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Improving biocompatibility by surface modification techniques on implantable bioelectronics

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ABSTRACT

For implantable bioelectronic devices, the interface between the device and the biological environment requires significant attention as it dictates the device performance in vivo. Non-specific protein adsorption onto the device surface is the initial stage of many degradation mechanisms that will ultimately compromise the functionality of the device. In order to preserve the functionality of any implanted bioelectronics overtime, protein adsorption must be controlled. This review paper outlines two major approaches to minimize protein adsorption onto the surface of implantable electronics. The first approach is surface coating, which minimizes close proximity interactions between proteins and device surfaces by immobilizing electrically neutral hydrophilic polymers as surface coating. These coatings reduce protein fouling by steric repulsion and formation of a hydration layer which acts as both a physical and energetic barrier that minimize protein adsorption onto the device. Relevant performances of various conventional hydrophilic coatings are discussed. The second approach is surface patterning using arrays of hydrophobic nanostructures through photolithography techniques. By establishing a large slip length via super hydrophobic surfaces, the amount of proteins adsorbed to the surface of the device can be reduced. The last section discusses emerging surface coating techniques utilizing zwitterionic polymers where ultralow-biofouling surfaces have been demonstrated. These surface modification techniques may significantly improve the long-term functionality of implantable bioelectronics, thus allowing researchers to overcome challenges to diagnose and treat chronic neurological and cardiovascular diseases.

Contents

1. Introduction

Advances in nanofabrication and the understanding of human biology have promoted the design of more compact, selective and efficient bioelectronics, which has opened numerous avenues for

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medical practitioners to diagnose and treat diseases that were previously considered incurable (Van Dijk et al., 2006; Jui-Mei Hsu et al., 2006; Svennersten et al., 2011; Boss et al., 1995). Neurological disorders are extremely difficult to diagnose and treat due to the complexity of the disease. Recent advances in molecular and cell biology have allowed scientists to pinpoint the exact location of several incurable disorders including Alzheimer's disease. According to World Health Organization, there is currently an estimate of 18 million people worldwide with Alzheimer's disease and is projected to nearly double to 34 million by 2025 (Alzheimer Disease International, 2012). Recently emerging researches have demonstrated promising results utilizing transcutaneous electrostimulation on the central nervous system of Alzheimer's patients to improve memory, alertness (Scherder et al., 1992,1995) and rest–activity rhythm (Van Dijk et al., 2006) without severe side effects. This is merely one example of the driving force behind the development of bioelectronics that is capable of synchronizing communication between biological and electrical platforms.

The scope of bioelectronics can be considered to incorporate an exploitation of biology in conjunction with electronics for information processing, information storage, electronic components and actuators (Biosensor and Bioelectronics, 2012). Miniaturized, implantable bioelectronics –such as neurostimulators and biosensors – are crucial in providing convenient continuous functionality in diagnostic or treatment without the need to interrupt the everyday life of the patients with psychological concerns of their health. Even though there have been numerous successful demonstrations of implantable biosensors and neurostimulators (Jui-Mei Hsu et al., 2006; Svennersten et al., 2011; Boss et al., 1995; Gough et al., 2010), the primarily challenge of current implantable bioelectronics still revolves around the long-term functionality of the device. In most cases, the development of successful implantable biosensors and neurostimulators has been severely hindered due to unreliable in vivo performance after a few hours or days.

The success of any implantable bioelectronics depends heavilyon preserving the devices' functionality in vivo throughout the course of the implantation. The implantation period can be chronicled into several stages, each with a distinct host response (Fig. 1). Upon surgical insertion of any implantable devices, tissue inflammation and foreign body response is immediately invoked as the initial stage of the body's natural defense system. The short term host response, or the acute inflammation phase, can last from hours to days depending on the surgical procedure. The next stage of the host response against implanted bioelectronics is indicated by fibrous encapsulation, which is the formation of a layer of fibroblast or smooth muscle cell sheet approximately50–200 μm in thickness to isolate the device (Williams and Williams, 1983; Kovacs, 1991). The formation of fibrous capsule will prevent further interaction of the bioelectronics with the surrounding host environment and compromises the functionality of the device. As a result, implanted bioelectronics often requires a secondary surgery to remove or replace the device. Taking implantable glucose sensors as an example, as of 2010, there are six minimally invasive glucose sensors approved by FDA that provides periodic readings (Wilson and Gifford, 2005); however, the longest marketed in vivo functionality is 7 days (Wilson and Gifford, 2005). Aside from the obvious that the fibrous capsule hinders the transport of glucose molecules(Wilson and Gifford, 2005), several investigations indicated that non-specific protein adsorption also hinder glucose diffusion to the sensor (Wilson and Gifford, 2005; Kyrolainen et al., 1995; Rigby et al., 1999). As a result, in order to prolong the functionality of any bioelectronics, the progression undesirable host responses must be delayed if not completely prevented.

