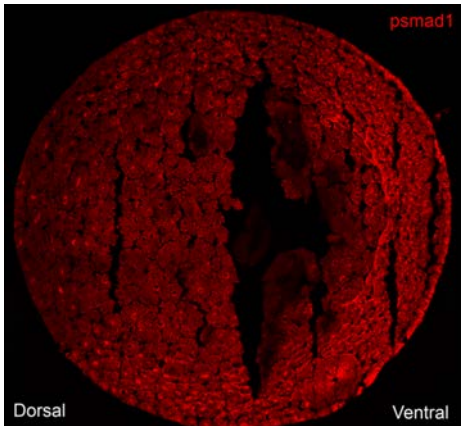
A novel role for negative feedback of BMP4 in embryonic development

Morphogenetic genes play a vital role in embryonic development and the control of tissue architecture. They are often found near genes responsible for their regulation, i.e. in so called "synexpression groups". Research started at the German Cancer Research Center (DKFZ) in the labs of Christof Niehrs and Stefan Legewie, both now based at the Institute for Molecular Biology (IMB) in Mainz, has identified a novel role for the synexpression group that includes BMP4 (bone morphogenic protein 4). As a number of other growth factor pathways are organized into synexpression groups these findings may represent a new mechanism by which growth factors are regulated. This has important implications for embryonic development and the groups findings were recently published in the multidisciplinary journal Proceedings of the National Academy of Sciences (PNAS).

The Niehrs and Legewie groups demonstrated that the BMP4 synexpression group is responsible for modulating the BMP4 concentration range which cells respond to. It is also responsible for limiting the phenotypic effect of environmentally-induced and stochastic variations in BMP4 concentration, an important check that ensures normal development of the embryo. The researchers elucidated this through an interdisciplinary combination of *in vivo*, *in vitro* and *in silico* approaches.

Experiments conducted by Malte Paulsen found that knockdown of *bambi*, a negative regulator of BMP4 and member of the same synexpression group, resulted in a ten-fold reduction in the range of BMP4 concentrations to which cell lines and *Xenopus* frog embryos were able to respond. Furthermore, the *in vivo* knockdown of *bambi* or two other BMP4 negative regulators in the same synexpression group, *smad6* or *smad7*, resulted in increased variation in *Xenopus* embryo tail length and eye size. This demonstrates a role for BMP4 negative regulation in the maintenance of phenotypic fidelity. Importantly, the wide-spread presence of negative regulators in other synexpression groups indicates a role for this mechanism in the regulation of other growth factors.



Confocal microscopy image of the psmad1 gradient in a gastrula stage Xenopus *embryo. Cryo-sections were stained with a psmad1-specific antibody and reveal the mesoderm surrounding the embryo, which is patterned by a BMP4 gradient.*

In silico modeling by Stefan Legewie supported these findings. His simulations showed that negative regulation of BMP4 by BAMBI is essential for extending the range of BMP4 concentrations that cells respond to. This occurs due to negative regulation acting to reduce the signalling triggered by

intermediate BMP4 levels. His modelling also supported experimental data showing that *bambi, smad6* and *smad7* act synergistically to reduce cell-cell variations in BMP4 target gene expression.

These new findings suggest that synexpression groups increase the concentration range at which signalling molecules can be effective and strengthen the robustness of embryonic development. This is achieved through suppression of the effects of natural variations in morphogenetic protein concentration. Such control is therefore vital to maintaining the phenotypic consistency that is required for embryonic development.

Webpage of Prof. Niehrs' Research Group: www.imb-mainz.de/research-at-imb/niehrs

Webpage of Dr. Legewie's Research Group: www.imb-mainz.de/research-at-imb/legewie/

Further reading:

- Paulsen M*, Legewie S*, Eils R, Karaulanov E, Niehrs C (2011). Negative feedback in the bone morphogenetic protein 4 (BMP4) synexpression group governs its dynamic signaling range and canalizes development. *PNAS*, 108, 10202-10207. (* Shared first authors)

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