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Grant Title: Glycan-driven neuronal migration and its application in regenerative medicine

Abstract

【Purpose】

The adult mammalian brain is equipped with mechanisms that maintain the stability of neural circuits while simultaneously enhancing plasticity. Proteins containing sugar chains—such as chondroitin sulfate proteoglycans (CSPGs), heparan sulfate proteoglycans (HSPGs), and neural cell adhesion molecules modified with polysialic acid (PSA)—play a crucial role in these mechanisms; however, their regulatory mechanisms and significance remain unclear.



In recent years, it has become clear that neurons are capable of active migration even in the stable adult brain. Immature newborn neurons generated from neural stem cells in the ventricular-subventricular zone form chains and migrate to the olfactory bulb through tunnels formed by astrocytes. Recent studies have shown that neurons also migrate in chains in the postnatal human brain, suggesting that chain migration is a common mode of movement in the postnatal brain and plays a crucial role in brain development by dynamically remodeling neural circuits.

In recent studies, we focused on the role of glycans in neuronal migration and revealed that the cancelation of the repulsive effect of CSPG by HSPG (Nakajima et al., *Nat Commun* 2024) and the maintenance of PSA by neuraminidase inhibitors (Matsumoto et al., *EMBO Mol Med* 2024) promote neuronal migration and regeneration following brain injury. Therefore, the objective of this study is to elucidate the functions of these glycans at the molecular level and to develop innovative neural regenerative medical technologies by manipulating them.

【Methods】

In this study, we focused on the glycoproteins, CSPG, HSPG, and PSA-NCAM, to elucidate their functions and significance in neuronal migration and regeneration processes in both normal and injured brains. First, we analyzed the detailed molecular mechanisms underlying the roles of CSPG and HSPG in neuronal migration in the normal brain by combining knockout and knockdown experiments with live imaging. Next, applying the identified HSPG-mediated control mechanisms and the PSA regulation mechanism by neuraminidase, we conducted experiments to establish therapeutic methods that promote the process from neuronal migration to neural circuit regeneration in mouse and common marmoset (a primate model) brain injury models.

【Results】

In this study, we demonstrated that neuronal migration can be controlled by utilizing HSPG to antagonize the repulsive effects of CSPG or by regulating PSA with neuraminidase inhibitors. Furthermore, by applying the molecular mechanisms elucidated in this study, we developed a novel therapeutic approach that guides newly generated neurons derived from neural stem cells to their intended locations, thereby regenerating the neurons lost due to brain injury.