

Molecular Regulation of Hinge Point Formation

It is known that the notochord induces the medial hinge point (MHP) cells to become wedge-shaped (see Figure 13.6B–D; van Straaten et al. 1988; Smith and Schoenwolf 1989). The morphogen Sonic hedgehog (Shh) is expressed in the notochord and is required for the induction of floor plate cells in the neural plate (Chiang et al. 1996), which in turn form the MHP. The persistence of the MHP in Shh knockout mice suggests that other notochord-derived signals may be required for its morphogenesis (Ybot-Gonzalez et al. 2002).

In the dorsolateral hinge points (DLHPs), *Noggin* appears to be critical for proper hinge formation. In mice, loss of *Noggin* results in a severe failure of neural tube closure (Figure 1; Stottman et al. 2006). *Noggin* is expressed in the neural folds, and this expression is sufficient to induce the DLHP to form; *Noggin* is also expressed transiently in the notochord (Ybot-Gonzalez et al. 2002, 2007). It is important to note that *Noggin* binds to and inhibits bone morphogenic proteins (BMPs). Could it be the inhibition of BMPs that results in cell shape changes in the DLHP? Several experiments indicate it is more complicated than that.

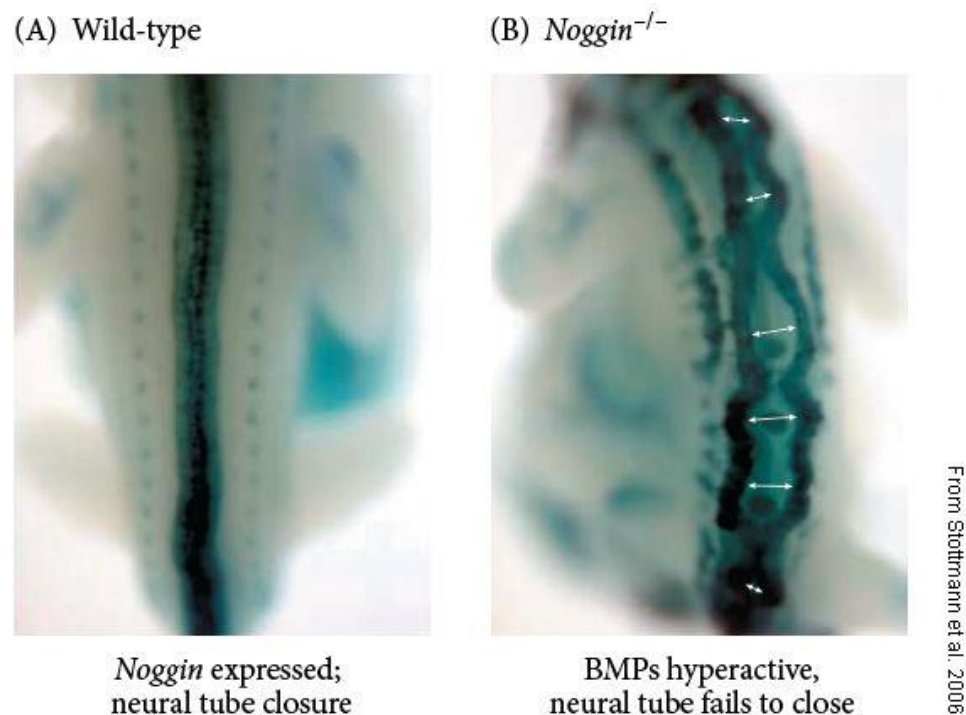


Figure 1 Activated BMP signaling leads to neural tube defects. (A) In the wild-type mouse, *Noggin*—a direct antagonist of BMP ligands—is expressed in the notochord and neural folds. The darkly stained region marks the dorsal neural folds and tube. (B) Loss of *Noggin* results in failure of neural tube closure (arrows), perhaps due in part to a lack of BMP inhibition.

