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Mechanoresponsive Micro- and Nanoparticles

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Abstract: Mechanical stimuli are ubiquitous in the human body. In contrast to biochemical stimuli such as pH, redox, hypoxia or enzymes as well as exogenous stimuli such as magnetic fields, temperature or ultrasound, endogenous biomechanical stimuli have only received relatively limited attention as a means to trigger stimuli-sensitive materials. The aim of this short article is to highlight the potential of endogenous biomechanical stimuli to control the behaviour of biomaterials relevant to, for example, drug delivery or tissue repair and regeneration. This article will first provide an overview of the different biomechanical stimuli present at the cellular and tissue level in the human body. After that, examples from recent work will be presented that illustrate the use of biomechanical stimuli. This article ends with an outlook for future research.

Keywords: Biomechanics · Drug delivery · Mechanoresponsive materials · Shear stress · Stimuli-responsive materials

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1. Introduction

Many biological processes are the result of a sophisticated interplay between biochemistry and biomechanics. The connective link between both is the ability to translate mechanical stimuli into signals, which is known as mechanotransduction.[1–3] This can result in the release of chemical transmitters or neuronal impulses. Examples for the latter are hearing and touching.[4–6] Dysfunction of mechanical processes plays a major role, for example, in cancer metastasis development, cardiovascular diseases, asthma and inflammation.[3,7,8] A better understanding of the role of mechanical forces in (patho-)biological processes is crucial to develop better prevention and therapies. The interest in mimicking biological stimuli-responsive systems to develop new materials and therapies is high.[9] Biochemical stimuli such as pH, redox potential, hypoxia or enzymes as well as exogenous stimuli such as magnetic fields, temperature changes or ultrasound have been extensively explored to develop stimuli-responsive drug delivery systems.[9–12] Although mechanical forces are ubiquitous in the human body, the use of biomechanical stimuli to trigger and control drug release is relatively unexplored.[10,11] In this article, we will not consider the use of exogenous mechanical stimuli such as ultrasound, but will concentrate on endogenous biomechanical stimuli as they provide unique spatiotemporal control. We will first present biomechanical stimuli at the cellular and tissue level that may be explored for the development of mechanoresponsive materials for therapeutic or regenerative applications. After that, we will present examples of mechanoresponsive materials and we will end this contribution with an outlook for future research.

2. Biomechanical Stimuli at the Cellular and Tissue Level

Mechanical forces in the human body can be divided into compressive, tensile and shear forces.[10,11] Tensile and compressive forces are found at the tissue level through movement of muscles or joints while shear forces are mainly found in the cardiovascular system.[10] Forces at the cellular level can be externally imposed on cells as a consequence of physiological or pathological processes or can be generated by cells themselves.[2,13] In addition to forces that act at the cellular and tissue level, the evaluation of mechanical forces generated by living tissue at the molecular level has attracted much attention. For example, the origin of cell-generated contractile forces is found at the molecular level, namely the contractile actomyosin machinery.[10,14] Traction forces are transferred to neighbouring cells *via* cell–cell adhesions[15] or to the surrounding extra-

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Table 1. Overview of biomechanical stimuli at the cellular and tissue level in the human body.

Stimulus	Physiological system	Pathological system	Reference
Cell traction forces	Myocytes: 20 nN; Fibroblasts: 70 nN; Tensile stress single focal adhesion: 5.5 kPa		[17]
Fluid shear stress in bones	Osteocyte canaliculi: 8–30 dyn/cm^2 (calculated)		[34]
Fluid shear stress in cardiovascular system	Large veins: < 1 dyn/cm^2; Small veins: 20–40 dyn/cm^2; Small arteries: 60–80 dyn/cm^2; In general: 0.35–70 dyn/cm^2	≤ 1500 dyn/cm^2 (depending on the degree of stenosis)	[8], [28]
E-modulus tissue	Breast: 3.25 kPa Brain: 2.0–6.0 kPa	Breast cancer: 10.0–42.0 kPa Brain cancer: 35 kPa	[31], [32]

cellular matrix (ECM) *via* cell–ECM adhesion points, so-called focal adhesions.[13,16] Cellular traction forces range from piconewtons to nanonewtons, depending on the cell type.[13,17] Some examples of cellular traction forces are given in Table 1. As cell-generated forces affect focal adhesions,[17,18] they play a crucial role in cell migration and metastasis development.[19,20] They are also involved in cell division,[21] gene expression[18] and differentiation,[22–26] especially in embryonal development.[23,26,27] Cells act as mechanotransductors and are therefore able to sense forces with following transduction into biochemical signals.[2]

Fluid circulating in the human body induces shear stress on the cells present at the vessel walls and within the fluid. Endothelial cells at the inner layer of blood vessel walls are steadily exposed to vascular shear stress. The range of these shear stresses depends on the vessel diameter and is around 70 dyn/cm^2 for healthy blood vessels (Table 1). Abnormal constriction of blood vessels (stenosis) can lead to an increase in shear stress up to 1500 dyn/cm^2.[8,28] Within bone tissue, fluid flows through small canals, the osteocyte canaliculi, which are known to be shear stress-responsive. They release biochemical signals that regulate bone growth and regeneration by osteoclasts and osteoblasts.[3,29,30]

Cell proliferation in solid tissues leads to a pressure that affects vascular architecture and the ECM. The rapid cell proliferation in tumors causes compression of cells and blood vessels within the tumor. Due to the fast expansion, additional compression of the tumor by the surrounding host tissue occurs. Therefore, the elastic moduli of tumors are increased in comparison with healthy tissue.[7,31–33] These stresses contribute to the invasive and metastatic potential of the cancer cells.[7] Examples for elastic moduli of healthy and cancerous tissues are listed in Table 1.

