



Nerve Guidance by a Decellularized Fibroblast Extracellular Matrix



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Abstract

Spinal cord and peripheral nerve injuries require the regeneration of nerve fibers across the lesion site for successful recovery. Providing guidance cues and soluble factors to promote neurite outgrowth and cell survival can enhance repair. The extracellular matrix (ECM) plays a key role in tissue repair by controlling cell adhesion, motility, and growth. In this study, we explored the ability of a mesenchymal ECM to support neurite outgrowth from neurons in the superior cervical ganglia (SCG). Length and morphology of neurites extended on a decellularized fibroblast ECM were compared to those on substrates coated with laminin, a major ECM protein in neural tissue, or fibronectin, the main component of a mesenchymal ECM. Average radial neurite extension was equivalent on laminin and on the decellularized ECM, but contrasted with the shorter, curved neurites observed on the fibronectin substrate. Differences between neurites on fibronectin and on other substrates were confirmed by fast Fourier transform analyses. To control the direction of neurite outgrowth, we developed an ECM with linearly aligned fibril organization by orienting the fibroblasts that deposit the matrix on a polymeric surface micropatterned with a striped chemical interface. Neurites projected from SCGs appeared to reorient in the direction of the pattern. These results highlight the ability of a mesenchymal ECM to enhance neurite extension and to control the directional outgrowth of neurites. This micropatterned decellularized ECM architecture has potential as a regenerative microenvironment for nerve repair.

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Introduction

Peripheral nerve and spinal cord injuries are a critical problem in the United States, leading to devastating functional disability, impacting long term quality of life, and causing significant social and economic burden for thousands of individuals each year [1]. In general, all central nervous system (CNS) injuries and most peripheral nervous system (PNS) injuries over approximately 3 cm lead to poor prognoses for recovery of neurologic function. After injury, failure to recreate the proper extracellular matrix (ECM) microenvironment to guide neurites down specific tracts can lead to insufficient axonal growth and neuronal survival resulting in scarring and poor clinical outcomes [2–4].

Inhibitory factors, wound ECM, and inflammatory cells at the lesion site do not provide the trophic support and axon guidance needed for the injured nerve cells to regenerate across a large gap [5]. Identifying a regenerative microenvironment that facilitates neurite growth by providing inductive cues and survival signals, while being devoid of inhibitory factors, could advance biomaterial design for repair of nerve injuries.

The ECM is a naturally occurring protein network that provides structure, support, and guidance to cells [6]. It also relays biological signals to the cells through specific binding sites and serves as a reservoir for soluble factors bound to ECM components. Laminins are perhaps the most significant class of ECM proteins in the nervous system, playing

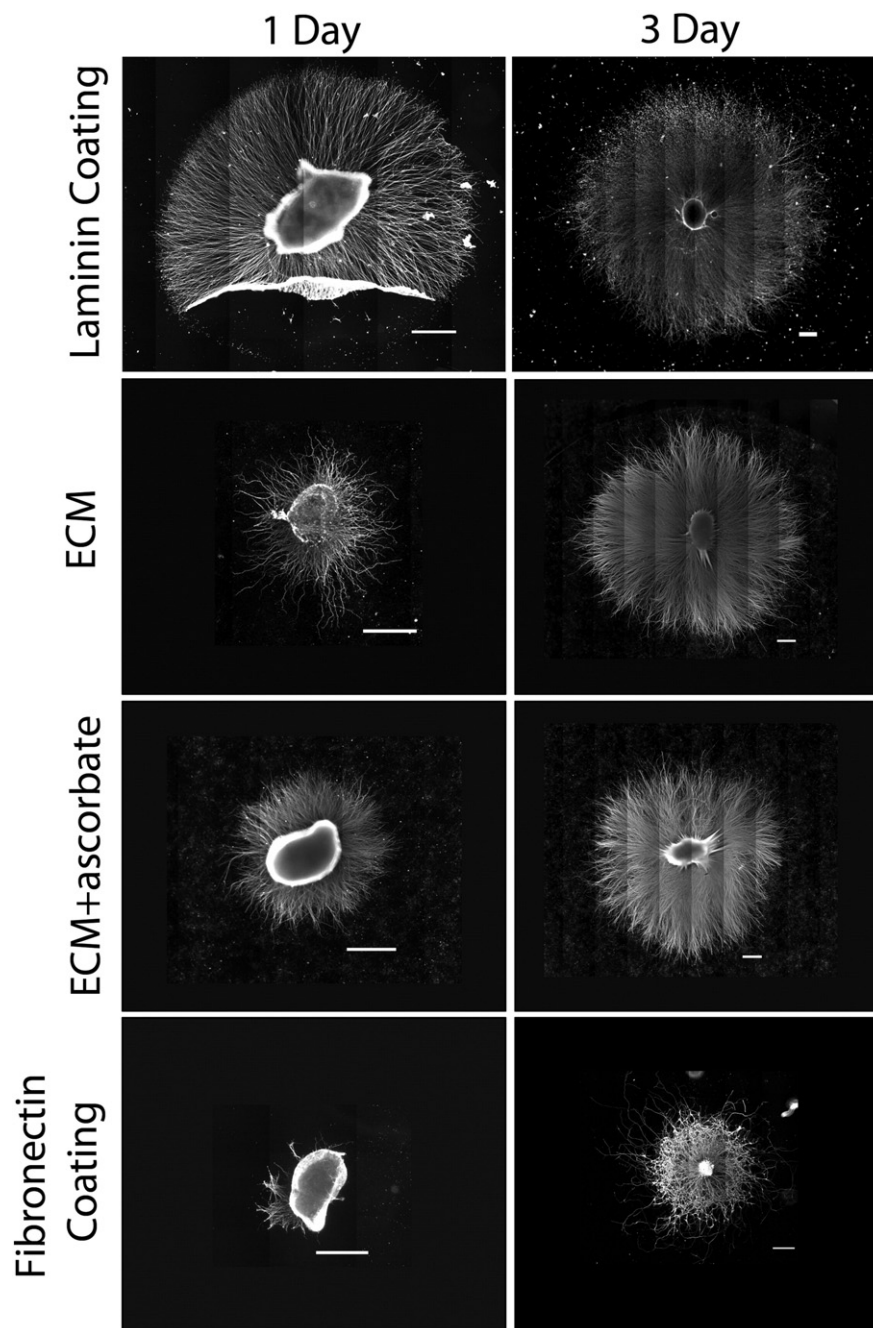


Fig. 1. Neurite extension from SCG explants. SCGs were placed on the indicated substrates and cultured for 1 or 3 days to allow neurite outgrowth. Explants were stained with anti- α -tubulin antibody. Multiple images were captured across each sample and were subsequently assembled into a mosaic to show total neurite outgrowth. SCGs and neurites tend to be more loosely attached to laminin than to the other substrates resulting in frequent folding over of neurites during the staining procedure (as in the laminin 1 day sample). Scale bars are 500 microns.

critical roles in both the CNS and PNS by supporting diverse functions including neuronal migration, axonal outgrowth, myelination and formation of the neuro-muscular junction [7]. In fact, laminin-111 is commonly used as the substrate of choice for

neurite outgrowth assays [8–10]. However, laminins are not structural components of the ECM at injury sites. Fibronectin, on the other hand, is a major component of the wound ECM with plasma fibronectin deposited during blood coagulation and cell-derived

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