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COMMENTARY

Neogenin-YAP signaling in neocortical astrocytic differentiation

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ABSTRACT

Astrocytes, a major type of glial cells in the mammalian central nervous system (CNS), have a wide variety of physiological functions, including formation of the blood brain barrier, and modulation of synaptic transmission and information processing, and maintenance of CNS homeostasis. The signaling pathway initiated by bone morphogenetic protein (BMP) is critical for astrogliogenesis. However, exactly how this pathway regulates astrogliogenesis remains poorly understood. We have recently provided *in vitro* and *in vivo* evidence for neogenin's function in neural stem cells (NSCs) to promote neocortical astrogliogenesis. Neogenin in NSCs as well as astrocytes is required for BMP2 activation of RhoA that promotes YAP (yes-associated protein) nuclear translocation, consequently, YAP interaction with nuclear p-Smad1/5/8, and stabilization of Smad1/5/8 signaling. We have also provided evidence that YAP in NSCs is necessary for neocortical astrogliogenesis, and expression of YAP in neogenin deficient NSCs diminishes the astrogliogenesis deficit. These recent findings identify an unrecognized function of neogenin in promoting neocortical astrogliogenesis, and reveal a pathway of BMP2-neogenin-YAP-Smad1 underlying astrogliogenesis in developing mouse neocortex.

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Nearly 50% of the cells in the adult human brain are glial cells.[1] Among which, astrocytes are the most abundant glial cell type in the mammalian brain, which play a wide variety of roles in brain development and functions, such as regulating the cerebral blood flow, forming and maintaining blood brain barrier, supporting the central nervous system (CNS) metabolism, clearing the neurotransmitter between synapse, and specific effects on synaptogenesis and synaptic plasticity.[2-5] In addition, astrocytes also play critical roles in pathological CNS such as spinal cord injury and stroke.[2,6,7] Defects in astrocyte generation during development contribute to dysfunctions of synaptic plasticity, neuropsychological disorders, and brain tumors.[6,8] Thus, it is of considerable interest to investigate how astrocytes are generated. During mammalian brain development, astrocytes are derived from neural stem cells (NSCs) in the ventricular and sub-ventricular zone. Rodent cortico-cerebral astrogliogenesis mainly takes place at the late embryonic stages and the first 3 postnatal weeks, following neurogenesis,[4,9,10] which is consisted of 2 concurrent regulatory processes: astrocyte differentiation from NSCs and the local proliferation of astrocytes.[9,11] Pioneer studies have shown that rodent cortico-cerebral astrogliogenesis is controlled by both intrinsic factors[12] and extracellular factors,[13] which induce astrocytic gene transcription such as GFAP and S100beta. Nowadays, although studies from culture system and mouse model have demonstrated that bone morphogenetic protein (BMP)-Smads signaling,[9,10,14] Notch signaling,[9,10,15] and Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathways control the appropriate timing of astrogliogenesis,[10,16,17] exactly how these pathways regulate astrogliogenesis remains poorly understood. Here, we mainly focus on recent molecular insights into the role of BMP signaling in neocortical astrogliogenesis in the developing mouse brain.

BMPs are members of the transforming growth factor β (TGFβ) superfamily of signaling ligands.[18] BMPs mediate a highly conserved signal transduction cascade through the type-I and type-II receptors and intracellular Smad proteins, which regulate a wide

