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Leading Opinion

Phenotypic dichotomies in the foreign body reaction ☆

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Abstract

To better understand the relationship between macrophage/foreign body giant cell adhesion and activation on surface-modified biomaterials, quantitative assessment of adherent cell density (cells per mm^2) and cytokine production (pgs per mL) were determined by ELISA. Further analysis to identify cellular activation was carried out by normalizing the cytokine concentration data to provide a measure of cellular activation. This method of analysis demonstrated that hydrophobic surfaces provided statistically significantly greater adherent cell densities than hydrophilic/neutral surfaces. However, when cell activation parameters were determined by normalization to the adherent cell density, the hydrophilic/neutral surfaces demonstrated statistically significantly greater levels of activation and production of IL-10, IL-1β, IL-6, IL-8, and MIP-1β. With increasing time, production of the anti-inflammatory cytokine IL-10 increased, whereas IL-1β, IL-6, and IL-8 decreased and MIP-1β was relatively constant over the culture time period. This observed dichotomy or disparity between adhesion and activation may be related to surface-induced adherent cell apoptosis. Further evaluation of macrophage activation on biomaterial surfaces indicated that an apparent phenotypic switch in macrophage phenotype occurred over the course of the in vitro culture. Analysis of cytokine/chemokine profiles with surface-modified biomaterials revealed similarities between the classically activated macrophages and the biomaterial-adherent macrophages early (day 3) in culture, while at later timepoints the biomaterial-adherent macrophages produced profiles similar to alternatively activated macrophages. Classically activated macrophages are those commonly activated by lipopolysaccharide (LPS) or interferon-γ (IFN-γ) and alternatively activated macrophages are those activated by IL-4/IL-13 or IL-10. Surface modification of biomaterials offer an opportunity to control cellular activation and cytokine profiles in the phenotypic switch, and may provide a means by which macrophages can be induced to regulate particular secretory proteins that direct inflammation, the foreign body reaction, wound healing, and ultimately biocompatibility.

Keywords: Macrophages; Adhesion; Activation; Hydrophilic; Hydrophobic; Ionic surface chemistry

1. Introduction

The effects of surface chemistry on adherent cellular behavior have been a key area of research for years. This research is driven by the notion that defining these relationships will aid in establishing criteria for designing biomaterials utilized in future applications. Complexities in defining these relationships arise in the not fully understood mechanisms by which adherent cells interact with the surface involving protein adsorption, integrin expression, ligand–integrin binding, cell signaling and the subsequent effects these interactions have on the resulting cellular behavior. The concept that minimizing cellular adhesion minimizes cellular activity on a biomaterial surface has

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been an accepted tenet prompting numerous studies to investigate ways to minimize cellular adhesion. Recent research has focused on understanding how biomaterial surface chemistry directs adherent macrophage activity and behavior including cytokine and chemokine production as a means to direct subsequent juxtacrine and paracrine biological responses (i.e. inflammation and wound healing) to implanted biomaterials.

Our recent studies have demonstrated that hydrophobic surfaces support macrophage adhesion and fusion, while hydrophilic/neutral surfaces markedly inhibit macrophage adhesion and fusion [1,2]. Monocyte/macrophage adhesion and fusion was seen on PET surfaces coated with hydrophobic poly(styrene-co-benzyl *N*,*N*-dimethyldithiocarbamate) (BDETDC) as shown in Fig. 1. On surfaces in which the PET was rendered hydrophilic using a photografted acrylamide modification (PAAm), macrophage adhesion and fusion was significantly inhibited to values equal to or less than a third of the values seen on BDEDTC. These findings were supported by previous research in our laboratory by Brodbeck et al. [3,4] and confirmed with the increase in macrophage fusion seen with the incorporation of hydrophobic silicone modifications to polyurethanes. Interestingly, when the PET surface was modified with a hydrophilic/anionic (PAANa) or hydrophilic/cationic modification (DMAPAAmMeI), cellular adhesion levels were markedly greater than the hydrophilic/neutral surfaces (2–26 fold greater) and were comparable to values observed on hydrophobic surfaces (Fig. 2).

