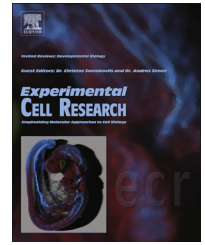


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Review Article

Active signals, gradient formation and regional specificity in neural induction[☆]

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ABSTRACT

The question of how the vertebrate embryo gives rise to a nervous system is of paramount interest in developmental biology. Neural induction constitutes the earliest step in this process and is tightly connected with development of the embryonic body axes. In the *Xenopus* embryo, perpendicular gradients of BMP and Wnt signals pattern the dorsoventral and anteroposterior body axes. Both pathways need to be inhibited to allow anterior neural induction to occur. FGF8 and IGF are active neural inducers that together with BMP and Wnt signals are integrated at the level of Smad 1/5/8 phosphorylation. Hedgehog (Hh) also contributes to anterior neural induction. Suppressor-of-fused plays an important role in intertwining the Hh and Wnt pathways. Distinct mechanisms are discussed that establish morphogen gradients and integrate retinoic acid and FGF signals during posterior development. These findings not only improve our understanding of regional specification in neural induction, but have profound implications for mammalian stem cell research and regenerative medicine.

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The organizer and regional specification of the CNS

Few experiments in biology have been as influential as the transplantation experiment reported by Spemann and Mangold in 1924 [34]. Grafting of the dorsal blastopore lip from a salamander gastrula into the ventral side of a host gastrula induced a twinned embryo with a brain and spinal cord [34]. How can the Spemann–Mangold organizer (as the dorsal lip and homologous cell clusters in other vertebrates are now called) induce surrounding ectoderm to become central nervous system (CNS) and confer axial polarity to the developing embryo? The activation–transformation model of Peter Nieuwkoop postulates that the initially induced neural tissue is of anterior (forebrain) character, and that later signals from the chordamesoderm transform parts of it to more posterior midbrain, hindbrain, and spinal cord tissue [23]. As discussed below, anterior neural tissue is considered to be a default state that requires inhibition of bone morphogenetic protein (BMP) and Wnt signalling. Wnt, retinoic acid (RA) and fibroblast growth factor (FGF) signals are distributed in a gradual manner along the rostrocaudal neuraxis and exert posteriorizing activity.

In this review, we focus on active signals that contribute to anterior neural induction and ask of how they are integrated in the *Xenopus* embryo. We further discuss the mechanisms that establish a linear RA gradient and long-range FGF signalling in embryonic patterning. Finally we review how RA, FGF, and Wnt signals interact during posterior development in different vertebrates. An important message is that active signals not only play an important role in neural induction but are re-used and engage in complex feedback interactions during regionalization of the CNS.

Soluble BMP and Wnt antagonists promote anterior neural induction

Studies primarily in *Xenopus* have shown that two main signalling gradients exist in the early embryo, activated by the BMP and Wnt proteins [7,22]. These two gradients are perpendicular to each other and allocate positional information along the dorsoventral (DV) and anteroposterior (AP) body axes. The main BMPs in the *Xenopus* embryo are the ventrally expressed BMP4 and BMP7 and the dorsally expressed BMP2 and ADMP. Depletion of all four BMPs by antisense morpholino oligonucleotides converts the entire ectoderm into CNS, mostly brain tissue [26]. At the onset of gastrulation, the organizer secretes the soluble BMP antagonists Noggin, Chordin, and Follistatin [39,11,6]. Removal of all three BMP inhibitors in *Xenopus tropicalis* results in severe loss of neural and expansion of ventral tissue [15], stressing the essential function of BMP antagonism in the induction of neural fate.

In frogs, sperm entry causes Wnt-mediated stabilization of beta-catenin in the dorsal blastomeres, leading to initial DV

asymmetry [11]. At the blastula stage, Wnt/beta-catenin signals induce neural fate in the dorsal ectoderm through blocking BMP4 transcription [1] and promoting expression of secreted BMP antagonists [40]. However, Wnt/beta-catenin signals have also been reported to stimulate epidermis at the expense of neural fate [12]. Temporal analysis with an inducible Tcf construct showed that canonical Wnt signalling can inhibit neural plate formation at the onset of gastrulation [19]. Thus, Wnt signals appear to shift from an early pro-neural to a late anti-neural function. The organizer secretes the Wnt antagonists Frzb1, Cerberus, and Dkk1, which during gastrulation translocate to the anterior pole of the embryo and establish a Wnt/beta-catenin gradient that determines the AP polarity of the neural plate [7,22].

Perpendicular activity gradients of BMP and Wnt signals are not restricted to *Xenopus*. Chordin and BMP have universal functions in bilateria for patterning the DV axis during gastrulation [6]. Key roles for anterior Wnt inhibition by Dkk and posterior Wnt signals have been validated in most animals [22]. Together, anterior neural tissue is a default state that depends on the dual inhibition of BMP and Wnt signals.

FGF and IGF signals are active neural inducers

Studies in the chick have challenged the idea that neural induction relies exclusively on the extracellular suppression of BMP signalling and suggested that instructive signals like FGF8 participate in the induction of neural tissue. FGF is now a well-established neural inducer in planarians, ascidians, fish, *Xenopus* and the chick [35,2].

In *Xenopus*, it was first shown that IGFs (insulin-like growth factors) are important for head and neural induction [24,25,29]. Misexpression of IGF and IGFBP5 (IGF binding protein-5) leads to the induction of ectopic head-like structures containing eye and brain tissue (Fig. 1A and A'). IGF signals promote anterior neural induction through intracellular inhibition of BMP and Wnt signals. The inhibition of the Wnt pathway occurs upstream or at the level of beta-catenin.

Thus, multiple signals promote neural induction, raising the question of whether a common molecular explanation may exist that integrates these different pathways?

The BMP signal transducer Smad1/5/8 integrates multiple neural inducers

Recent studies performed by the De Robertis laboratory in the frog gave evidence for a unifying mechanism by which FGF8, IGF and Wnt converge with BMP signals at the level of Smad1/5/8, resulting in differential phosphorylation of this transcription factor [7]. The BMP antagonists Noggin and Chordin block phosphorylation of Smad1 at its C-terminal end and allow the

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