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variety of cellular processes, including cell fate specification, cell proliferation, cell migration and cell death during development.[19] BMPs play dynamic roles in neurogenesis and astrogliogenesis.[9,10,14,18] During late embryonic and early postnatal periods, BMP signaling promotes astroglial differentiation.[9,14,20] Combination treatment of BMP2 with LIF accelerates the induction of astrocytes from the cultured E14.5 mouse telencephalic precursors,[21] and such capability of BMP2 and LIF to synergically promote astrogliogenesis was further confirmed in E16.5 cortico-cerebral precursors kept under thyroid hormones.[22] Mechanistically, BMP signaling is mediated by heteroterameric serine/threonine kinase receptors and their downstream transcription factors Smad1/5/8. In the nuclei, Smads form a complex with STAT3 that is bridged by the transcriptional co-activators p300/CBP,[9,10,23] and participate in the induction of astrocytic gene expression. Knockout *LIF*[24] and its receptors *LIFRβ*[25] and *gp130*[26] or downstream of *STAT3*[27] all result into the impairment of astrocytic differentiation, indicating that the JAK-STAT3 pathway is essential for astrogliogenesis in the developing brain. Interestingly, treatment of BMP2 alone to $gp130^{-/-}$ cultures, elicits a moderate but reproducible activation of the GFAP promoter,[21] suggesting that pSmads might also directly activate GFAP promoter, independently of JAK-pSTAT3 pathway. In our recent studies, in the receptor and downstream levels, we provide new insights on the BMPs signaling for the neocortical astrogliogenesis.

Neogenin, a member of the DCC family transmembrane protein, serves as a receptor for the axon guidance cue netrins, the repulsive guidance molecules (RGMs) and BMPs.[28,29] By taking advantage of X-gal reporter in *neogenin* mutant mice and antibodies, we have demonstrated neogenin's expression in embryonic NSCs *in vitro* and *in vivo*,[30] in consistent with the previous reports.[31-34] *Neogenin* deficient mice or NSCs showed normal self-renewal or proliferation of NSCs or neurogenesis,[30] but impaired neocortical astrogliogenesis. Note that neogenin is reported to regulate adult neurogenesis by promoting neuroblast migration and cell cycle exit,[35] suggesting that neogenin may play an age-dependent function during neurogenesis. Although neogenin is not required for neural differentiation in cultured NSCs and in neonatal age, multiple *neogenin* mutant mice, including neogenin hypomorphic allele, $neogenin^{Nestin}$-CKO, and $neogenin^{GFAP}$-CKO, show an impairment in neocortical, but not hippocampal, astrogliogenesis.[30] In addition, *neogenin* depletion in E15.5 cortical NSCs by in utero electroporation also results in impaired astrogliogenesis, providing additional evidence for neogenin's function in promoting neocortical astrogliogenesis. It remains unclear regarding the mechanisms underlying neogenin's selective regulation of neocortical astrogliogenesis. We propose the following potential possibilities. First, the temporal and spatial expression patterns of BMPs and neogenin may be different between cortex and hippocampus. Second, neogenin may have different signaling and functions in NSCs between cortex and hippocampus. These possibilities require further investigations in future.

Neogenin appears to be a co-receptor for BMPs signaling. It regulates iron homeostasis by regulating BMP induction of hepcidin.[36] It also promotes chondrogenesis and endochondral bone formation by enhancing and sustaining BMP-Smad1/5/8 signaling in chondrocytes.[37] In consistent, our recent study supports a role for neogenin in BMP-2-induced astrocyte differentiation.[30] Exactly how neogenin regulates BMP signaling remains poorly understood. Several mechanisms may underlie neogenin regulation of BMP signaling. First, in the ligand level, neogenin may play a role in process and secretion of soluble HJV, an inhibitor of BMP signaling.[36] Second, at the receptor level, upon BMP2 treatment, both neogenin and BMP receptors are recruited to the lipid raft microdomains, and neogenin is required for the recruitment or stabilization of BMP receptors in lipid rafts.[37] Interestingly, recent structure studies have shown that neogenin ligands, RGMs, serve as a bridge between neogenin and BMPs.[29,38] Third, in the downstream signaling level, our recent findings suggest that neogenin in NSCs or astrocytes is required for BMP2 activation of RhoA, which promotes YAP (yes-associated protein) nuclear translocation, consequently, YAP interaction with nuclear p-Smad1/5/8[30]. This event is critical for stabilization of nuclear pSmad1/5/8 signaling and neocortical astrogliogenesis.[30] *YAP* knockout in NSCs also results in a similar cortical astrogliogenesis deficit *in vitro* and *in vivo*.[30,39] Overexpression of YAP in neogenin deficit NSCs diminishes the astrocytic differentiation deficit.[30] These observations suggest that neogenin/YAP pathway is essential for cortical astrogliogenesis in the developing brain.

