European Journal of Pharmaceutical Sciences 57 (2014) 74–86

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Microdialysis sampling techniques applied to studies of the foreign body reaction

Cynthia R. Sides, Julie A. Stenken *

Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, AR 72701, USA

ARTICLE INFO

Article history:
Received 20 September 2013
Accepted 5 November 2013
Available online 21 November 2013

Keywords:
Microdialysis
Cytokines
Foreign body reaction
Matrix metalloproteinase

ABSTRACT

Implanted materials including drug delivery devices and chemical sensors undergo what is termed the foreign body reaction (FBR). Depending on the device and its intended application, the FBR can have differing consequences. An extensive scientific research effort has been devoted to elucidating the cellular and molecular mechanisms that drive the FBR. Important, yet relatively unexplored, research includes the localized tissue biochemistry and the chemical signaling events that occur throughout the FBR. This review provides an overview of the mechanisms of the FBR, describes how the FBR affects different implanted devices, and illustrates the role that microdialysis sampling can play in further elucidating the chemical communication processes that drive FBR outcomes.

1. Introduction

Microdialysis sampling has been used to address many diverse basic and clinical research problems (Müller, 2013; Robinson and Justice, 1991; Westerink and Cremers, 2007). The extensive efforts of Dr. Urban Ungerstedt to promote creative thought in the uses of the microdialysis sampling technique to allow for studies he termed "tissue biochemistry" have resulted in many diverse sampling applications in living systems (Lunte et al., 1991; Ungerstedt, 1991). The diversity of solutes that have been collected from the extracellular fluid space (ECS) using microdialysis sampling include classical neurotransmitters (Robinson and Justice, 1991), energy metabolites including glucose and lactate (Benveniste et al., 1987; Lonnroth et al., 1987), pharmaceutical compounds (de Lange et al., 1994; Elmquist and Sawchuk, 1997; Hammarlund-Udenaes, 2000), trace metals (Su et al., 2008), neuropeptides (Kendrick, 1990; Wotjak et al., 2008), and signaling proteins including cytokines (Ao and Stenken, 2006; Clough, 2005).

Over the past decade, our research group has been interested in using microdialysis sampling as a method to monitor different chemical events that occur during a process known as the foreign body reaction (FBR) (Fig. 1). We have been specifically interested in this topic from an analytical chemistry standpoint since the FBR seriously affects the data reliability from implanted sensors, particularly glucose sensors implanted into the subcutaneous space (Wilson and Gifford, 2005). The FBR is a complex, multi-step process, including wound healing, that occurs to resolve injury in response to any implanted object. The FBR is a dynamic continuum of biochemical and cellular changes (Anderson et al., 2008); therefore, monitoring the spatiotemporal evolution of cell types present at the foreign body site and their localized chemical communication through the ECS environment surrounding the implanted material is necessary to elucidate mechanisms that may alter FBR outcomes. Since microdialysis sampling has previously been used to monitor different chemical events, this sampling technique is ideal for elucidating FBR molecular mechanisms.

2. Foreign body reaction (FBR)

As early as the 1970s, the FBR was hypothesized to be a chronic inflammatory response (Coleman et al., 1974). During the FBR, implanted objects or biomaterials are recognized in the body as unwanted, foreign objects that must be destroyed or walled-off from healthy tissue (Castner and Ratner, 2002). In addition to attempting to rid the perceived invading biomaterial, the cascade of events in wound healing and the FBR processes aim to restore function to the site by preventing infection and repairing tissue.

Characteristic stages recognized for the FBR in response to a biomaterial are protein adsorption, cell recruitment (including monocyte/macrophage adhesion, foreign body giant cell formation, and inflammatory/wound healing cell presence), extracellular matrix formation, and fibrosis. The molecular and cellular interactions, including elaborate, successive immune pathways, are distinct for each phase of the FBR, thereby making the unique molecular mechanisms of each stage attractive and ideal for pharmaceutical and clinical research involving microdialysis sampling. Upon implantation of the biomaterial, a layer of plasma proteins

* Corresponding author. Tel.: +1 479 575 7018.
E-mail address: jstenken@uark.edu (J.A. Stenken).

0928-0987/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejps.2013.11.002

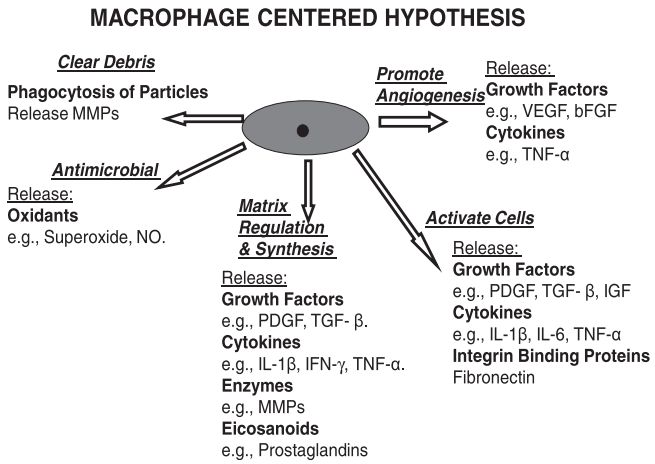

Fig. 1. Macrophage chemical products released during the healing phase of the foreign body response.

forms, adheres to the implant, and dictates the recruitment and adhesion of inflammatory cells, which subsequently direct the wound healing process (Junge et al., 2012). This is followed by an intricate progression of successive, yet overlapping phases, including inflammation, reepithelialisation/angiogenesis, and extracellular matrix remodeling (Cardoso et al., 2011; Gurtner et al., 2008; Heydari Nasrabadi et al., 2011; Janis et al., 2010; Nilani et al., 2011; Rodero and Khosrotehrani, 2010).

