DAAM2 PHOSPHORYLATION BY CK2 FACILITATES OLIGODENDROCYTE DIFFERENTIATION

Chih-Yen Wang[1]

[1] Baylor College of Medicine, Department of Texas Children's Hospital

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Background: Oligodendrocyte (OL) differentiation is a critical step for tissue repair in white matter injury such as cerebral palsy (CP) and multiple sclerosis (MS). Although OL precursor cells (OPCs) are recruited and proliferative in demyelinating lesions, differentiation processes are blocked by various pathological factors and signaling pathways. We previously identified Daam2 is a positive modulator of Wnt signaling and inhibits OL differentiation, yet how Daam2 function is regulated remains unknown.

Materials/Methods: For cellular and molecular mechanism study, Daam2 mutant animals and primary OPC culture were used and analyzed by immunostaining and western blot. For mouse white matter injury models, neonatal hypoxic injury and lysolecithin-induce focal lesion that are relevant to CP and MS respectively were performed.

Results: In this study, we confirmed a phosphorylation modification at S704/T705 of Daam2 protein in the mouse brain by mass spectrometric analysis. Mice with phospho-mimetic (E) mutation of Daam2 display early OL development, which is similar to the phenotype in Daam2-KO mice. To dissect possible mechanism, we discovered Daam2-E mutant is susceptible to degradation and polyubiquitination and unable to inhibit OL differentiation. In addition, Daam2 can be phosphorylated by CK2α at S704/T705 and promotes OL differentiation. In white matter injury models, Daam2-E mutant mice show protection and better recovery in white matter development against neonatal hypoxia. After lysolecithin-induced focal demyelination, remyelination process around lesion is also improved by Daam2-E mutation. Moreover, OL-targeting CK2α overexpression by AAVs increases OL differentiation during development and after injury.

Conclusions: Daam2 phosphorylation by CK2α leads to its protein instability, which in turn promotes OL differentiation. To phosphorylate Daam2 through CK2α after injury could be a novel therapeutic strategy for improving remyelination.

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