3. Biomechanically Responsive Delivery Systems

In this section, selected examples will be highlighted, which illustrate how shear forces can be harnessed to trigger and control drug release. More comprehensive reviews about mechanoresponsive materials for drug delivery, including the use of endogenous and exogenous stimuli, have been published recently.[10,12,35,36]

Shear forces can be explored in a number of ways to trigger drug release. A first example is their use to disassemble or dissociate self-assembled particles such as liposomes, polymersomes or polymer micelles. Takeda *et al.* investigated the structural stability of polyplex micelles generated from poly(ethylene glycol)-co-poly(L-lysine) (PEG-PLL) block copolymers and plasmid DNA (pDNA) under exposure to physiological shear stress.[37] Shear stress led to deformation and partial removal of the shielding PEG-PLL chains from the polyplex core, which caused intermolecular aggregation of pDNA (Fig. 1). They also found that the introduction of disulfide crosslinks enhanced the robustness of the polyplex micelles and resulted in longer blood-circulation times without aggregation. Shear forces, however, can also be harnessed in a productive manner to trigger drug release. Holme *et al.* used specially designed lenticular vesicles made from the phospholipid 1,3-dipalmitamidopropan-2-yl-2-(trimethylammonio)ethyl phosphate, which leak under exposure to such shear stresses as found in patients with atherosclerosis.[38] Thus, a non-invasive, target-specific drug release could be achieved. The non-spherical design of the vesicles facilitates stress-induced deformation and leakage.[38,39] However, vesicle response to shear stress is complex and not only a function of the shape but also of the size of particles. Bernard *et al.* investigated the leakage of unilamellar lipid vesicles made of 1,2-dimyristoyl-sn-glycero-3-ethylphosphocholine. They observed that leakage is a result of vesicle deformation and pore formation under exposure to shear stress and that larger particles are more sensitive to shear stress than smaller particles.[40] Pommella *et al.* generated spherical multilamellar vesicles from alkyl benzene sulfonic acid surfactants.[41] They found that deformation and defect formation was more pronounced for larger particles under exposure to shear stress.

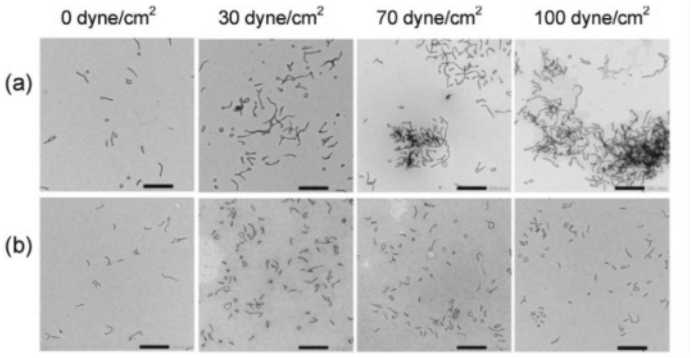

Fig. 1. TEM images of pDNA within (a) polyplex micelles and (b) cross-linked polyplex micelles after exposure to 0, 30, 70, and 100 dyn/cm^2 shear stress for 30 min (Scale bar = 500 nm). Figure reproduced with permission from ref. [37], copyright Elsevier 2017.

Another example of the use of shear forces in drug delivery is the shear stress-triggered dissociation of nanoparticle aggregates.[11] Korin *et al.* published an example of shear-activated nano-therapeutic aggregates (SANT) in 2012.[42] This work used tissue plasminogen activator (tPa) modified poly(lactic-co-glycolic acid)-nanoparticles. These particles form microaggregates under exposure to normal physiological shear stress. As the shear stress increases in stenotic blood vessels, the nanoparticles are activated *via* disaggregation and bind onto the clot *via* enzymatic tPa-fibrin interactions, followed by dissolution of the clot in the blood-stream (Fig. 2).[42,43]

Finally, shear stresses can also have an impact on the interactions between synthetic particles and cells. Chen *et al.,* for example, coated red blood cells (RBCs) with positively charged nanoparticles generated from heparin and thiolated poly(L-lysine).[44] The positively charged nanoparticles are attracted to negatively charged cells *via* electrostatic interactions. Exposing these surface-decorated RBCs to shear stresses of 10 Pa, which mimic the conditions at the thrombus site, was found to result in significantly increased detachment of the nanoparticles from the RBCs. Another study that illustrates the impact of shear stresses on the interactions between cells and nanoparticles was reported by Teo *et al*.[45] The uptake/association of liposomes and their PEGylated counterparts show different shear stress-dependences for myoblasts and hepatocytes. The uptake/association to myoblast cells increased for both types of liposomes under exposure to shear stress whereas for hepatocytes only for the unfunctionalized liposomes an increase could be observed.