When chick embryos are genetically manipulated to contain constitutively active BMP receptors in

the neural tube, these receptors bind the BMPs secreted by the surface ectoderm, which is still intimately connected to the neural plate and folds, with the result that all hinge points are repressed from forming. In contrast, when manipulations cause the total loss of BMP signaling in the neural plate, the result is ectopic and exaggerated MHP and DLHPs (Figure 2A; Eom et al. 2011, 2012, 2013). It therefore seems that intermediate amounts of BMP signaling in the neural plate are required for normal hinge point size and location (Figure 2B). The neural plate cells at this level of BMP signaling will undergo apical constriction and basal thickening to form the hinge points. This process occurs through a modification of the junctional complexes holding the cells together (Figure 2C, D). Specifically, when BMP signals are present in higher amounts, they promote the recruitment of proteins that serve to stabilize junctional proteins and maintain size equality between the apical and basal membranes, which prevents folding. In contrast, attenuation of BMP signaling (by Noggin) leads to a relaxation in these cell-to-cell junctions, which then permits apically restricted actinomyosin contractions and a shortening of the apical membrane. In summary, hinge point formation appears to center around the precise control of BMP signaling. BMP inhibits MHP and DLHP formation, whereas repression of BMP by Noggin enables DLHPs to form, and Shh from the notochord and floor plate prevent precocious and ectopic hinges from forming in the neural plate (see Figure 15.7).

