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·Letter to the Editor·

Dose-dependent regulation of oligodendrocyte specification by β-catenin signaling

Dear Editor,

Although various components of the Wnt/β-catenin pathway have been investigated, there are conflicting reports on the roles of Wnt/β-catenin signaling in oligodendrogenesis and differentiation. For instance, the ΔExon3 mutation of β-catenin[1-4], which stabilizes β-catenin by deletion of the phosphorylation site for the destruction complex, significantly inhibits the differentiation of oligodendrocytes, but knockout of β-catenin also delays it[4]. In addition, overexpression of dominant-negative (dn) forms of *Tcf/Lef* increases the number of oligodendrocyte progenitors (OLPs)[3, 5], and knockout of *Tcf7l2* (also known as *Tcf4*) impairs myelin formation[3, 6]. In contrast, another study showed that overexpression of dn*Tcf7l2* decreases the number of OLPs[7].

Although some of these conflicts could be explained by the finding that Wnt/β-catenin signaling regulates oligodendrocyte development in a stage- and region-specific manner[4, 8-10], its role in the differentiation of oligodendrocytes remains elusive. To address whether Wnt/β-catenin signaling regulates oligodendrocyte development in a dose-dependent manner, we generated mice with different mutations of β-catenin in early OLPs, β-catenin$^{\Delta Exon3/+}$, β-catenin$^{\Delta Exon2\text{-}6/\Delta Exon2\text{-}6}$, and β-catenin$^{\Delta Exon3/\Delta Exon2\text{-}6}$. Quantitative reverse-transcription PCR showed that the dose of Wnt/β-catenin signaling in the compound β-catenin$^{\Delta Exon3/\Delta Exon2\text{-}6}$ mice was lower than that in β-catenin$^{\Delta Exon3/+}$ mice but higher than that in the WT (β-catenin$^{+/+}$) (Supplementary information, Fig. S1). For clarity, β-catenin$^{\Delta Exon2\text{-}6/\Delta Exon2\text{-}6}$, β-catenin$^{\Delta Exon3/\Delta Exon2\text{-}6}$, and β-catenin$^{\Delta Exon3/+}$ mice are referred to as Cat^{Low}, Cat^{High}, and Cat^{High+}, respectively. Consistent with previous work[4], *in situ* hybridization showed that during oligodendrogenesis, *Sox10*- and *Pdgfrα*-positive cells were not present in the spinal cord of Cat^{High+} mice at embryonic day 14.5 (E14.5) (Fig. 1A b and f). In contrast, excess *Sox10*- and *Pdgfrα*-positive cells were present in Cat^{Low} mice (Fig. 1A c and g). Interestingly, compared with WT mice, fewer *Sox10*- and *Pdgfrα*-positive cells were produced in the compound Cat^{High} mice (Fig. 1A d and h, and Ca). Together, these results suggested that at the early stage of oligodendrocyte development in the spinal cord, Wnt/β-catenin signaling inhibits OLP specification of neural stem cells by a dose-dependent mechanism.

We next determined whether the number of OLPs returned to normal in the compound Cat^{High} mice. Although fewer *Sox10*-positive cells were observed in the white matter, both Cat^{Low} and Cat^{High} mice contained normal numbers of *Sox10*- and *Pdgfrα*-positive cells in the gray matter of the spinal cord (Fig. 1B c, d, g, and h, and Cb). Considering that *Sox10* is expressed in both OLPs and differentiated OLs, and *Sox10*-positive cells in the white matter represent mature oligodendrocytes, this result indicates that the number of OLPs returns to normal in the Cat^{Low} and Cat^{High} mice in the perinatal stage. In contrast, there were still no detectable *Sox10*- and *Pdgfrα*-positive OLP cells in the spinal cord of Cat^{High+} mice (Fig. 1B b and f), indicating that a higher level of β-catenin activity leads to a stronger inhibition of OLP generation.

To analyze β-catenin function in OLP differentiation, we assessed the differentiation of OLPs in compound β-catenin mutant mice in the perinatal stage. On postnatal day 0 (P0), expression of the mature OL markers *Mbp* and *Plp* was significantly reduced in Cat^{Low} mice compared to controls (Fig. 1B k and o, and Cc), consistent with the previous observation that β-catenin functions to promote OLP differentiation at late embryonic stages. However, expression of *Mbp* and *Plp* was almost completely inhibited in the spinal cord of Cat^{High+} and Cat^{High} mice (Fig. 1B j, n, l, and p, and Cc). These results demonstrated that full-length β-catenin cannot be replaced by β-catenin with the ΔExon3 mutation, suggesting that a dose of β-catenin activity slightly higher than that in the WT inhibits OLP differentiation. Further studies are needed to test the possibilities that full-length β-catenin regulates OLP differentiation partially independent of Wnt signaling, and β-catenin with the ΔExon3 mutation causes a dominant effect of other signal pathways.

