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Research review paper

Nano-structured and functionalized surfaces for cytocompatibility improvement and bactericidal action

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ABSTRACT

The field of material surface modification with the aim of biomaterial construction involves several approaches of treatments that allow the preparation of materials, which positively influence adhesion of cells and their proliferation and thus aid and improve tissue formation. Modified materials have a surface composition and morphology intended to interact with biological systems and cellular functions.

Not only surface chemistry has an effect on material biological response, surface structures of different morphology can be constructed to guide a desirable biological outcome. Nano-patterned material surfaces have been tested with the aim of how surface geometry and physical properties on a micro- and nano-scale can affect cellular response and influence cell adhesion and proliferation.

Biological functionality of solid state substrates was significantly improved by the irradiation of material with plasma discharge or laser treatment. Commonly used "artificial" polymers (e.g. polyethylene (PE), polystyrene (PS), polytetrafluoroethylene (PTFE), polyethylene terephthalate (PET), polyethylene naphthalate (PEN)) and biopolymers (e.g. Poly-L-Lactic acid (PLLA), polymethylpentene (PMP)) were treated with aim of biocompatibility improvement. The treatment of polymer/biopolymer substrates leads to formation of ripple or wrinkle-like structures, supported also with heat treatment or other subsequent surface processing. Several types of chemically different substances (e.g. metal or carbon nano-particles, proteins) were grafted onto material surfaces or built into material structures by different processes.

Surface physico-chemical properties (e.g. chemistry, charge, morphology, wettability, electrical conductivity, optical and mechanical properties) of treated surfaces were determined. The enhancement of adhesion and proliferation of cells on modified substrates was investigated in vitro. Bactericidal action of noble metal nano-particles (e.g. Au, Ag) on polymers was characterized. The influence of metal nano-particle grafting by using metal nano-particle suspension prepared by "green" methods was determined. Micro- and nano-patterned surfaces can be constructed as tissue scaffolds with specific functions regarding cell adhesion and proliferation or potential biosensor applications.

Contents

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Introduction

Polymeric materials can be used for construction of replacements of irreversibly damaged tissues and organs. As the best replacements (or the "golden standard" for all replacements), the autologous tissue is still considered. However, obtaining this tissue is associated with several drawbacks, such as limited availability, additional surgery for the patient and donor site morbidity. Allogenous and xenogenous transplants are burdened with a risk of immune rejection and disease transmission, and if the donor tissue is preserved by chemical agents crosslinking (e.g. glutaraldehyde), also with potential toxic damage of the recipient's tissues (for a review, see Filová et al., 2009; Chlupáč et al., 2009). Thus, a new advanced interdisciplinary field called "tissue engineering" is quickly developing, and according its classical definition, it "applies the principles of engineering and the life sciences towards the development of biological substitutes that restore, maintain, or improve tissue function" (Langer and Vacanti, 1993).

The tissue substitutes created by methods of tissue engineering contain a cell component and a material component, which serve as a carrier for the cells since they are generally anchorage-dependent. The material component can comprise either synthetic molecules (e.g., various synthetic polymers, ceramics) or biological molecules (e.g., polysaccharides or proteins, which are often molecules of the extracellular matrix, such as collagen, fibronectin etc.; see Bačáková and Švorčík, 2008; Bačáková et al., 2004, 2014). For advanced tissue engineering, the biological molecules are used as recombinant. This means that specific human proteins or their functional parts are expressed and synthesized in bacteria, such as *Escherichia coli* (E. coli), in a defined, tunable and reproducible form. This technology also enables to avoid the use of allogeneic and xenogeneic proteins which have the same problems as the allogeneic and xenogeneic transplants of the whole tissue (for a review, see Romano et al., 2011).

Irrespective of the fact if the material designed for body implantation is biological, synthetic, organic or inorganic, it is referred as "biomaterial", because it enters in interaction with biological environments in vivo or in vitro. The biomaterial should operate as an analogue of native extracellular matrix. A relative simple and commonly used way how to regulate the cell behavior by a material is to modulate its physico-chemical properties, e.g. chemistry, polarity, surface energy, wettability, morphology, pH, zeta potential, or rigidity and deformability (Bacakova et al., 2011).

