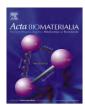
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In vivo effects of L1 coating on inflammation and neuronal health at the electrode-tissue interface in rat spinal cord and dorsal root ganglion

C.L. Kolarcik^a, D. Bourbeau^b, E. Azemi^{a,c}, E. Rost^a, L. Zhang^a, C.F. Lagenaur^{c,d}, D.J. Weber^b, X.T. Cui^{a,c,e,*}

^a Department of Bioengineering, University of Pittsburgh, 5057 Biomedical Science Tower 3, 3501 Fifth Avenue, Pittsburgh, PA 15260, USA

^b Department of Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, PA, USA

^c Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA, USA

^d Department of Neurobiology, University of Pittsburgh, Pittsburgh, PA, USA

^e McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, USA

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ABSTRACT

The spinal cord (SC) and dorsal root ganglion (DRG) are target implantation regions for neural prosthetics, but the tissue–electrode interface in these regions is not well-studied. To improve understanding of these locations, the tissue reactions around implanted electrodes were characterized. L1, an adhesion molecule shown to maintain neuronal density and reduce gliosis in brain tissue, was then evaluated in SC and DRG implants. Following L1 immobilization onto neural electrodes, the bioactivities of the coatings were verified in vitro using neuron, astrocyte and microglia cultures. Non-modified and L1-coated electrodes were implanted into adult rats for 1 or 4 weeks. Hematoxylin and eosin staining along with cell-type specific antibodies were used to characterize the tissue response. In the SC and DRG, cells aggregated at the electrode–tissue interface. Microglia staining was more intense around the implant site and decreased with distance from the interface. Neurofilament staining in both locations decreased or was absent around the implant, compared with surrounding tissue. With L1, neurofilament staining was significantly increased while neuronal cell death decreased. These results indicate that L1-modified electrodes may result in an improved chronic neural interface and will be evaluated in recording and stimulation studies.

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1. Introduction

Neural prosthetic devices implanted into the nervous system to bypass and/or restore sensory-motor or cognitive functions have enormous clinical potential. There are a variety of situations in which such devices can be of use, with proposed applications in the fields of gerontology, rehabilitative medicine, psychiatry, neurology and clinical research [1]. More specifically, neural interface systems can be used for communication [2], to restore lost functional movement [3], to reinnervate target locations for bladder control and for the treatment of neurological conditions such as epilepsy [4,5] and Parkinson's disease [6], among others. While much effort has been devoted to brain interfaces, both the spinal cord (SC) and dorsal root ganglion (DRG) are also target implantation regions for these promising rehabilitative and therapeutic devices. For example, SC stimulation has been investigated for pain control [7] and restoration of motor functions [8,9], while the DRG

* Corresponding author at: Department of Bioengineering, University of Pittsburgh, 5057 Biomedical Science Tower 3, 3501 Fifth Avenue, Pittsburgh, PA 15260, USA. Tel.: +1 412 383 6672; fax: +1 412 383 5918.

E-mail address: xic11@pitt.edu (X.T. Cui).

is an attractive site for recording or stimulating primary afferent neurons to provide sensory feedback [10,11].

Irrespective of the implant location, these neural interfaces must remain stable throughout the lifespan of the user. However, biocompatibility issues have limited the success of chronically implanted devices [12–15]. The fate of implanted devices is often determined by the effective integration with the surrounding neural tissue, a current and major roadblock in neuroengineering [1,16–18]. In brain tissue, immune and inflammatory reactions, including gliosis at the implant site, result in decreased performance of microelectrodes. Gliosis is thought to be mediated by macrophages, activated microglia and reactive astrocytes, resulting in the formation of a glial sheath that can encapsulate and isolate the implanted probe from the surrounding tissue [19]. In addition, significant decreases in neuronal density in the area immediately surrounding the implant site (the "kill zone") are problematic. For the long-term success of chronically implanted electrodes, maintaining neurons close to the implant site (within 50-100 µm), minimizing astrogliosis and reducing or eliminating microglial activation are necessary. In the peripheral system, manipulation or damage to a neural structure also leads to anatomic, metabolic and physiological alterations [20]. However, the reactions surrounding these peripheral interfaces highlight the



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