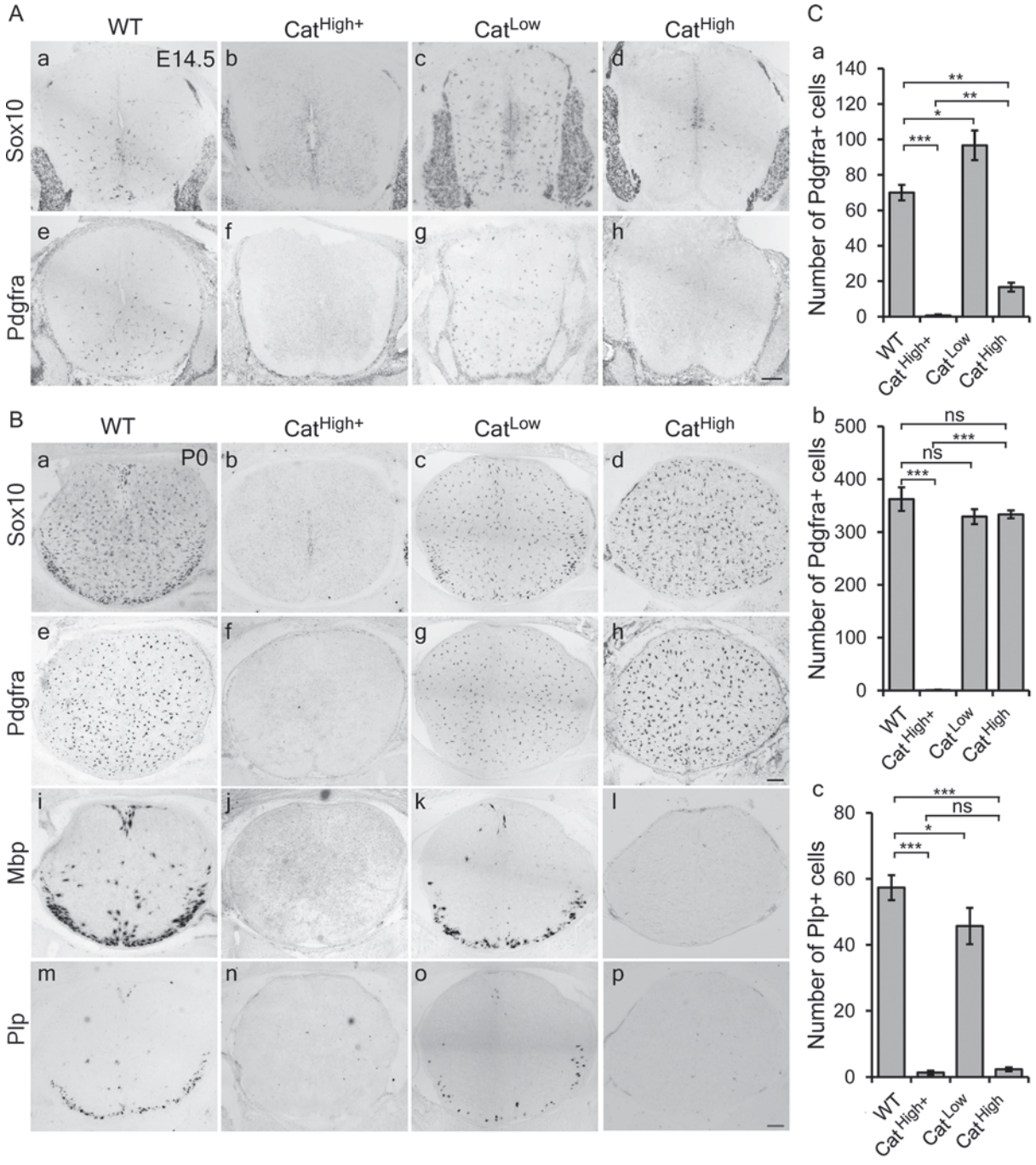

Fig. 1. β-catenin regulates the specification and differentiation of oligodendrocyte progenitors (OLPs). (A) Wnt/β-catenin signaling inhibits the specification of OLPs in a dose-dependent manner. Transverse sections of spinal cord at E14.5 from different β-catenin mutant mice subjected to *in situ* hybridization with *Sox10* (a–d) and *Pdgfrα* (e–h) riboprobes as OLP markers. Cells positive for *Sox10* and *Pdgfrα* were absent, increased, or decreased in the spinal cord from *Olig1*^{Cre}-mediated Cat^{High+}, Cat^{Low}, or Cat^{High} mice, respectively. Scale bars, 100 μm. (B) β-catenin mutations impaire OLP differentiation. All mutants except Cat^{High+} contained normal numbers of cells positive for *Sox10* and *Pdgfrα* at P0 (a–h). Expression of *Mbp* and *Plp* was reduced in Cat^{Low} mice and greatly inhibited in β-catenin^{High+} and β-catenin^{High} mice (i–p). Scale bars, 100 μm. (C) Numbers of *Pdgfrα*$^+$ and *Plp*$^+$ cells per section (mean ± standard deviation of three sections) in the spinal cord of different β-catenin mutant mice at E14.5 (a) and P0 (b and c) ($^*P$ <0.05; $^{**}P$ <0.01; $^{***}P$ <0.001; ns, not significant; *t*-test).

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