

Investigating Role of Novel Molecular Players in Forebrain Roof-Plate Midline Invagination

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Abstract : In the vertebrate embryo, the forebrain anlagen develops from the anterior-most region of the neural tube which is the precursor of the central nervous system (CNS). The roof plate located at the dorsal midline region of the forebrain anlagen, acts as a source of several secreted molecules involved in patterning and morphogenesis of the forebrain. One such key morphogenetic event is the invagination of the forebrain roof plate which results in separation of the single forebrain vesicle into two cerebral hemispheres. Retinoic acid (RA) signaling plays a key role in this process. Blocking RA signaling at the dorsal forebrain midline inhibits dorsal invagination and results in the absence of certain key features of this region, such as thinning of the neuroepithelium and a lowering of cell proliferation. At present we are investigating the possibility of other signaling pathways acting in concert with RA signaling to regulate this process. We have focused on BMP signaling, which we found to be active in a mutually exclusive domain to that of RA signaling within the roof plate. We have also observed that there is a change in BMP signaling activity on modulation of RA signaling indicating an antagonistic relationship between the two. Moreover, constitutive activation of BMP signaling seems to completely inhibit thinning and partially affect invagination, leaving the lowering of cell proliferation in the midline unaffected. We are employing in-silico modeling as well as molecular manipulations to investigate the relative contribution if any, of regional differences in rates of cell proliferation and thinning of the neuroepithelium towards the process of invagination. We have found expression of certain cell adhesion molecules in forebrain roof-plate whose mRNA localization across the thickness of neuroepithelium is influenced by Bmp and RA signaling, giving regional rigidity to roof plate and assisting invagination. We also found expression of certain cytoskeleton modifiers in a localized small domains in invaginating forebrain roof plate suggesting that midline invagination is under control of many factors.

Keywords : bone morphogenetic signaling, cytoskeleton, cell adhesion molecules, forebrain roof plate, retinoic acid signaling

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