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Cell Adhesion and Spreading on an Intrinsically Anti-Adhesive PEG Biomaterial

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1. Introduction

This Chapter deals with bulk hydrogels consisting of a widely used biomaterial: poly(ethylene) glycol (PEG). PEG is renowned for its bio-inertness; it is very effective in suppressing non-specific protein adsorption (NSPA) and thereby preventing cell adhesion. However, we have observed unexpected adhesion of fibroblast cells to the surface of bulk PEG hydrogels when the surface was decorated with micrometer-sized, topographic patterns. This Chapter describes the aim of our investigations to unravel the biophysical, biochemical and biomechanical reasons why these cells do adhere to the intrinsically anti-adhesive PEG material when it is topographically patterned.

1.1 Application of hydrogels in biomaterial science

Amongst the different classes of materials which find use in the field of medicine and biology, hydrophilic polymers have demonstrated great potential. Networks formed from hydrophilic polymer often exhibit a high affinity for water, yet they do not dissolve due to their chemically or physically crosslinked network. Water can penetrate in between the chains of the polymer network, leading to swelling and the formation of a hydrogel (Langer & Peppas, 2003; Peppas et al., 2000; Wichterle & Lim, 1960). Generally such polymer networks can be formed via chemical bonds, ionic interactions, hydrogen bonds, hydrophobic interactions, or physical bonds (Hoffman, 2002; Peppas, 1986). Hydrogels have found numerous applications in drug delivery as well as in tissue engineering where they are used as scaffolds for the cultivation of cells to enable the formation of new tissues (Jen et al. 1996; Krsko & Libera, 2005; Langer & Tirrell, 2004; Peppas et al., 2006). Hydrogels are especially attractive for this purpose as they meet numerous characteristics of the architecture and mechanics of most soft tissues and many are considered biocompatible (Jhon & Andrade, 1973; Saha et al., 2007). Furthermore, concerning the intended purpose of cell encapsulation and delivery, hydrogels support sufficient transport of oxygen, nutrients and wastes (Fedorovich et al., 2007; Lee & Mooney, 2001; Nguyen & West, 2002).

In general, hydrogel matrices can be prepared from a variety of naturally derived proteins and polysaccharides, as well as from synthetic polymers (Peppas et al., 2006). Depending on their origin and composition, natural polymers have specific utilities and properties. Hydrogels from natural sources have for example been fabricated from collagen, hyaluronic acid (HA), fibrin, alginate and agarose (Hoffman, 2002). Collagen, HA and fibrin are

components which are in vivo present in the extracellular matrix (ECM) of mammalian cells. Since they are derived from natural sources, hydrogels formed from these polymers are inherently cytocompatible and bioactive. They can promote many cellular functions due to a diversity of endogenous factors present. However, scaffolds fabricated from natural sources are rather complex and often ill-defined, making it difficult to determine exactly which signals are promoting the cellular outcome (Cushing & Anseth, 2007). Furthermore they can possess an inherent batch-to-batch variability which can affect sensitive cells in their viability, proliferation, and development (Cushing & Anseth, 2007). Due to these limitations of gels formed from natural polymers, a wide range of synthetic polymers has been found suitable regarding their chemical and physical properties (Hoffman, 2002). The advantages of synthetic gels include their consistent composition and predictable manipulation of properties.

A few examples of synthetic hydrogel building blocks are given in **Figure 1**, including neutral (upper row) and ionic (bottom row) monomers (Peppas et al., 2006).

