

IIT Kanpur team finds possible cause of neurodevelopmental disorders

BMP signalling plays an important role in cerebral cortex development

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Bone morphogenetic proteins (BMP) are secreted signalling molecules which are already known to regulate the production of neurons from neural stem cells. Now, using mice models, a team of researchers led by Prof. Jonaki Sen from the Indian Institute of Technology (IIT) Kanpur has found that BMP signalling is active in the cerebral cortex during embryonic development as well as during later stages of development after birth, too.

They found that BMP signalling regulates three processes – the migration of newborn neurons from stem cell niche to their destined place in the cortex, polarity (the axon forming the base and the dendrites forming the apical or top side) of neuronal cells, and branching of dendrites in the upper layer neurons of the cerebral cortex.

The cerebral cortex has six neuronal layers formed in an inside-out manner. The early-born neurons form the inner cortical layers while the late-born neurons form the outermost layers. So any perturbation or delay in the migration of newborn neurons results in disturbed layer formation and lack of proper connec-



BMP signalling doesn't control migration of neurons that form the lower neuronal layers, says Jonaki Sen (right).

tivity between neurons.

Similarly, when polarity (alignment) or branching of dendrites is affected, the neurons will not be able to form proper electrical connections. Though there are other factors that determine migration and polarity, the role of BMP signalling in these two processes was not known till now.

BMP signalling

"BMP signalling was previously known to play an important role in the early development of the brain. Our study is the first to show that BMP signalling plays an important role in cortex development by regulating the migration of newborn cortical neurons and the establishment of

polarity in the upper layer of cerebral cortex," says Dr. Monika Saxena from the Department of Biological Sciences and Bioengineering at IIT Kanpur and first author of the paper published in the journal *Development*.

"There are many neurodevelopmental disorders linked to aberrant migration of neurons such as lissencephaly, autism, epilepsy and schizophrenia," says Prof. Sen who is with the Department of Biological Sciences and Bioengineering. "We now know that inhibition of BMP signalling leads to delayed migration and this may be one of the causes for such disorders. Thus, it might be possible to prevent or treat these diseases if

further research is carried out."

Two pathways

BMP signalling can be through two pathways – phospho-SMAD or LIM kinases. When BMP signalling was totally inhibited, both the pathways were affected. As a result, all the three processes – migration, polarity and neurons not making enough branches – were affected.

To understand the role of each pathway in affecting any of the three stages of neuronal development, the researchers selectively blocked one pathway at a time.

"Both pathways have a role in the migration of neurons. When only one of the pathways was blocked, migration was affected but to a lesser extent than when both pathways were inhibited," Prof. Sen says.

In the case of polarity, inhibiting the LIM kinase pathway seemed to be less effective than inhibiting the phospho-SMAD pathway. "Using mice models we determined that the phospho-SMAD pathway was more important than LIM kinase pathway for polarity establishment," Prof. Sen says.

But the reverse was true in the case of the branching of dendrites. Inhibiting the LIM kinase pathway

had a greater effect on dendrites branching than inhibiting the phospho-SMAD pathway.

The researchers found that BMP signalling seems to selectively regulate migration of upper-layer neurons. The migration of neurons to form the lower layers, which are the first to be formed, is not affected even when BMP signalling is blocked.

Even when both the pathways of BMP signalling were blocked, migration was only delayed and not completely stopped. But the delay in migration causes problems. "When neurons finally reach the upper layers (layer II/III), they don't have proper polarity," Prof. Sen says.

Evidence in mice

The gestation period in the case of mice is 20 days. The migration delay was seen two days after BMP signalling was blocked on gestation day 15.5 and continued till at least the day of birth. Disturbed polarity was manifested on the sixth day after birth. Defects in dendrite branching was first seen 15 days after birth and fully manifested 21 days after birth.

"BMP signalling is involved in regulating multiple phenomena at different stages of cortex development," says Prof. Sen.