A Novel Approach to Guiding Neurogenesis: Manipulation of Neural Stem Cell Differentiation and Growth Using Glycan-Based Small Molecules

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Neurodegenerative diseases and central nervous system (CNS) injuries are characterized by cerebral atrophy and neuronal circuitry abnormalities. Neural stem cell (NSC) transplantation is of interest for neuronal repair, as demonstrated by functional recovery in preclinical animal studies. However, clinical challenges remain in NSC usage; for instance, uncontrolled proliferation may invoke immunological responses. NSC differentiation is heavily dependent on cellular interaction with glycosaminoglycans (GAGs), which are known to regulate many aspects of cell behavior and signaling. GAG biosynthesis can be modulated with small molecules termed xylosides. Therefore, this project investigated mechanisms in guiding NSC fate and subsequent growth, from a GAG point of view. H-9 derived human NSCs and E18 hippocampal neurons were treated with different xylosides and immunofluorescently stained after a time period. NSCs were differentiated over two weeks, then stained for neuronal and glial populations. GAG profile of the NSCs was analyzed through radiolabelling. E18 hippocampal neurons were grown for 24 hours and fluorescence intensity was used to determine growth. Depending on the type of xylosides, NSCs exhibited different patterns of differentiation, resulting in significantly increased differentiation into neurons ($P<0.05$). Treatment with mono-xylosides in the NSC cultures promoted neurogenesis by 50%, while bis-xylosides doubled neuronal growth. Additionally, xylosides were revealed to change GAG profile, highlighting the crucial role of the xyloside-primed GAGs in guiding NSC differentiation. This research presents a novel usage of glycan-based small molecules, which function through altering the cells' GAG profile, as a solution to control NSC fate and growth.