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Commentary

WNT Takes Centre Stage in Border Control

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Those who follow politics know that the borders between countries can cause disagreements and sometimes even war, and that border control is an ongoing source of controversy. A different—but not less controversial—border is established during embryogenesis in vertebrates: the *neural plate border* (NPB) that separates neural and non-neural ectoderm (Streit and Stern, 1999; Patthey and Gunhaga, 2011; Groves and LaBonne, 2014). A study in this issue of EBioMedicine implicates WNT signalling in cell specification in this region and, for the first time, links this signalling pathway to the emergence of neural tube defects (NTDs) (Kimura-Yoshida et al., 2015—in this issue).

The neural plate is a sheet of pseudostratified epithelium in the centre of the ectoderm (the outermost layer of an embryo) that goes on to generate the central nervous system. It is surrounded by non-neural surface ectoderm (SE) that goes on to form the outer covering of the organism, the epidermis. Shortly after neural plate formation, its longitudinal midline dips in, resulting in lateral elevation of the *neural folds*. Subsequently these neural folds roll inwards, and the NPBs from the opposite sides of the neural plate meet and fuse, thereby forming the *neural tube*. If this process, *neurulation*, is defective, NTDs such as craniorachischisis, anencephaly and spina bifida can ensue (Greene and Copp, 2014). However, the importance of the NPB reaches further than just functioning as a zipper during neurulation as this region also gives rise to the neural crest, a multipotent cell population that migrates to different parts of the embryo and contributes to various organs and tissues. How exactly neural crest cells become specified has been a bone of contention for some time (Schlosser, 2008; Weston and Thiery, 2015; Simões-Costa and Bronner, 2015).

Enter Kimura-Yoshida et al. who have studied NPB specification in the mouse embryo and found that this region contains a stripe of cells that until neural tube closure express neither markers of the neural plate nor markers of the SE, but instead known markers of stem cell identity. Neural crest cells are often considered 'stem cell-like', but only minimal overlap was found between the uncommitted NPB cells and a neural crest marker, indicating that these two populations are distinct.

Upon neural tube closure NPB cells finally become specified as either neural or epidermal. In order to identify candidate molecular signals that may bring about this decision, Kimura-Yoshida et al. microdissected neural plate and SE tissue and compared their respective gene expression profiles using DNA microarray analysis. A striking number of factors of the WNT signalling pathway were found to be differentially

regulated suggesting that WNTs could be decisive for NPB fate acquisition. In order to test this hypothesis, the authors overexpressed DKK1, a potent inhibitor of WNT signalling. They found ectopic induction of neural markers and a concomitant downregulation of epidermal markers in the SE of their transgenic mice, and the simple epithelium characteristic of SE acquired a pseudostratified appearance characteristic of the neural plate. Conversely, experimental activation of the WNT pathway resulted in an expansion of SE at the expense of neural identity.

Thus, WNTs are indeed required and sufficient to promote SE identity, but how do they mediate their effects in the NPB? In their microarray screen, Kimura-Yoshida et al. found that the gene *Grainyhead-like 2* (*Grhl2*) is significantly upregulated in SE versus neural plate tissue. Furthermore both *Grhl2* and its close relative *Grhl3* were found by in situ hybridisation to be expressed in the SE, but not in the neural plate. This finding was intriguing since the knockout of *Grhl3* in the mouse constitutes a well known NTD model (Ting et al., 2003).

So, are *Grhl* genes really required for SE specification? Removal of one copy of *Grhl3* resulted in NPB cells that co-expressed neural and SE markers (suggesting that they are somewhat 'confused' about their identity), whereas removal of both copies resulted in SE cells of the NPB erroneously ending up in the neural plate. But is *Grhl3* really a downstream effector of WNT signalling? Expression of *Grhl3* is expanded in *Dkk1*-deficient mouse embryos (that have excessive WNT signalling), and removal of one copy of *Grhl3* partially rescued the forebrain defects of these *Dkk1*^{-/-} mice. Furthermore, removal of one copy of *β-catenin*, the key intracellular transducer of WNT signals, severely aggravated the NTDs in *Grhl3*-deficient mice. These genetic interaction studies strongly support the idea that WNT signalling and *Grhl3* function the same pathway.

Finally, if the authors' hypothesis—that NPB specification through WNT signalling is essential for neural tube closure—is true, defective WNT signalling in the NPB itself should result in NTDs. To test this prediction, the authors conditionally eliminated *β-catenin* from the *Grhl3* lineage. They found that such mice indeed developed severe spina bifida. Thus, the balance between WNT inhibition and WNT → *Grhl3* signalling regulates the acquisition of neural and SE identity in the NPB, respectively, and this binary cell fate choice is essential for proper neural tube closure.

Taken together, this study links up several previously unconnected factors that are relevant to the emergence of NTDs: neural plate border specification, WNT signalling and neural tube closure. However it also raises a number of novel questions: for example, what are the precise relationships between the uncommitted NPB region, the dorsal midline of the neural tube and the neural crest? What are the *Grhl3* targets that

mediate its role in neural tube closure? And could it be that β -catenin's function as a component of the cytoskeleton, in addition to its role in WNT signalling, also plays a part in neural tube closure? By all means, this study makes a good case for the importance of border control, but at this point I would caution against drawing any geopolitical conclusions from it.

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Conflict of Interest Statement

The author declares no conflict of interest.

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