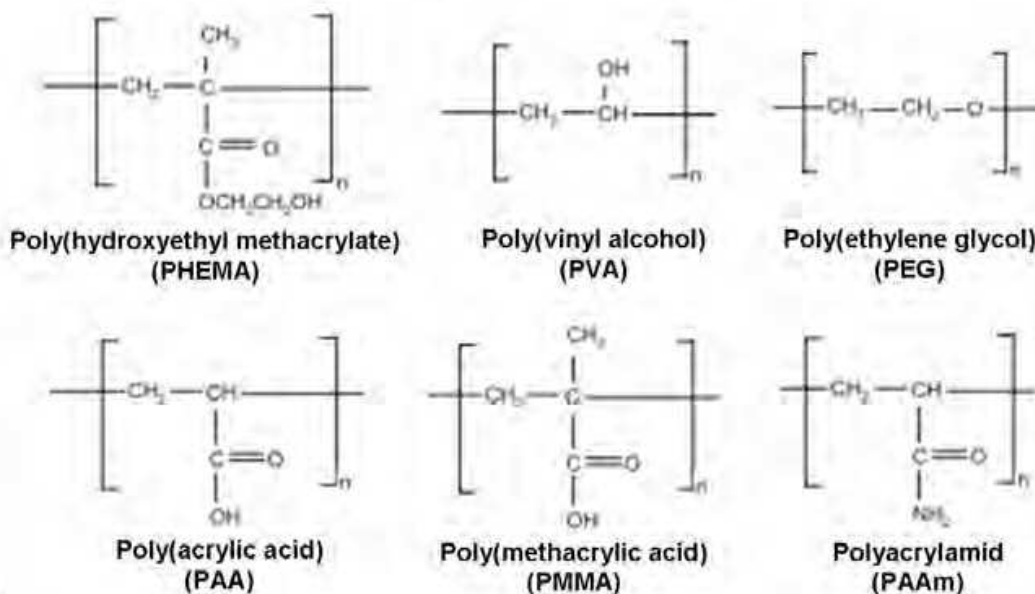


Fig. 1. Some examples of synthetic hydrogels that are used in biomedical applications. Reproduced with permission from Peppas et al., *Adv. Mater.*, 18, 1345-60. Copyright 2006 John Wiley and Sons.

Proteins are molecules, which often adsorb unspecifically from solution at biomaterial interfaces, a phenomenon that has been documented in a wealth of publications, e.g. references: (Andrade & Hlady, 1986; Andrade et al., 1992; Wahlgren & Arnebrant, 1991). Almost any material, when exposed to a physiological, protein-containing solution, becomes coated with proteins within seconds. As widely recognized, this adsorption of proteins to synthetic material surfaces is of great importance in the field of biomaterials as it plays a determining role for the subsequent cellular responses. Failure of most implant materials stems from an inability to predict and control the process of protein adsorption and cell interaction, resulting in an inappropriate host response to the material (Castner & Ratner, 2002; Hlady & Buijs, 1996; Tsai et al., 2002). Biomaterial surface-induced thrombosis, for example, one of the major problems in clinical applications of materials in contact with

circulating blood, begins with the unspecific adsorption of plasma proteins (Andrade & Hlady, 1986; Harris, 1992; Horbett, 1993).

Not only with regards to tissue engineering and implant design unspecific protein adsorption is a highly critical process, also different devices in diagnostics (e.g. protein arrays) and biosensors are based on specific receptor-ligand binding, demanding a non-interacting background. Therefore, much effort has been focused on the development of inert, protein resistant materials and coatings (Chapman et al., 2000; Elbert & Hubbell, 1996). Many synthetic hydrophilic polymers, including PAA, PHEMA, PVA, PEG and poly(ethylene oxide) (PEO) have been applied for this purpose (see Figure 1) (Castillo et al., 1985).

1.2 Biomedical applications of PEG- or PEO-based hydrogels

Some of the earliest work on the use of PEG and PEO as hydrophilic biomaterials showed that PEO adsorption onto glass surfaces prevented protein adsorption (Merrill et al., 1982). Several subsequent studies confirmed that PEO, or its low molecular weight ($M_w < 10$ kDa) equivalent, PEG, were showing the most effective protein-repellent properties (Harris, 1992). PEG-modified surfaces are non-permissive to protein adsorption, bacterial adhesion and eukaryotic cell adhesion (Zhang et al., 1998; Desai et al., 1992; Drumheller et al., 1995; Krsko et al., 2009).

Based on these properties, PEG hydrogels are one of the most widely studied and used materials for a variety of biomedical applications such as tissue engineering, coating of implants, biosensors, and drug delivery systems (Langer & Peppas, 2003; Langer & Tirell, 2004; Krsko & Libera, 2005; Tessmar & Gopferich, 2007; Veronese & Mero, 2008; Harris & Zalipsky, 1997). PEG substrates have also been used to generate patterns of proteins or cells using for example the technique of microcontact printing (Whitesides et al., 2001; Mrksich & Whitesides, 1996; Mrksich et al., 1997). PEG hydrogels are approved by the US Food and Drug Administration (FDA) for oral and topical application; they are little immunogenic and non-toxic at molecular weights above 400 Da. Since PEG itself is not degradable by simple hydrolysis and undergoes only limited metabolism in the body, the whole polymer chains are eliminated through the kidneys or eventually through the liver ($M_w < 30$ kDa) (Harris, 1992; Knauf et al., 1988).