There are several established strategies for improving biocompatibility of implantable devices. One approach is by minimizing acute inflammation phase by refining and enhancing different aspects of the surgical procedure; these methods are often referred to as indirect influences and can generally be applied to implantable bioelectronics regardless of their applications. One strategy is to refine the surgical insertion techniques with the goal of minimizing implant injury, which will reduce the degree of homeostatic responses as well as the amount of blood-to-device exposure (Fournier et al., 2003; Ratner et al., 2004). Another

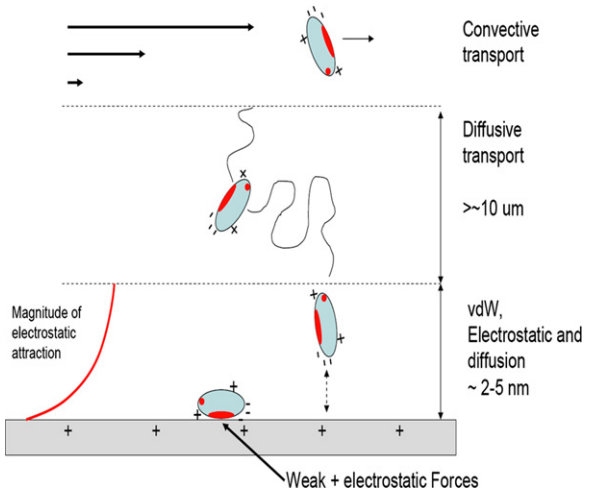

Fig. 2. Schematic representation of the protein adsorption process. Outlining the conductive transport region (top), diffusive transport region (middle), and close proximity region (bottom).

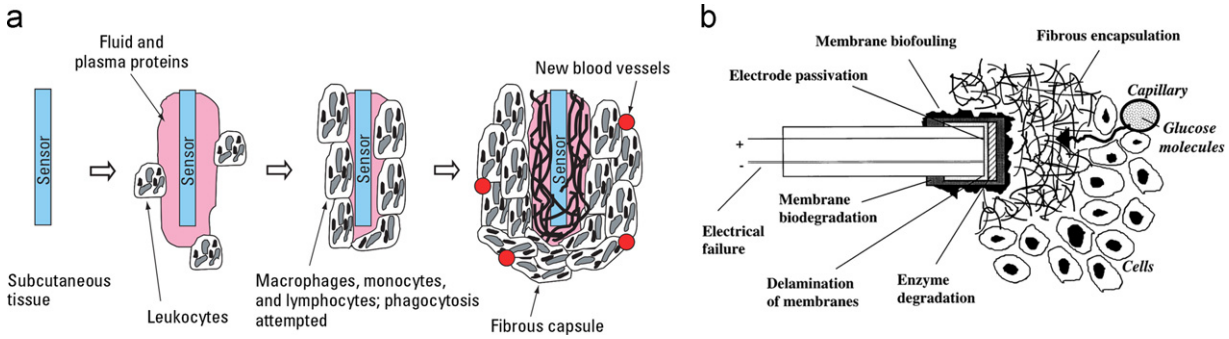

Fig. 1. (a) Sequence of events that are initiated around an implant leading to the formation of fibrous capsules around implantable systems. (b) Various failure mechanisms reported for an implantable biosensor. (Reprinted with permission from Frost and Meyerhoff, 2006. Copyright 2006 American Chemical Society). (Reprinted with permission from Wisniewski and Reichert, 2000. Copyright 2000 Elsevier). (Santhisagar et al., 2010).