharides, to tailor specific immune responses and avoid general immunogenicity and inflammation. Nanotopographies, for example, nanogrooves, can also guide T cell migration[132]. Depending on the confinement from the surrounding environment, T cells exhibit different mechanisms for nanotopography-guided migration. Without confinement, actin-polymerization leads to edge protrusion along nanogrooves through integrin-mediated adhesion. With confinement, migration is purely driven by mechanical effects, independent of integrin signalling. Elucidation of how natural nanotopographies, such as spiky nanostructures on bacteria and viruses, participate in the activation of the innate immune system during microbial invasion will aid in the engineering of synthetic bioinspired nanotopographical surfaces to improve the immunogenicity or adjuvanticity of biomaterial-based cancer immunotherapy and prophylactic vaccines.

Surface nanotopography also plays an important role in regulating protein adsorption onto biomaterial surfaces and modulating subsequent inflammatory responses[133–135]. For example, pre-adsorption of albumin onto gold nanoparticles with hill-like nanoprotrusions results in the loss of the α-helical structure of the protein. This, in turn, decreases the level of pro-inflammatory cytokine expression in the human monocytic cell line dTHP-1 (ref. 136). IgG antibodies adsorbed onto nanotopographical surfaces formed from silica nanoparticle deposition onto two-dimensional substrates lead to particle size-dependent and curvature-dependent immune complement C1q binding. The low curvature on the largest nanoparticles (68 nm) leads to increased binding of C1q compared to smaller nanoparticles, likely owing to the geometric arrangement of adsorbed IgG and distance between the C1q binding regions on neighbouring IgG molecules rather than to the total IgG absorption levels or secondary structural changes in IgG[137].

It is important to investigate the relationship between specific surface features and their biophysical influence on cellular behaviour, for example, using large-scale combinatorial nanotopographical cue arrays[51]. Importantly, combining the controlled release of cargos, such as cytokines and growth factors, with nanotopographical features may induce synergistic effects on cell signalling.

Antimicrobial interfaces

Nanoscale drug delivery strategies are being explored for the treatment of microbial infections, mainly bacterial pathogens[138,139]. Nanomaterials can work synergistically with antibiotics to enhance antibiotic activity against resistant bacterial biofilms[139–142]. For example, antibiotic-releasing nanotopographical materials, such as titania nanotubes, can prevent biofilm formation on implant materials and promote osseointegration through nanostructured integrin clustering on the nanotube biointerface[55,143,144]. Such titania nanotube arrays can deliver nucleosidase inhibitors to prevent the formation of *Staphylococcus cohnii* biofilms and promote osteogenic differentiation of human mesenchymal stem cells in vitro[145]. Therefore, such drug-eluting titania nanotubes are promising as orthopaedic and dental implants; however, only few antimicrobial-eluting titania nanotube materials have been tested in animal models of infection thus far[55,144].

Bioinspired nanotopography can further promote the antimicrobial properties of nanomaterials (Fig. 4). Natural antimicrobial microtopographical and nanotopographical surfaces and biointerfaces can be divided into anti-biofouling and bactericidal surfaces[146]. Anti-biofouling topographies are best represented by lotus leaves, which

contain microstructured and nanostructured superhydrophobic wettable surfaces that prevent bacterial adhesion and biofilm formation[147,148], which can be mimicked by slippery liquid-infused porous surfaces[89,149]. Bactericidal nanotopographies cause direct bacterial killing through membrane rupture and cell lysis[31]. Natural bactericidal nanotopographies include nanopillars on the wings of cicadas and dragonflies as well as nanospikes on the skins of lizards[31,150,151]. In contrast to anti-biofouling surfaces, these high-aspect-ratio nanostructures are bacterio-adhesive. Upon microbial attachment, bacterial membranes deform around the nanostructures, causing membrane stress and subsequent cell death[146,150–152]. Interestingly, such high-aspect-ratio nanostructures are not toxic to mammalian cells. Owing to their elastic membranes and larger size, mammalian cells can withstand the stress that causes bacterial membrane rupture, instead leading to mammalian cell membrane deformation and nanostructured invagination[146]. Similarly, cell-penetrating nanoneedles can enable cytosolic uptake of drugs into mammalian cells without causing cell death[104].

