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Review

Temporally coordinated signals progressively pattern the anteroposterior and dorsoventral body axes

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ABSTRACT

The vertebrate body plan is established through the precise spatiotemporal coordination of morphogen signaling pathways that pattern the anteroposterior (AP) and dorsoventral (DV) axes. Patterning along the AP axis is directed by posteriorizing signals Wnt, fibroblast growth factor (FGF), Nodal, and retinoic acid (RA), while patterning along the DV axis is directed by bone morphogenetic proteins (BMP) ventralizing signals. This review addresses the current understanding of how Wnt, FGF, RA and BMP pattern distinct AP and DV cell fates during early development and how their signaling mechanisms are coordinated to concomitantly pattern AP and DV tissues.

Contents

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1. Introduction

The anteroposterior (AP) and dorsoventral (DV) axes are the foundation for the bilateral body plan. In vertebrates both the AP and DV axes are generated by distinct signaling proteins that act as morphogens. Morphogens specify discrete cell fates over a distance in a concentration-dependent manner and generate activity gradients of high, intermediate, and low to specify distinct cell fates [1]. During axial patterning, these gradients span the entire length of an embryo and the amount of each signal at precise AP and DV locations patterns the entire organism. Accordingly, spatial regulation of morphogen signaling is critical to ensure the correct morphogen levels in particular positions. Moreover, this precise distribution of morphogen signaling across each axis cannot be established instantaneously and entire body axes cannot be patterned all at once. Correct morphogen signaling levels must be maintained throughout the patterning process and cells must also be equipped to know exactly when to respond to morphogen signals to adopt their correct fate [2]. Therefore, temporal regulation of morphogen signaling and target cell competence is also essential to pattern a complete body axis. Furthermore, patterning of all AP and DV tissues spans late blastula, gastrula, and somitogenesis stages, which are distinct and dynamic physical environments. Thus, spatial and temporal regulation of morphogen signaling must also be coordinated to navigate the challenges of early embryo development. Critically, although separate mechanisms exist for patterning the AP and DV axes, both axes are patterned concomitantly; these orthogonal patterning mechanisms must work in harmony across both space and time to properly pattern the organism.

This review will address the current understanding of *Xenopus* and zebrafish AP and DV axial patterning as separate processes during gastrulation, as well as more recent advances in uncovering the mechanisms that coordinate AP and DV patterning. Finally, this review will discuss current and novel techniques for manipulating spatial and temporal aspects of patterning, including the associated caveats and prospects for future development and application of these techniques.

2. Combinatorial Wnt, FGF, Nodal, and RA morphogenetic signaling patterns the AP axis

Although initial AP polarity in amphibians and fish is determined by the maternally established animal–vegetal axis of the egg, patterning of distinct AP cell fates in all vertebrates is controlled during late blastula and gastrula stages. By the end of gastrulation in *Xenopus*, zebrafish, chick, and mouse, a clear division of anterior and posterior cell fates has been established [3–11]. AP patterning is mediated by Wnt, fibroblast growth factor (FGF), Nodal, and retinoic acid (RA) signaling. Specifically, Wnt, FGF, Nodal, and RA specify posterior cell fates and the specification of anterior cell fates relies on the graded inhibition of these signals (Fig. 1a–c). During blastula and gastrula stages Wnt, FGF, and Nodal establish the broad regions of the AP body axis (the head, trunk, and tail as most posterior) (Fig. 1a and b). Additionally, Nodal patterns the mesendoderm while Wnt, FGF, and RA specify distinct AP cell fates in the neural plate, dividing it into four distinct regions to establish the central nervous system (CNS). These four rostral (anterior) to caudal (posterior) subdivisions are the forebrain, midbrain, hindbrain, which is further subdivided into rhombomeres (numbered 1–7 from rostral to caudal in the zebrafish), and spinal cord (Fig. 1a) [12]. Although the complete specification of CNS fates extends beyond gastrulation, these subdivisions of the CNS can be used as a reliable readout of AP axial patterning. The roles of Wnt, FGF, Nodal, and RA signaling in patterning the AP body axis and/or the CNS are described below.

2.1. A Wnt gradient specifies posterior cell fates

Wnts are secreted cysteine-rich glycoproteins that bind to the Frizzled (Fz) family of receptors with the assistance of co-receptors such as low-density lipoprotein receptor-related proteins (LRPs) and heparin-sulphate proteoglycans (HSPGs) [13]. During AP patterning, Wnt signaling activates the canonical Wnt/β-catenin pathway and promotes the expression of posterior genes [14,15]. During early and mid-blastula stages in the frog and zebrafish embryo, maternal Wnt signaling is localized dorsally and establishes the dorsal organizer, which establishes DV asymmetry (Section 3) [14]. However, during late blastula and gastrula stages zygotic Wnt signaling is excluded from the dorsal organizer, and localized to the ventrolateral embryo margin; this change in localization during gastrulation coincides with a dramatic change in Wnt function. Zygotic Wnt functions in posterior tissue development (Fig. 1b): increasing zygotic Wnt signaling results in the loss of head structures [16–20], whereas embryos deficient in zygotic Wnt signaling exhibit a dramatic loss of the tail and a reciprocally enlarged head [21–25]. AP patterning by Wnt also depends on Wnt antagonists, including secreted Frizzled-related proteins (sFRPs) and Dickkopf (Dkk), which are localized anteriorly (Fig. 1b) [15,17,26]. sFRPs are secreted proteins that contain domains homologous to the Wnt binding site of Fz receptors and thus bind Wnt and prevent Fz activation, while Dkk proteins are membrane-bound and bind LRP co-receptors to prevent the propagation of Wnt signaling [13].

Wnt signaling is also key to AP neural patterning, specifying caudal CNS cell fates [19,20,23,27–33]. Studies of AP patterning in the CNS beautifully show that Wnt acts as a morphogen to specify caudal cell fates in a concentration-dependent manner [23,27,31–34]. Remarkably, grafting Wnt-expressing cells or beads near forebrain progenitors [33,35] or incubating *Xenopus* animal cap explants (the most anterior tissue) with Wnt [31] induces caudal cell fates that vary depending on the amount of Wnt expressed. This supports a prominent role for Wnt signaling in establishing the broad subdomains of the AP axis, since Wnt can directly convey posterior positional information to specify the proportion and distribution of caudal cell fates in multiple regions of the developing CNS. Importantly, the most rostral cell fates, like the forebrain, require Wnt signal inhibition, which underscores the equal importance of Wnt antagonism in AP patterning (Fig. 1b) [30,36].

Although as a morphogen Wnt must function over a distance, Wnt is post-translationally modified with lipids that make it hydrophobic, insoluble, and poorly mobile, thus limiting its ability to form a signaling gradient by free diffusion [37]. Recent studies of fluorescently tagged Wnt in live zebrafish embryos offer an alternative mechanism for generating a gradient: short, actin-based filopodia can transport Wnt to the contact point between neighboring cells and activate Wnt signaling, increasing its effective signaling range [38].