4. Outlook: Harnessing Biomechanical Stimuli to Make and Break Covalent Bonds

In all the examples that were discussed in the previous section, biomechanical forces were explored to modulate non-covalent interactions; *e.g.* to trigger the disassembly of self-assembled nanoparticles, to disrupt nanoparticle aggregates or to detach electrostatically attached nanoparticles from cell surfaces. An interesting open question is whether the forces that act on synthetic materials in biological milieu can be put to use to cleave covalent bonds. This could pave the way, for example, to crosslinked polymer networks that could degrade upon being presented to the appropriate biological environment. Swelling of crosslinked polymer networks may present one possible strategy to generate forces that may be sufficient to facilitate cleavage of covalent bonds. There are a number of reports in the literature, which indeed suggest that swelling of polymer networks can promote the scission of covalent bonds. Lee *et al*., for example, studied the effect of solvent swelling of poly(methyl methacrylate) (PMMA) networks, which incorporated a spiropyran crosslinker.[46] Swelling with solvents of intermediate polarity was found to generate forces that were sufficient to facilitate the electrocyclic ring-opening of the colorless spiropyran to the colored and fluorescent merocyanine. Li *et al.* used spiropyran crosslinks to develop CO_2-responsive poly(2-(diethylamino)ethyl methacrylate) microparticles.[47] In this case, CO_2 aeration of the microgel led to swelling and conversion of the crosslinker from the colorless spiropyran to the colored and fluorescent merocyanine state. Clough *et al.* observed swelling-induced mechanoluminescent scission of bis(adamantly)-1,2-dioxetane crosslinkers in a glassy PMMA network upon chloroform sorption.[48] Another example that illustrates the effects of swelling-induced forces on bond cleavage reactions is the degrafting of surface-tethered polymer brushes, which has been observed for a number of different substrates. Degrafting of hydrophilic polymer brushes from silicon oxide substrates is thought to be the result of swelling-induced tension amplification at the polymer brush-substrate interphase, which facilitates siloxane and/or amide/ester bond hydrolysis.[49]

While the examples discussed above may not directly seem relevant in the context of drug delivery, they illustrate that swelling of bulk polymer networks, microgels or surface-tethered polymers can induce mechanical forces that are sufficient to facilitate bond cleavage reactions. In biological environments, such as the human body, the tensions that result from network swelling may be further enhanced due to the action of endogenous forces (*e.g.* shear forces). Adapting and implementing these concepts to generate hydrogel systems that swell in biologically relevant environments could allow access to new biomechanically responsive materials, which could be of use for drug delivery or tissue repair and regeneration.

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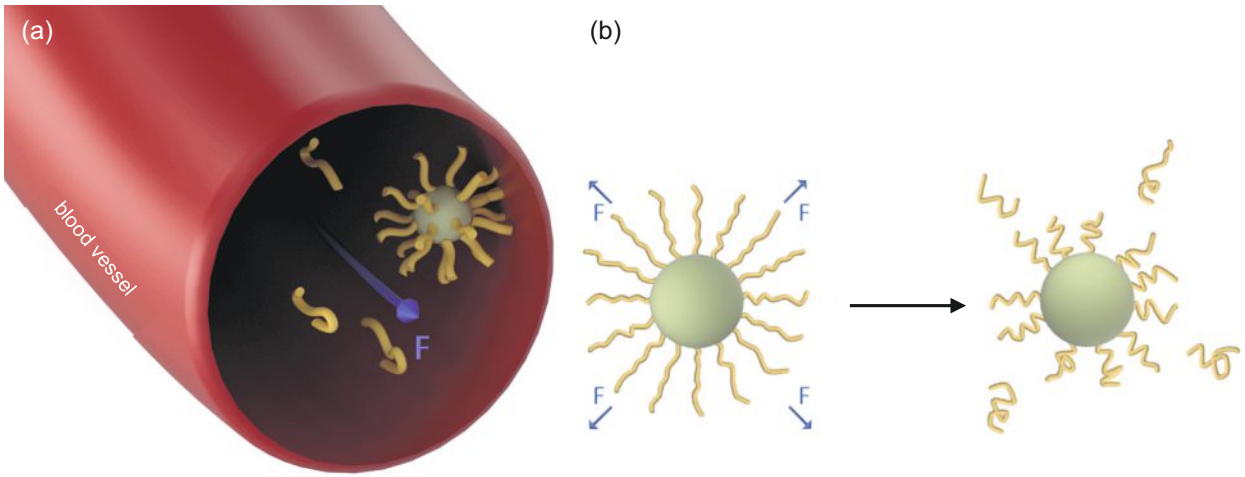

Fig. 2. (a) Illustration of a polymer-coated nanoparticle in a blood vessel. (b) Exposure of the polymer-coated nanoparticle to shear stresses such as for example in the blood circulation may be harnessed to cleave polymer chains from the nanoparticle surface.

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