Synthetic nanospike and nanopillar topographic materials, inspired by insect wings, allow contact-based killing of bacteria and inhibition of biofilm formation (Fig. 4a). For example, nanotopographical bactericidal black silicon that contains nanospike arrays can kill both gram-negative and gram-positive bacteria at a rate of up to 450,000 cells per minute per square centimetre in planktonic bacterial cultures[153]. Other nanotopographies, such as nanopillars inspired by cicada wings, are less effective against more rigid gram-positive pathogens, which can withstand greater mechanical forces and resist membrane rupture when compared to their less rigid counterparts[152]. Combining bactericidal nanotopographies with antibiotic-eluting materials could offer a synergistic approach to eradicate antibiotic-resistant bacterial infections. For example, boron nitride films with bactericidal nanospike surfaces can be loaded with gentamicin and amphotericin B[154]. These drug-eluting nanomaterials are effective against bacterial and fungal infections (*Escherichia coli* and *Neurospora crassa*, respectively). A potential complication of contact-mediated bacterial killing for the development of sterile surfaces is the presence of residual dead bacteria, which can impair material functionalities over time. To address this problem, a nanopillar array can be functionalized with thermoresponsive poly(*N*-isopropyl acrylamide) polymer brushes, which change from a hydrophobic to hydrophilic architecture in response to temperature[155]. At temperatures less than 37 °C, the nanopillars become hydrophilic and release the adhered dead bacteria, which may allow the development of antimicrobial surfaces that can be washed and recycled for repeated use.

In addition to macroscopic surfaces and films, antimicrobial particles can be designed with bioinspired nanotopographical features such as spikes and pillars (Fig. 4b). For example, pollen-inspired silica nanoparticles can be loaded with the antimicrobial enzyme lysozyme for sustained release over 72 h (ref. 156). Upon addition to *E. coli* cultures, pollen-inspired silica nanoparticles adhere to bacterial membranes and release lysozyme in proximity to bacterial targets for enhanced antimicrobial effect, both in planktonic in vitro models and in an ex vivo rat intestinal infection model. Similarly, spiky virus-inspired mesoporous silica nanoparticles can be loaded with the antimicrobial peptide cathelicidin LL-37 (ref. 157), which destabilizes bacterial membranes, causing membrane rupture and cell lysis. The spiky particles promote particle penetration into bacterial membranes and membrane-targeted release of the antimicrobial peptide, enhancing bacterial killing compared to smooth, drug-loaded particles. Alternatively, nanoscale surface features can be implemented in materials with inherent antimicrobial properties[158] such as silver and gold nanoparticles, as well as natural and synthetic polymers[139].

Nanomaterial-based drug delivery strategies are also applied to treat or prevent viral infections, for example, in the form of mRNA COVID-19 vaccines[140,159]. Nanotopographical materials, such as nanofibrous mats, are often employed to improve the delivery of antivirals by enabling long local retention and strong bio-adhesion[78,160]. Viruses, such as SARS-CoV-2, typically have nanotopographical surface adhesive properties that are dependent on biointerfacial physicochemical characteristics such as electrostatics and hydrophobicity[161]. Nanotopographical, virus-mimetic particles can be applied to inhibit the