Many groups have investigated surface coverings of PEG or PEO in order to try to elucidate why PEG has such remarkably effective properties and different theories have been proposed (Jeon et al., 1991; Prime & Whitesides, 1993). First, there are generally only weak attractive interactions between the PEG-coatings and a wide range of proteins, as protein adsorption is generally known to be more pronounced on hydrophobic surfaces in comparison to hydrophilic ones (Morra, 2000). Furthermore, as the interaction between water and PEG via hydrogen bonds is more favorable and surpasses possible attractive interactions of proteins with the surfaces, a repulsion force is created. Therefore the hydration of the layer, i.e. the binding of interfacial water is of high relevance for the exclusion of other molecules coming near the polymer surface (Harris, 1992; Harder et al., 1998). Additionally, molecules approaching the rather flexible, loosely crosslinked PEG hydrogel from the surrounding medium initiate the compression of the extended PEG molecules inducing a steric repulsion effect (Jeon et al., 1991; Morra, 2000). More specifically, a loosely crosslinked gel has relatively long segments between the crosslinks, which can take a relatively large number of conformations. The number of segment conformations would be substantially restricted by the binding of a protein molecule to the gel surface. This

would lead to a relatively large unfavorable entropic change, making the process of protein adsorption very unfavorable for thermodynamic reasons. Additionally, the high mobility of PEG chains allows little time for proteins to form durable attachments.

Many techniques have been developed to create PEG or PEO-bearing surfaces, e.g. exploiting physical adsorption, chemical coupling, and graft polymerization (Harris, 1992; Harris & Zalipsky, 1997; Prime & Whitesides, 1993; Fujimoto et al., 1993; Prime & Whitesides, 1991). Whitesides and co-workers have studied covalent coatings of oligo(ethylene glycol)s, so-called self-assembled monolayers (SAMs) and found that the resistance to protein adsorption increased with the chain length of the oligomers (Prime & Whitesides, 1991 and 1993). Furthermore, it has been demonstrated that the adhesion resistance of PEG increases with chain packing density (Sofia et al., 1998; Malmsten et al., 1998).

In recent years the versatility of star-shaped PEG molecules has been recognized, as they present a high number of end-groups per molecule allowing interconnectivity and functionalization (Groll et al., 2005a & 2005b; Lutolf et al., 2003). Some star polymers have been shown to achieve a high surface coverage and localization of the end-groups near the top of the star polymer (Irvine et al., 1996). Therefore, star-shaped PEG molecules are an interesting and promising alternative to linear PEG.

1.3 PEG-based hydrogels formed by UV-curing: patternable biomaterials

We have been using PEG hydrogels that are prepared by UV-based radical crosslinking of six-armed star-shaped macromonomers via acrylate (Acr) end-groups. The polymer backbone consists of a statistical copolymer of 85 % ethylene oxide and 15 % propylene oxide (P(EO-stat-PO)) and each star molecule bears 6 reactive Acr end-groups. The formal notation of the precursor polymer would thus be Acr sP(EO stat PO). Nevertheless, in the following the resulting, crosslinked network will be denoted PEG-based (hydro)gel, even though the arms of the precursors do not consist of pure PEG, but contain a fraction (15%) of propylene glycol units in the copolymer. These PO-units give the prepolymer its unique and very useful property of being a liquid at room temperature, before crosslinking. The crosslinking reaction was initiated by a UV-based radical reaction with benzoin methyl ether as photoinitiator (PI) and an additional crosslinker (CL) (pentaerythritol triacrylate). Further experimental details concerning the synthesis and the curing conditions can be found in our recent publications (Lensen et al., 2007; Diez et al., 2009).

The hydrogel substrates were applied as free-standing bulk gels for 2D cell culture studies. Due to the fact that the prepolymer Acr-sP(EO-stat-PO) is liquid before crosslinking, the precursor mixture can be molded in any shape, which has enabled us to imprint desired micro- and nanometer topographic patterns into the hydrogel surface (Lensen et al., 2007; Diez et al., 2009). In the following, the properties of this hydrogel system in view of its use in biomedical applications will be evaluated, e.g. the cytotoxicity and cytocompatibility will be assessed, and the cell behavior on the surface of the hydrogels will be demonstrated. Finally, the remarkable effect of surface topography and substrate elasticity on protein adsorption, cell adhesion and cell spreading will be discussed.

