Nectin-like 2 (Necl-2) cell adhesion molecule is a negative regulator of Schwann cell myelination

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Axo-glial interactions are critical for Schwann cell genesis, myelination and domain organization of myelinated fibers. Axon-bound type III neuregulin-1 (Nrg-1) regulates Schwann cell proliferation, survival and myelination by activating the PI3K/Akt pathway through the ErbB2/ErbB3 tyrosine kinase receptors. Nectin-like proteins (Necls) are homo- and heterophilic cell adhesion molecules. Recent studies have shown that Schwann cell Necl-4 and its *bona fide* binding partner, axonal Necl-1 promote axon-glia interactions along the internode. Further studies, *in vitro* and *in vivo*, have shown that Necl-4 promotes Schwann cell myelination. Surprisingly however, *in vitro* data suggest that axonal Necl-1 negatively regulates myelination. This raises the question of how Necl-4 and Necl-1, which are strong heterophilic binding partners, have opposite effect. The response may lie in Necl-2, a lower affinity heterophilic binding partner for Necl-1 that is also expressed by Schwann cells. We could then envision the following hypothesis: a myelin-promoting Necl1/Necl4 interaction, and a myelin-inhibiting Necl-1/Necl-2 interaction. To start testing the idea that Schwann cell Necl-2 may therefore be inhibitory to myelination, we have used lentiviral-mediated knockdown or ectopic expression of Necl-2, associated with the well-established Schwann cell-DRG myelinating coculture system. We show that Necl-2 negatively regulates myelin formation by Schwann cells, without affecting the axon contact-mediated Schwann cell proliferation. In the context of axo-glial interaction, we observed a marked increase (Necl-2 KO Schwann cells), or decrease (Necl-2 over-expressing cells), in Akt activation in direct correlation with the observed myelination results. The effects were specific to Akt, with no observable changes in activation of ErbB2, ErbB3, Erk1/2, PTEN and PDK1. Interestingly Necl-2 over-expression or knockdown did not affect the activation of the ErbB/PI3K/Akt signaling cascade by soluble neuregulin. In Schwann cells, co-immunoprecipitation studies suggest that Necl2 does not form a complex with ErbB3, or ErbB2. Necl-2 also did not prevent the recruitment of ErbB2 by ErbB3 upon neuregulin stimulation. Taken together, these results suggest that Necl-2 may

regulate Schwann cell myelination by affecting Akt activity in a mechanism independent of the Nrg-1/ErbB/PI3K signaling cascade. Our future studies will aim to identify the axonal signal provided to Necl-2 (possibly Necl-1 and/or Necl-2) as well as the molecular machinery linking Necl-2 to Akt.