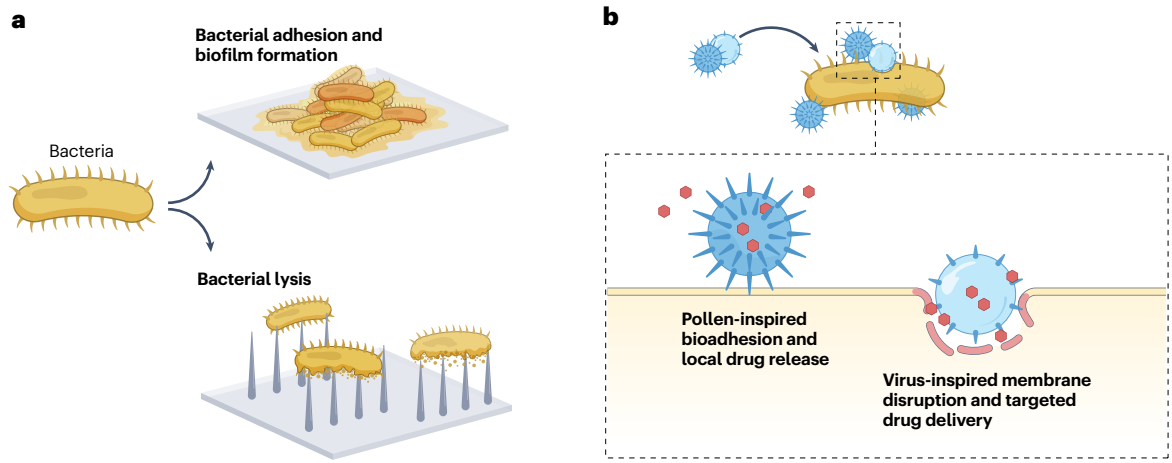

Fig. 4 | Antimicrobial nanotopographical interfaces. a, Nanotopographical surfaces with spike and pillar arrays, inspired by insect wings, cause bacterial membrane disruption through biophysical stress, leading to bacterial lysis. This is in comparison to flat non-structured surfaces that can promote biofilm formation and development. Nanospiked surfaces can create sterile antimicrobial surfaces and prevent biofilm formation on orthopaedic and dental implants. **b**, Nanotopographical particles as antimicrobial drug carriers enable pollen-inspired bio-adhesion for local drug release, virus-inspired membrane destabilization and drug delivery into bacterial membranes. Virus-inspired membrane destabilization offers particular promise in the delivery of antimicrobials, which act on the bacterial membrane.

infectivity of the influenza A virus[162]. The particles closely match the size and spiky topography of the influenza A virus and are functionalized with ligands to bind to haemagglutinin and neuraminidase viral coat proteins. Owing to the topology-matching design, the synthetic virus-mimetic particles attach to the virus through multivalent interactions and inhibit viral uptake into host cells and viral replication. Such strategies could be applied with drug-loaded nanoparticles to block viral cell entry and replication and stimulate the immune system for local inflammation and viral clearance. Thus, bioinspired nanotopographical materials show promise in the prevention and treatment of various microbial infections, including bacterial, fungal and viral infections.

Outlook

Nanostructured drug carriers have revolutionized the field of drug delivery by enabling nanoscale interactions and interfaces with key biological systems, including tissue and mucosal barriers, the immune system, and cellular membranes[3]. By getting inspiration from natural nanotopographical materials and biointerfaces, drug delivery systems can improve therapeutic outcomes by regulating biofunctionalities such as bio-adhesion and cellular uptake. Design criteria for the creation of biointerfacing nanotopographical drug carriers for various biomedical applications, including cancer treatment, regenerative medicine and infectious disease, include size, nanotopographical features, material components and drug release profiles. Furthermore, stability, administration route, biodegradation pathways and possible immunogenicity of the drug carrier material need to be considered. Careful investigations of these properties and how they are influenced by nanotopographical features are essential in evaluating the therapeutic potential of each drug carrier under development.

In addition, several key challenges remain to be addressed to enable the clinical translation of nanotopographical nanoscale drug delivery devices. Investigations of the effects of nanotopographical cues on biological systems need to decouple variables, such as surface chemistries and material components, to elucidate the mechanisms of action. Moreover, model organisms and in vitro cell culture setups need to recapitulate the physiological target of interest. Importantly,

Box 1

Translational considerations

Several nanotopographical drug delivery systems have undergone commercialization and evaluation in clinical trials such as the SOFUSA nanotopographical microneedle patch and the Nano+ (Lepu Medical) drug-eluting stent[33,34]. However, challenges remain to promote the clinical translation of nanotopographical drug delivery systems.