Contrary to physiological wound healing and scar formation, the FBR resulting from the implant of a biomaterial persists for the *in vivo* lifetime of the implanted device due to cellular interactions at the biomaterial/tissue interface (Anderson et al., 2008; Junge et al., 2012). The degree of the cellular activity, and thus the FBR, at this interface directly corresponds to the extent of fibrosis induced. Fibrosis occurs when the rate of collagen formation exceeds the rate at which it is degraded (Wynn, 2008). Typical tissue reconstruction is replaced by a fibrotic encapsulation of the foreign body in an effort to segregate the object from the surrounding tissue, as illustrated for a microdialysis probe in Fig. 2. A collagenous bag forms around the implanted biomaterial through the role of growth factors and other cellular mediators secreted by macrophages, foreign body giant cells, neutrophils, and fibroblasts.

While biomaterials research has fervently studied the biochemical, cellular, and immunological dynamics that drive the FBR in response to different implanted materials, a significant portion of the research is concerned with biomaterial properties. The extent of the elicited FBR is influenced by the biomaterials' chemical (i.e., hydrophilic, hydrophobic, or charged surfaces), physical, and morphological (i.e., porosity and roughness) properties. For example, the surface chemistry of a biomaterial modulates the secretion of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) from adherent macrophages (Jones et al., 2008). Research has shown that biomaterial surface properties significantly contribute to the extent of the FBR during the first two to four weeks after implantation (Anderson et al., 2008). Therefore, a biomaterial's *in vivo* biocompatibility and functional longevity are determined chiefly by the consequential FBR. The different stages and resulting chemical production resulting from the FBR are outlined in more detail in the subsequent subsections.

2.1. Protein adsorption

Blood-derived proteins adsorb onto all polymeric biomaterials after implantation. Many of these proteins, e.g., fibrinogen and fibronectin, contain specific amino acid motifs, e.g., RGD, that bind to important cell-surface receptors called integrins. Different cells (e.g., macrophages) bind to surfaces via their integrin receptors, which serve as cell surface cues. Integrin binding of inflammatory cells to the implanted material initiates a signaling cascade that directs the FBR (Bellis, 2011; Garcia, 2005; Perlin et al., 2008; von der Mark et al., 2010). This signaling cascade leads to transmission of inflammatory and recruiting chemical signals, recruitment of different inflammatory cells, and extracellular matrix restructuring via metalloproteinases enzymes.

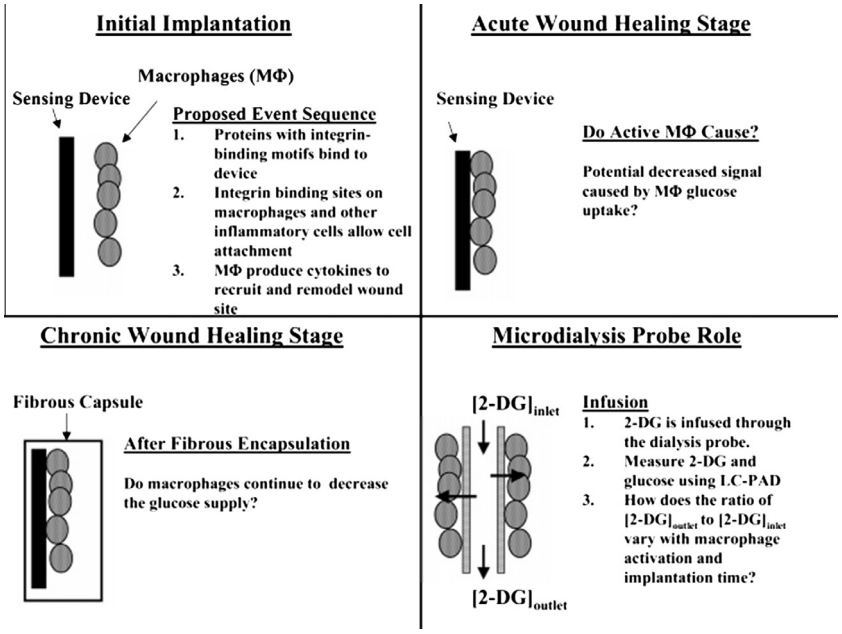

Fig. 2. Stages of wound healing. The microdialysis probe can be used with internal standards to test different aspects of the tissue biochemistry. Reprinted with permission from Analytical Chemistry 78(22), 7778–7784. Copyright 2006 American Chemical Society.