

Alternative Views on the Dual Gradient Model: Can a Single Gradient Do the Job?

The dual gradient model is not without its controversies. The model is largely based on data generated solely in the chick, and some inconsistencies exist with comparable data generated in the mouse. Most striking of these inconsistencies is that RA appears to be dispensable for hindlimb development and patterning in mice (Sandell et al. 2007; Zhao et al. 2009; Cunningham et al. 2011, 2013), thus leaving open the question of whether opposing gradients of RA and FGF/Wnt function in the mouse forelimb as they do in the chick wing. However, several studies examining the loss of RA revealed that although mouse forelimbs were shortened, their patterning was relatively normal, including proximal expression of *Meis1/2* (Sandell et al. 2007; Zhao et al. 2009; Cunningham et al. 2011, 2013). This shortened forelimb phenotype has been interpreted to mean that RA plays a role in establishing the early limb field, as opposed to RA affecting patterning along the proximal-distal axis.

As an alternative to the dual gradient model, Cunningham and colleagues have proposed a single gradient model that focuses on the instructive patterning signals from proteins derived from the AER (Cunningham et al. 2013; reviewed in Cunningham and Duester 2015). Specifically, initial expression of *Meis1/2* throughout the early limb bud specifies stylopod fates; then, distal FGF expression functions both to repress *Meis1/2*, preventing the adoption of more proximal fates by distal mesenchyme, and to repress RA through *Cyp26b1* induction, thus preventing RA from interfering with distal patterning. The keys to this proposed single gradient model are, first, that RA does not play an instructive role beyond forelimb field induction and, second, that the autonomously timed collinear expression of Hox genes along the proximal-distal axis (see Tarchini and Duboule 2006) will be permitted to appropriately pattern cell fates in the absence of excessive RA signaling.

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