2. Fabrication and properties of PEG-based substrates

2.1 Synthesis of PEG-based hydrogels from Acr-sP(EO-stat-PO) macromonomers

Hydrogels fabricated for the application in cell culture studies were crosslinked from Acr-sP(EO-stat-PO) prepolymers. UV-irradiation was used to initiate radical polymerization of the macromonomer mixture with added photoinitiator (PI) and crosslinking agent (CL) (**Figure 2**).

observed to adsorb to virtually any surface, and because FN is generally considered to be the most important cell adhesion mediating protein in serum and consequently has been much more studied than VN.

Solution for Incubation		Protein detected by antibody staining	
		VN	FN
FBS	10 % in PBS	+++	
FBS	100 %	+++	
VN FN	5 µg/ml in PBS 50 µg/ml in PBS	+	+
VN FN	5 µg/ml in PBS 20 µg/ml in PBS	++	+
VN FN	10 µg/ml in PBS 20 µg/ml in PBS	++	
VN FN	10 µg/ml in PBS 50 µg/ml in PBS	+	

Table 1. Protein adsorption to the surface of the (topographically patterned) PEG-based hydrogel; qualitative results are given for samples that were incubated with serum (100% or 10% in buffer solution) or with buffer solutions containing a mixture of the pure proteins Vitronectin (VN) and Fibronectin (FN) in various ratios. Reproduced from: Schulte et al., (2011) *Macromol. Biosci.* (in press). Copyright 2011 John Wiley and Sons.

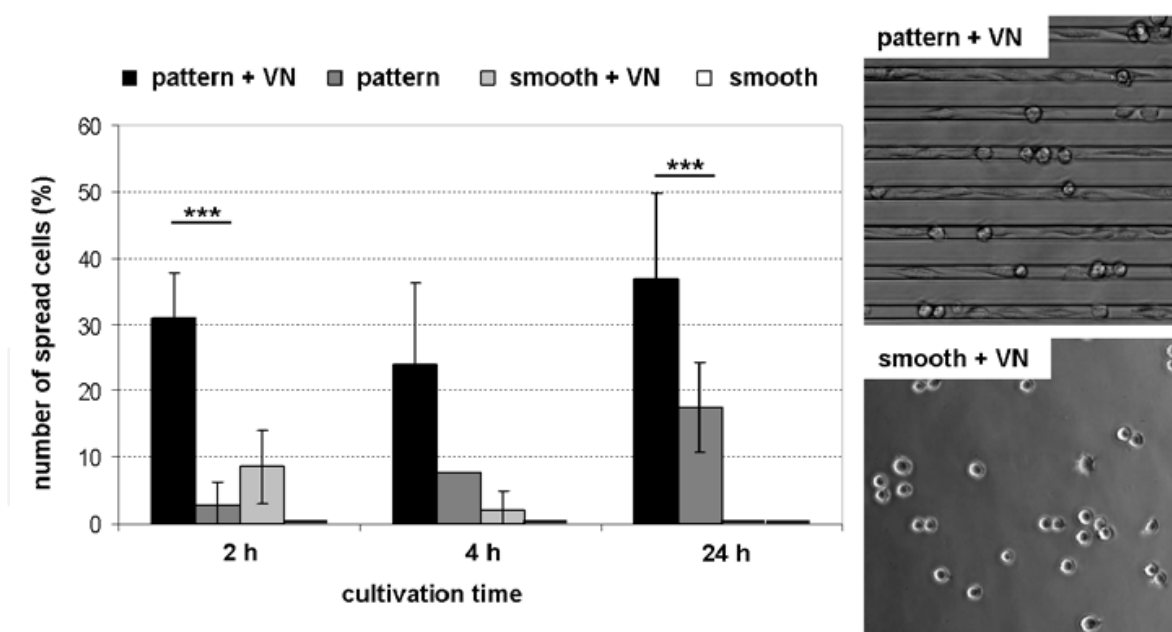


Fig. 10. Cell adhesion on PEG hydrogels enabled by surface topography and/or pre-incubation with the cell adhesion-mediating protein VN. Reproduced from: Schulte et al., *Macromol. Biosci.* (in press). Copyright 2011 John Wiley and Sons.

In order to verify whether this small but significant amount of adsorption of VN to the PEG surface is responsible for the observed cell adhesion on topographically patterned hydrogels we investigated the pre-incubated hydrogels (both smooth and patterned) in cell culture.

We analyzed the number of adherent cells and found an increased number of cells on the VN-incubated hydrogels. This effect was also found for the unpatterned, smooth hydrogels; after VN-incubation a very small but significant number of cells were able to adhere to the PEG surface. In **Figure 10** these results are depicted; comparing smooth and patterned hydrogels with and without VN-incubation.