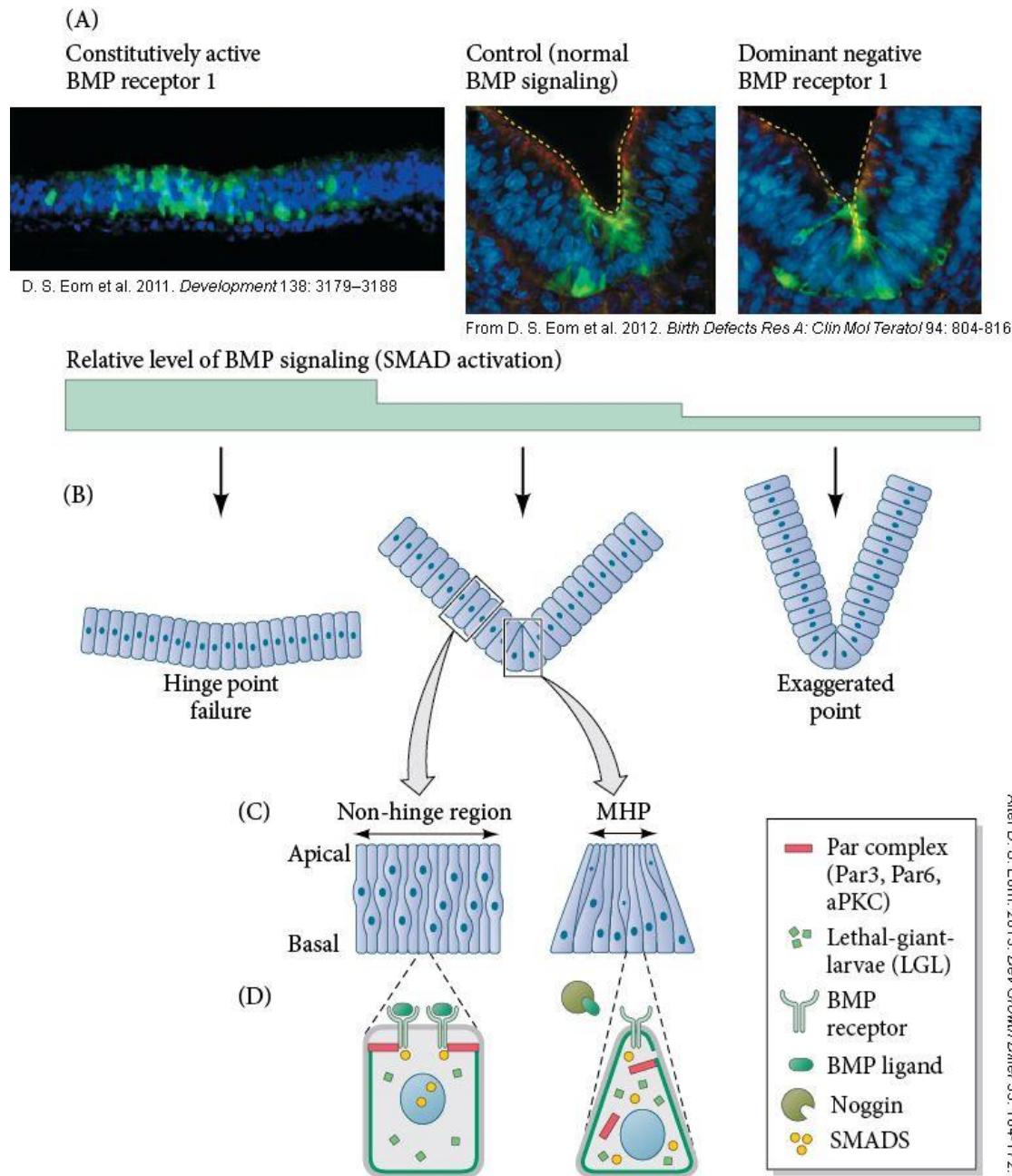


Figure 2 BMP prevents MHP formation by regulating apical-basal polarity. This experiment demonstrates that high levels of BMP signaling inhibit MHP formation, while low levels promote excessive folding at the midline. (A) Electroporation of a constitutively active BMP receptor (left) or a dominant negative form of BMP receptor (right) into the chick neural plate prior to folding. The normal (control) condition is seen in the center. Electroporated cells are visible through GFP expression (green); nuclei are visible (blue), as are apical cell membranes marked by Par3 in the middle and right sections (red). (B) Schematic representation of the results in A. (C) Illustrations of the cell shape and nuclear positions in the non-hinge region of the neural plate (left) and at the MHP (right). Preferential positioning of nuclei (blue) to the basal cell compartment paired with apical actin-myosin contraction promotes apical constriction. (D) Illustrations of a single cell in non-hinge (D, left) and hinge (D, right) regions of this epithelium, demonstrating the effect of BMP signaling on apical-to-basal polarity. BMP signaling on the apical surface leads to an apically stabilized Par complex that segregates basal defining components, such as LGL, all of which promotes an equal epithelial morphology. Attenuation of BMP signaling by Noggin can disrupt the division of these compartments, leading to an expansion of the regions in which typically basal components are located and a loosening of junctional complexes, all of which enables apical constriction.

Literature Cited

Chiang, C., Y. Litingtung, E. Lee, K. E. Young, J. L. Corden, H. Westphal and P. A. Beachy. 1996. Cyclopia and axial patterning in mice lacking *sonic hedgehog* gene function. *Nature* 383: 407–413.

[PubMed Link](#)

Eom, D. S., S. Amarnath, J. L. Fogel, and S. Agarwala. 2011. Bone morphogenetic proteins regulate neural tube closure by interacting with the apicobasal polarity pathway. *Development* 138: 3179–3188.

[PubMed Link](#)

Eom, D. S., S. Amarnath, J. L. Fogel, and S. Agarwala. 2012. Bone morphogenetic proteins regulate hinge point formation during neural tube closure by dynamic modulation of apicobasal polarity. *Birth Defects Res. A: Clin. Mol. Teratol.* 94: 804–816.

[PubMed Link](#)

Eom, D. S., S. Amarnath, and S. Agarwala. 2013. Apicobasal polarity and neural tube closure. *Dev. Growth Differ.* 55: 164–172.

[PubMed Link](#)

Smith, J. L. and G. C. Schoenwolf. 1989. Notochordal induction of cell wedging in the chick neural plate and its role in neural tube formation. *J. Exp. Zool.* 250: 49–62.

[PubMed Link](#)

Stottmann, R. W., M. Berrong, K. Matta, M. Choi, and J. Klingensmith. 2006. The BMP antagonist Noggin promotes cranial and spinal neurulation by distinct mechanisms. *Dev. Biol.* 295: 647–663.

[PubMed Link](#)

van Straaten, H. W. M., J. W. M. Hekking, E. J. L. M. Wiertz-Hoessels, F. Thors and J. Drukker. 1988. Effect of the notochord on the differentiation of a floor plate area in the neural tube of the chick embryo. *Anat. Embryol.* 177: 317–324.

[PubMed Link](#)

Ybot-Gonzalez, P., C. Gaston-Massuet, G. Girdler, J. Klingensmith, R. Arkell, N. D. E. Greene, and A. J. Copp. 2007. Neural plate morphogenesis during mouse neurulation is regulated by antagonism of BMP signalling. *Development* 134: 3203–3211.

[PubMed Link](#)

Ybot-Gonzalez, P., P. Cogram, D. Gerrelli, and A. J. Copp. 2002. Sonic hedgehog and the molecular regulation of mouse neural tube closure. *Development* 129: 2507–2517.

[PubMed Link](#)

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