The physico-chemical changes induced on solid state surfaces (e.g. polymers) due to different types of treatment procedures (heating, grafting, laser plasma or ion beam procedure), can be characterized e.g. by microscopic methods (atomic force microscopy (AFM), scanning electron microscopy (SEM), transmission electron microscopy (TEM)), ellipsometry, spectroscopic methods (e.g. Fourier transform infrared spectroscopy (FTIR), Rutherford backscattering spectrometry (RBS), X-ray photoelectron spectroscopy (XPS), UV–vis, Raman spectroscopy), gravimetry, electrical properties, electrokinetic potential and goniometry, allowing the detailed study of changes induced by the treatment. The material surface wettability is one of the most commonly used factors for characterization and tuning of the material. The material wettability is usually generated by the material polarity and surface free energy, and it is directly proportional to these properties. The material surface wettability can be achieved by chemical treatment, e.g. acid, alkali or hydrogen peroxide treatment, which leads to the material oxidation, namely the formation of oxygen-containing chemical functional groups which are polar and thus they produce the material wettability (Wang et al., 2011; Zhang et al., 2011). An alternative approach is physical treatment by irradiation with ion beam (Bačáková et al., 2001a), ultraviolet light (Mikulíková et al., 2005) or laser (Koufaki et al., 2011; Mirzadeh et al., 2011), or by exposure to plasma (Novotná et al., 2013; Parizek et al., 2009). The physical treatment is advantageous especially in synthetic polymers. The common consequences of this treatment is splitting the polymer chains, namely the C – H and C – C bonds, followed by the release of hydrogen, formation of conjugated double bonds in the polymer chains, and particularly by the creation of "oxygen groups" on the material surface. In addition, these treatments often produce a nanostructure of the substrate, which also supports the cell adhesion and growth (for a review, see Bačáková and Švorčík, 2008; Bacakova et al., 2011).

On moderately hydrophilic materials, the cell adhesion-mediating proteins, such as vitronectin, collagen, and laminin, are adsorbed from biological liquids (cell culture medium, blood, interstitial fluid) in a flexible, reorganizable, near-physiological conformation, advantageous for accessibility of specific bioactive spots in above spoken molecules (e.g. RGD) to cell adhesion receptors (of integrin and non-integrin families). Moreover, hydrophobic surfaces promote preferential albumin adsorption, which is poorly adhesive for cells (Bacakova et al., 2011; Bačáková et al., 2004). However, on highly hydrophilic surfaces, the cell adhesion is also low or disabled, because these surfaces prevent the protein adsorption, or the adsorption forces are weak and unstable (Bačáková et al., 2007a; Proks et al., 2012).

Another important material surface property is its roughness and morphology. In scientific literature, the roughness is most often described by R_a value, described as "the average deviation of the roughness profile from the mean line", that in fact reflects the size of the irregularities, i.e. the height of the prominences and the depth of the depressions (Bačáková et al., 2007b; Vandrovcová et al., 2012). It can be summarized that the macro roughness (size of the irregularities hundreds of μm and more) do not hamper the cell adhesion and spreading, because the cells usually spread over the distances of tens of μm only, and thus they can spread on the side walls of the irregularities on in valleys among them, and do not feel these irregularities. In addition, in case of the bone implants, the macro scale irregularities help to anchor mechanically the implant in the tissue and support its primary stability. The micro scale surface roughness (1 μm to 100 μm) is a more controversial issue. In some studies, it supported the cell's growth and adhesion, while in others it hampered the cell spreading and proliferation, although the lower proliferation activity was often associated with increased cell differentiation (Bacakova et al., 2011; Vagaská et al., 2010; Vandrovcova et al., 2008). Thus, for exact description of the micro roughness, the R_a parameter seems to be insufficient. Also other parameters has to be mentioned, particularly the shape and the distance of the irregularities. If the irregularities are rounded and relatively distant, they may have beneficial or neutral influence on cell spreading and growth, while sharp and densely distributed irregularities may attenuate these properties.

The nanoscale surface roughness (R_a less than 100 nm) is one of the most frequently studied material properties. The reason is that the nanostructured materials usually act as carriers supporting cell adhesion or proliferation. An explanation is that nanoscale irregularities mimic the irregularities in the native extracellular matrix molecules, i.e. their undulations, bending, branching etc., and also irregularities on membrane of cell. In addition, nanoscale surface roughness generates a higher surface wettability due to the larger surface area produced by the irregularities. Addition of nanoparticles (e.g. carbon nanotubes) to an originally highly hydrophobic polymer (a terpolymer of polytetrafluoroethylene, polypropylene and polyvinyldifluoride) and creation of its surface nanoroughness compensated its surface hydrophobicity and significantly increased the number and spreading of cells (Bačáková et al., 2007b; Staňková et al., 2014). The nanoscale surface roughness is considered as advantageous particularly for bone implants preparation and for the prevention of encapsulation of these implants with fibrous tissue (Bacakova et al., 2011; Price et al., 2004; Vagaská et al., 2010; Vandrovcova et al., 2008; Webster et al., 2001).

A certain controversy in the literature is apparent also for the influence of the material's surface electrical charge on the cell behavior. Some studies indicated that the positively charged surfaces increased

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