It can be seen that compared to the effect of topography alone, the VN-incubation alone was less effective in enabling cell adhesion. Remarkably, the effect of VN on cell adhesion was only evident at early time points; after 24 hours the enabling effect was completely lost. Finally, a striking synergistic effect was observed from the combination of VN-incubation and topography; the number of adherent and spread cells was larger than the sum of the individual contributions (Schulte et al., 2011). Taking into account the apparent difference in the effect of topography and VN with time, we tentatively conclude that the cell adhesion protein VN facilitates the initial cell adhesion, while the adhesion-enabling effect of surface topography becomes dominant at longer times and is necessary for the development of durable and stable adhesion complexes.

3. Conclusion

Hydrogels are of high relevance for several biomedical applications. We have described the fabrication of a hydrogel system based on poly(ethylene glycol) and evaluated the potential of this PEG-based gel as a patternable biomaterial. PEG-based polymers are of great importance as biomaterials for applications in cell and tissue engineering, as coating of implants or biosensors, and as drug delivery systems. In particular, PEG coatings have been used to minimize surface biofouling by plasma proteins to create surfaces that are “invisible” to cells. Cell biological studies with murine fibroblasts (NIH L929) confirmed the expected non-adhesive nature of the smooth hydrogel surfaces and furthermore ruled out any toxic effect of the material. Alterations of the mechanical properties could easily be achieved by varying the crosslinking density.

The most striking result from our studies is that the very popular and versatile PEG biomaterial is not cell-repellent per se. Only when the surface of the bulk PEG hydrogels is smooth it is anti-adhesive to cells, and this applies to all hydrogels we have investigated with a stiffness ranging from 0.1 to 1 MPa. However, we have discovered that on the same PEG hydrogels when decorated with micropatterns of topography, cells are able to adhere and spread. We have explored several underlying biochemical, biophysical and biomechanical factors that could attribute to this phenomenon and found that these factors do have an effect indeed, and notably the combination of these parameters, e.g. protein adsorption, surface topography and substrate compliance, work together to enable cell adhesion to the intrinsically anti-adhesive PEG biomaterial.

More specifically, three investigated PEG-based hydrogels with different stiffness were all cell anti-adhesive when smooth. However, in combination with topography, the softer gels were clearly more attractive for the cells; on softer gels with the same pattern geometry, significantly more cells adhered and spread than on the intermediate or stiffer gels. It seems that the compliance of the softer gels enables the cells to ‘squeeze’ into the grooves, although the cells apparently deform their own cytoskeleton rather than the topographic features.

We also discovered that a slight but significant amount of the ECM-protein Vitronectin is able to adsorb to the PEG surface and that this leads to an increase in initial cell adhesion during the first 4 hours of cell culture. However, this effect rapidly falls off. The effect of

topography is a more durable effect that dominates at longer time scales, suggesting its role in the enabling of stable adhesion complexes, which is a process that occurs during more than several hours. We consider that the topographic features may provide shelter to the cells and prolong their residence time inside of the grooves. Added to this, the 'pulling' of the cells on the weakly bound cell adhesion proteins may be less effective when they are confined between the vertical walls than when the surface is smooth; as a consequence focal adhesion contacts can develop into stable focal adhesion complexes.

Thus, the combination of different (bio)chemical, physical and mechanical properties of the PEG hydrogels results in the observed cell adhesion on this intrinsically anti-adhesive biomaterial. The effects are difficult to disentangle, and marked synergistic effects were observed for example when using topographically patterned hydrogels that were incubated with Vitronectin prior to cell culture.

As PEG is generally well known for its anti-adhesive properties and is widely applied in biomedical applications, it is important to take into consideration what our study has shown: physical and mechanical surface properties can impede the anti-adhesive characteristics of PEG. On the other hand it also opens new opportunities for biomimetic material design which does not rely on complicated and expensive biochemical surface functionalization for manipulating cellular responses.

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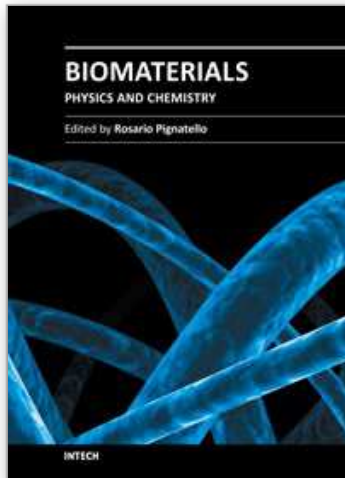
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