How does YAP regulate BMP2/Smad1 signaling? Our results suggest that YAP interaction with pSmad1 may be critical for maintaining pSmad1 protein stability. This view are in line with reports that YAP interacts with Smads in the nuclear to modulate BMP/Smad1 or TGF/Smad2 signaling in HEK293 cells or Eph4 cells,[40-43] and that YAP-pSmad1/5/8 complex in the nuclei of HEK293 cells prevents p-Smad1/5/8 degradation by Smurf1.[40,43] These reports, combine with our results, demonstrate the importance of YAP regulation of BMP2/Smad1 signaling in various cell types. Interestingly, our recent studies have shown that YAP may interact with STAT3 in the nucleus of astrocytes upon cytokine treatment.[44] Thus, it is of interest to test whether YAP forms a complex with smad1 and STAT3 in the nucleus to promote BMP2-induced astrogliogenesis in future (Fig. 1, Model).

Astrocytic glioma is the most common brain tumor in adult central nervous system.[45] The glioma initiating cells (GIC) are believed as be highly chemoresistant, thus they are responsible for glioma replase. One potential treatment for glioma is to induce differentiation of GICs to more benign and or/druggable cell type.[46] BMP signaling (p-Smad1/5/8) is decreased in patients with glioma, compared with that of normal brain and low grade astocytomas. The expression of BMPRIB receptor is down-regulated in high grade glioma.[47] Interestingly, neogenin is also reduced in these patients with glioma.[48] These observations thus demonstrate a negative correlation between BMP-neogenin signaling pathway and the malignant grade of glioma. This view is supported by additional observation that BMPs inhibit proliferation and promote differentiation of GICs, thus suppressing the growth of glioma.[49] Our studies suggest that neogenin/RhoA/YAP/Smad1 signaling plays a critical role in BMP2-induced astrocyte differentiation of NSCs. Although netrin-1 via DCC receptor up-regulates YAP expression, escalating YAP levels in the nucleus and promoting cancer cell proliferation and migration,[50] our results showed that netrin-1 did not regulate YAP level in WT or *neogenin* mutant astrocytes. Further investigation is necessary to illustrate whether neogenin/RhoA/YAP/Smad1 signaling pathway is involved in BMPs-induced differentiation of GICs, which may reveal novel therapeutic targets for astroglioma.

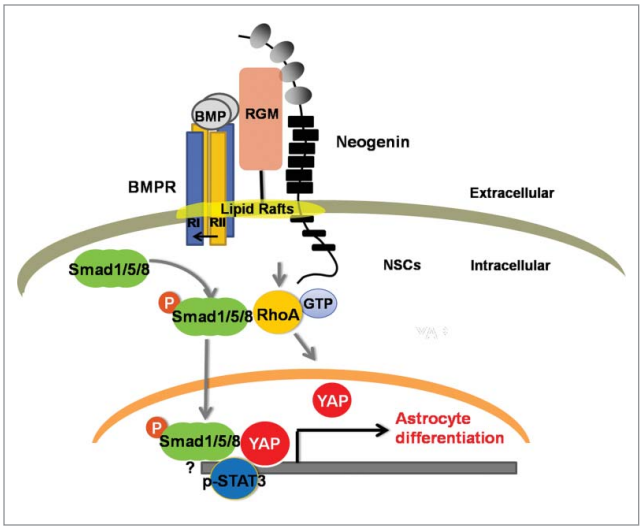

Figure 1. A model of neogenin and YAP in modulating BMP2-inducing astrocytic differentiation in NSCs or astrocytes. Neogenin in NSCs or astrocytes is required for BMP2 activation of RhoA, which promotes YAP nuclear translocation, consequently, YAP interaction with nuclear p-Smad1/5/8. This event is critical for stabilization of nuclear p-Smad1/5/8 signaling and neocortical astrogliogenesis. YAP is very likely form a complex with smad1 and STAT3 in the nucleus to promote BMP2-induced astrogliogenesis.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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