Application of HS Containing Biomatrices for Neural Repair

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The fine structure (sulfation position and density) of the HS side chains of perlecan is an important regulatory determinant in the differentiation of pluripotent stem cells in the niche environment in neural tissues. Interaction of HS with growth factors (FGF-2) and morphogens (Wnt, SHh) is also essential for the long-term viability of recycling stem cells and the proliferation and differentiation of stem cells that have escaped from quiescent recycling and along with interactions with niche ECM components regulates the development of stem cell lineages that attain migratory properties facilitating their participation in neural repair processes. The expression of HS biosynthetic enzymes in the niche and tissue environments also have important roles in determining the fine structure of HS and how it exerts these effects spatially and temporally in tissue development and neural repair processes and also has roles in the determination of synaptic specificity, axonal guidance, synapse development and synapse function.

Keywords: neural tissue repair ; extracellular matrix ; neural progenitor stem cells

1. Introduction

Hyaluronan (HA) is a major space-filling component of the CNS/PNS providing tissue hydration and a matrix for cell attachment and an environment conducive to cellular survival and cellular migration during CNS/PNS development [1][2][3]. HA also ensures specific niche environments, and ionic gradients are maintained in the 3D brain architecture to ensure optimal conditions for cellular activity. The brain extracellular matrix (ECM) is unusual in that it is dominated by glycosaminoglycans (GAGs), particularly HA, and it is one of the softest tissues in the human body. The immobilization of HA in the CNS ECM is critical to the optimal functional properties of the brain; however, HA is a soluble polymer, and it relies on interactions with proteoglycans (PGs), HA receptors and HA interactive glycoproteins for its immobilization in the CNS/PNS ECM [2]. HA is a component of both diffuse and condensed brain ECM structures known as perineuronal nets (PNNs), which protect neurons and are essential for the maintenance of optimal neural cellular activity [4]. HA is the only non-sulfated GAG and has a relatively simple repeat N-acetyl-glucosamine-D-glucuronic acid disaccharide structure. HA is highly interactive with the lectican PGs and HA-receptors and also influences cell migration in developing tissues [5]. High molecular weight HA is anti-inflammatory and mops up free radicals generated by inflammatory cells; thus, it counters the development of neuro-inflammation. The formation of HA-lectican aggregates (particularly HA-aggrecan aggregates) is critical to tissue hydration, brain volume, maintenance of cellular organization and micro-compartmentalization in the brain ECM. This provides niche and metabolite gradient environments that promote optimal cellular activities in the brain 3D environment. The importance of HA's roles in brain tissues becomes apparent in tissues that display an HA deficiency. For example, brain tissues that are deficient in HA synthase-3 activity (*Has3* KO) display frequent seizures and an epileptic phenotype [6][7].

2. Application of HS Containing Biomatrices for Neural Repair

Perlecan is also a major functional component of the stem cell niche and has many attributes with regard to tissue development and repair processes [8][9][10][11]. Perlecan is expressed in the basal neuroepithelium during neural development and is a crucial component of the neural niche [12][13]. Perlecan has multifunctional instructive properties [14] in developmental brain tissues [10][15] and promotes the proliferation and differentiation of neuroprogenitor stem cells in the sub-ventricular fractones through the sequestration of FGF-2 in the neural niche activating the Akt and Erk 1/2 cell signaling pathways [16]. The Wnt and ShH pathways also regulate stem cell proliferation, neurogenesis and neural network formation [17][18]. However, Wnt and Hedgehog proteins are relatively poorly soluble in aqueous media. Wnt and ShH bind to perlecan domain II, and this acts as a transport PG, aiding in the establishment of Wnt and ShH morphogen gradients in tissues that are important for tissue development [8]. The availability of recombinant perlecan domain I and domain V will allow investigations to be undertaken in the stimulation of neural repair processes in tissues [19][20][21][22] and

in repair of the blood–brain barrier following ischemic stroke [23][24][25]. Further studies with perlecan in neural repair processes are expected in the future, and these offer exciting possibilities.

2.1. Harnessing Cell Instructive Properties of Perlecan's HS Side Chains in Repair Biology

The fine structure (sulfation position and density) of the HS side chains of perlecan is an important regulatory determinant in the differentiation of pluripotent stem cells in the niche environment in neural tissues [26]. Interaction of HS with growth factors (FGF-2) and morphogens (Wnt, SHh) is also essential for the long-term viability of recycling stem cells and the proliferation and differentiation of stem cells that have escaped from quiescent recycling and along with interactions with niche ECM components regulates the development of stem cell lineages that attain migratory properties facilitating their participation in neural repair processes [11][23][27]. The expressions of HS biosynthetic enzymes in the niche and tissue environments also have important roles in determining the fine structure of HS and how it exerts these effects spatially and temporally in tissue development and neural repair processes and also has roles in the determination of synaptic specificity, axonal guidance, synapse development and synapse function [28]. Perlecan is an important regulatory cell instructive PG in the neural stem cell fractone [29]. The availability of recombinant perlecan domain I and domain V now makes it possible to incorporate these components into new generation bioscaffolds in neural repair strategies attempting to mimic the niche environment of native neural tissues. Such approaches used in combination with HA and neural progenitor stem cell preparations have a high probability of further improving on existing neural repair applications.

Collagen–HS porous scaffolds containing NSCs have been used to treat a rat model of traumatic brain injury, established using a controlled cortical impact [30]. Brain edema and cell apoptosis were significantly reduced, and motor and cognitive functions markedly improved using this procedure suggesting that porous collagen–HS scaffolds loaded with NSCs can improve neurological deficits in a rat model of traumatic brain injury [30]. Three-dimensional (3D) bioprinter-assembled collagen–HS scaffolds have also been used to treat controlled spinal cord injuries in rats [31]. The HS component of this scaffolding material crosslinks the collagen fibers, increasing its compression modulus and mechanical stability. This scaffold displays good biocompatibility with neurons co-administered within the scaffold. The HS component of this scaffold significantly improves the immobilization of bioavailable FGF-2, which promotes progenitor cell proliferation. A significant recovery in locomotor function and increased numbers of neurofilament positive cells were evident using this approach, suggesting that this matrix actively stimulates axonal guidance and neural repair processes. Porous bioscaffolds of chitosan–gelatin containing HA and/or HS have also been used in neural tissue engineering [32]. Such scaffolds contained highly interconnected pores ranging in size from 90 to 140 µm, and the scaffold had a porosity index of over 96%. Neural progenitor stem cells seeded into this matrix displayed adhesion, proliferation and multi-lineage differentiation in the 3D scaffold environment, indicating that this matrix may be useful in neural repair biology applications [32].

2.2. Development of Artificial Neural Stem Cell Niches

Significant improvements in bioscaffold microfabrication methodology has permitted the miniaturization of these platforms. Lithography and direct laser printing have been applied to prepare 2D patterns and 3D scaffolds to shape hydrogels and synthetic polymers to create niche-like structures for single neural cell culture [33]. Artificial laminin 3D neural stem cell niche-like structures have been developed to recapitulate the dynamic nature and some of the biological complexity of the neural stem cell niche and maintain laminin in a native conformation and orientation as found in the niche. These scaffolds support enhanced human NSC proliferation and neurite extension [34][35]. Stem cell niches are intricate spaces that provide specific chemical and biological environments that control stem cell fate [36]. Microdevices have been developed that have proved useful for the culture of NG108-15 neuroblastoma and human NPCs and represent a system amenable to modifications that promote these cellular activities for applications in neural repair biology [31][32][34].

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