Stony Brook University
The Graduate School

Doctoral Defense Announcement

Abstract

Cleavage of Amyloid Precursor Protein by ADAM10 and BACE1 Regulates Oligodendrocyte Development and Central Nervous System Myelination

By

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Oligodendrocytes are the myelin forming cells of the central nervous system (CNS), and are critical to the proper patterning of action potential propagation. Myelin generation, homeostasis, and repair are tightly regulated by the balance between oligodendrocyte progenitor (OP) cell expansion and differentiation during post-natal development. A range of signaling mechanisms that either promote or inhibit OP cell cycle progression have been elucidated. However, signaling cues that act as master regulators, capable of switching between and driving both states, remain elusive. In this context, I sought to identify new regulators of the oligodendrocyte lineage using developmental myelination as a model system, and uncovered Amyloid Precursor Protein (APP) as a novel candidate. APP is highly expressed in the brain, and plays a key role in Alzheimer's disease. Although the biological significance of APP is still largely unknown, new non-pathogenic roles for APP are slowly emerging. Consistent with the idea that APP may regulate normal CNS development, I found that cleavage of APP by the α-site protease ADAM10 and the β-site protease BACE1 controlled the timing of oligodendrogenesis in the neonatal subcortical white matter. Mechanistically, the ADAM10-specific cleavage product (sAPPα) activated the pro-progenitor Wnt pathway, and the BACE1-specific product (Aβ) inhibited Wnt signaling and triggered lineage progression. In line with these findings, sAPPα levels were elevated during early development when the OP pool is actively expanding, whereas BACE1 cleavage products were most abundant following OP differentiation. ADAM10 loss-of-function, specifically in OPs, resulted in reduced levels of sAPPα and Wnt activity, which accelerated CNS myelination. In contrast, treatment with sAPPα blocked OP differentiation. Specifically, I found that these effects were mediated by the interaction between the 751-amino acid isoform of sAPPα with the Wnt co-receptor LRP6. Furthermore, using two separate Cre-recombinase drivers, I demonstrated that the phenotype seen in conditional knockout mice was unique to that model, which indicated a stage-specific role for ADAM10 in OL development. Taken together, I concluded that temporal regulation of APP processing by α-/β-secretases serves as a platform to direct the outcome of postnatal myelination in the CNS.

Date: January 12th, 2018 **Program**: Genetics
Time: 10:00am **Dissertation Advisor**: Dr. Adan Aguirre
Place: Basic Science Tower (BST), Floor 8, Room 180