Experimental design

Most cell studies involving nanotopographical materials use two-dimensional cell cultures. However, three-dimensional cell culture models incorporating extracellular matrix-mimetic hydrogels and organoid models may be more appropriate for in vitro evaluation of nanotopographical materials to evaluate the effect of the surrounding cell and extracellular matrix microenvironments in wounds or tumours on, for example, cell behaviour. Selection and design of preclinical animal experiments to accurately model outcomes of clinical trials depend on the pathophysiology, disease processes and injury response. Therefore, animal models need to be selected that have similar physiological responses as humans. For example, transgenic mouse models, such as mucin knockout mice, allow the selection of mucus compositions that are associated with specific disease states[164]. Similarly, humanized immune system mouse models offer opportunities to test immunomodulatory nanotopographical materials in complex in vivo conditions that reflect the immune system in patients[165]. Alternatively, non-rodent models may provide more disease-relevant physiological conditions, depending on the target, such as ferret models with cystic fibrosis transmembrane receptor knockouts, which recapitulate the mucosal environment of lungs with cystic fibrosis[166]. Large animals, such as dogs, pigs and sheep, can serve as models for cardiovascular disease and vascular graft development because their vascular anatomy and haemodynamics are more similar to those of humans compared to those of rodents and rabbits[167]. Furthermore, the influence of nanotopography on the degradation and clearance of the delivery system remains largely unknown. The influence of other physicochemical design parameters, such as particle morphology and surface chemistry, has been well studied, which could inform the in vivo evaluation of nanotopographical drug carriers[7]. Lastly, drug carrier degradation products may be difficult to detect in short-term in vivo experiments and may require long-term observation to monitor side effects.

Production

Scale-up of nanotopographical feature fabrication and reproducibility of manufacturing remain key challenges, in particular for lithographic techniques, which can be time consuming and require specialized equipment that may only handle certain sizes of substrates. Additionally, the time required to install nanotopographies onto two-dimensional surfaces using lithography increases with surface size. Therefore, materials for large animal studies and clinical trials require substantially more time to fabricate compared to small animal models. Polymer mixing and porogen leaching offer more scalable approaches, although they may lack reproducibility; thus, there is a balance between reproducibility and scale-up that needs to be addressed.

Regulatory

Safety and efficacy need to be demonstrated to achieve regulatory approval. The regulatory process depends on the materials and whether any component has pre-existing approval. Many nanotopographical drug delivery systems contain polydimethylsiloxane, polystyrene and silica nanoparticles owing to their compatibility with diverse fabrication techniques. Clinically approved materials, such as titanium, poly(lactic-co-glycolic acid) or polycaprolactone, may expedite the transition to clinical trials.

owing to their 3D features, nanotopographical materials should be studied using 3D cell cultures or organoids. Furthermore, product scale-up and clinical translation need to be considered early in the development process (Box 1).

Nanotopographical biofunctionalities could further be combined with immunomodulation and cellular reprogramming to allow controlled drug release and to ultimately improve therapeutic outcomes. For example, microbe-inspired immunomodulatory nanotopographies could be combined with cytokine or chemokine delivery to trigger cell differentiation, deliver multiple growth factors with independent release kinetics, and enable cell-targeted adhesion and uptake of drug carriers. Integration with other physicochemical design parameters, such as surface chemistry modification, would allow the engineering of dynamic stimuli-responsive materials to enable site-specific triggering of biological events in response to microenvironmental cues[163]. Bioinspired bactericidal nanotopographical delivery systems could also contain antimicrobial material components and deliver antibiotics, providing a three-pronged approach to the treatment of antibiotic-resistant infections. Finally, drug carriers could be developed that alter their nanotopographical features in vivo depending on the surrounding environments to provide site-specific functions such as adhesion, cellular uptake, immunomodulation or drug release.

Citation diversity statement

Recent work in several fields of science has identified a disparity in citation practices, such that papers from women and other minority scholars are undercited relative to the number of papers in the field[168–171]. Additionally, citations have been skewed regarding the home institutes, nationalities and career stages of scholars. As citations directly influence the visibility and success of scientists and scholars[168], it is imperative that we make every effort to recognize and correct this bias. We have therefore worked diligently to ensure that we are referencing appropriate papers with the goal of fair inclusion regarding author gender, race, ethnicity, nationality, institute, and career stage. We further acknowledge that our efforts are limited, without full knowledge of author gender, race and ethnicity, and look forward to future work that could help us to better understand how to support equitable practices in science. This citation diversity statement was adapted in part from resources provided by the Biomedical Engineering Society and Zurn et al.[169,170]. We encourage authors of future review articles to adopt similar practices and include citation diversity statements.

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J.A.F. and T.A.D. conceived the idea of the Review and developed the outline. J.A.F., C.H. and X.H. surveyed relevant literature and wrote the manuscript. All authors contributed to the discussion, editing and finalizing of the content.

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