2. Inverse relationship of cellular adhesion and activation

Generally speaking, monocytes adhere to a biomaterial, differentiate into macrophages that become activated, and then fuse to form multinucleated giant cells. Naturally, the term cellular "activation" is very broad and may involve numerous responses. A given cell can be "activated" to varying degrees and produce varying responses. Nevertheless, macrophage activation has been investigated in-depth for well over 40 years and researchers have differentiated inactive cells from active cells based upon the up- or down-regulation of gene expression, protein production, biological surface molecules (i.e. receptors, integrins, and protein markers), and reactive oxygen species secretion in addition to the resulting behaviors

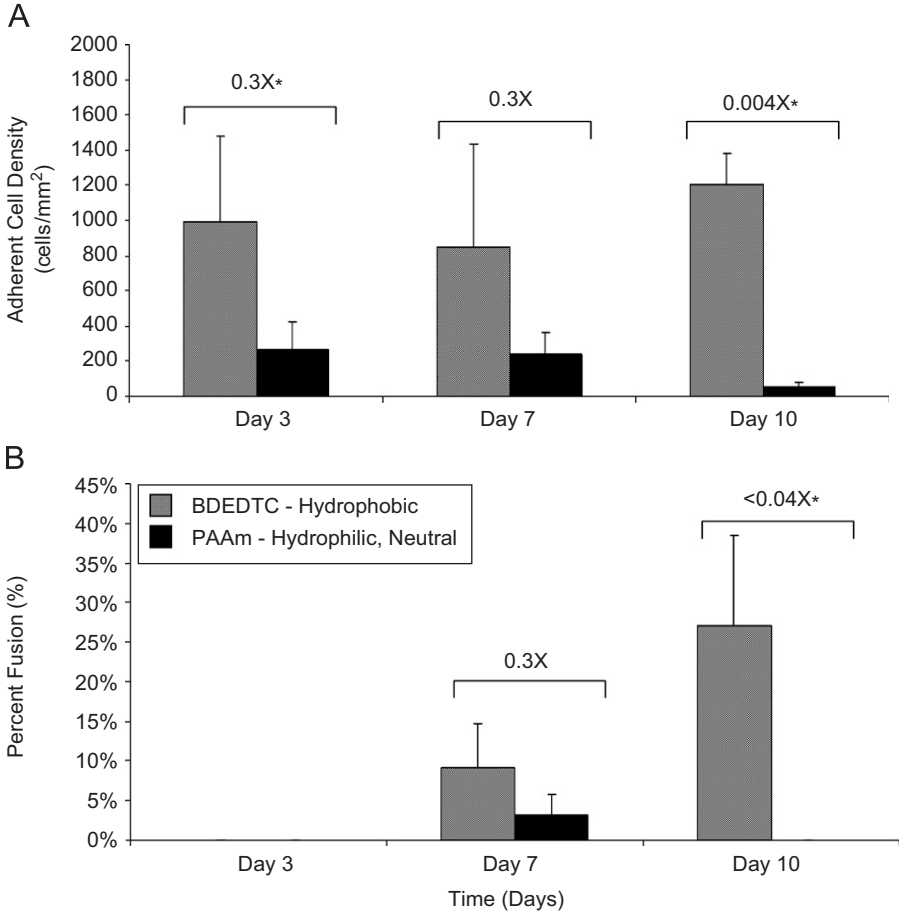

Fig. 1. Disparate effects of hydrophobic and hydrophilic surfaces on macrophage adhesion (A) and fusion (B). Numerical notations are the ratio of the data for PAAm surfaces to the data for BDEDTC surfaces. Mean ± SEM, $n = 3$. * A statistical difference between values ($p < 0.05$).