Wnt and Bmp Fit Germ Cells to a T

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Reporting in Developmental Cell, Aramaki et al. (2013) identify T as a key mediator of primordial germ cell (PGC) specification in the embryo. Deconstruction of how Bmp and Wnt signals regulate the expression and targeting of T to regulatory elements of either mesodermal or PGC genes has implications for differentiation in vitro.

An enduring question in developmental biology is how cells in the early embryo use a limited set of cues to make fate decisions. As in real estate, the answer lies in timing and location. In this issue of Developmental Cell, Aramaki et al. (2013) demonstrate that the transcription factor T integrates signals from two major pathways, delivered in precise sequence, to target the small cohort of cells that will carry the genome to the next generation.

Specification of these genomic heirs—primordial germ cells (PGCs)—occurs deterministically through inherited cytoplasmic factors in some organisms. However, a different mode of specification prevails in mammals. Pioneering transplantation experiments (Tam and Zhou, 1996) suggested that epiblast cells have equivalent germline potential if they land in the right place: the posterior corner of the proximal epiblast in the mouse. Bmp mutants pointed to signaling interactions that germline rather than mesoderm is the default T pathway in the epiblast when Bmp4 and Wnt3 are absent. However, T specificity to PGC genes was tightly regulated by timing of Wnt/β-catenin and Bmp4/Smad signals, with T-dependent expression of Blimp1 and Prdm14 precluded by early exposure to Wnt3. The authors propose a two-step model in which Wnt3 and Bmp4 synergize to induce T.

How do two pedestrian signaling pathways—like Wnt and Bmp—ordain a small handful of epiblast cells as PGCs? Aramaki et al. (2013) sought the answer in downstream molecular machinery and timing of PGC fate decisions. A critical tool was the in vitro generation of PGCs, which routes embryonic stem cells (ESCs) through an epiblast-like cell (EpiLC) intermediate in a recapitulation of development (Hayashi et al., 2011).

In both epiblasts and EpiLCs, current studies show that Wnt3 and β-catenin are required for Blimp1 induction by Bmp4. Strikingly, the authors noticed that Blimp1 and Prdm14 transcripts increased more slowly than classical targets of Bmp or Wnt signaling, suggesting their indirect induction. Boolean logic applied to gene expression analysis of EpiLCs identified immediate response genes to combined Wnt3 and Bmp4. Among these, the mesoderm and notochord transcription factor T (Brachyury) stood out for its consistent expression in both mesoderm and nascent germ cells. Aramaki et al. (2013) went on to demonstrate that T is necessary and sufficient for induction of Blimp1, and chromatin immunoprecipitation (ChIP) revealed enrichment of T at loci near Blimp1 and Prdm14. Together, these findings raise the tantalizing possibility that germine rather than mesoderm is the default T pathway in the epiblast when Bmp4 and Wnt3 are absent. However, T specificity to PGC genes was tightly regulated by timing of Wnt/β-catenin and Bmp4/Smad signals, with T-dependent expression of Blimp1 and Prdm14 precluded by early exposure to Wnt3. The authors propose a two-step model in which Wnt3 and Bmp4 synergize to induce T.

The subsequent direction of T to either mesodermal or PGC genes is determined by the absence or presence, respectively, of Wnt3 and Bmp4 (Figure 1). It is reasonable to hypothesize that Wnt- and Bmp-mediated transcription factors Tcf1 and Smad co-occupy PGC enhancers with T, but ChIP results did not concur. Alternatively, other Tcf family members may promote or inhibit transcription of PGC or mesoderm genes. Details of how Bmp4 antagonizes T targeting to mesodermal gene loci or promotes T occupancy of Blimp1 and Prdm14 remain to be clarified.

Temporal and spatial coordination of major signaling pathways to lock down expression of lineage-specific genes is an emerging theme in development. In the case of PGCs versus mesoderm, T hangs in the balance between Wnt and Bmp signaling. Elsewhere, Wnts and Bmps collaborate in different ways to dictate cell fate decisions. In zebrafish and mouse hematopoietic development, downstream transcription factors Tcf2 and Smad colocalize with cell-fate-specific transcription factors at genes critical for hematopoietic lineages (Trompouki et al., 2011). In human cells, precise timing of Wnt and Bmp signaling dictates hematopoietic versus mesenchymal cell fate specification from a common...
progenitor pool (Gertow et al., 2013). Aramaki et al. (2013) join these studies in highlighting specific mechanisms employed by broad signaling networks in different cell contexts at distinct times in development. The temporal and geographic juxtaposition of blood islands in the extraembryonic mesoderm to the PGC birthplace in the proximal epiblast raises the question of whether Bmp and Wnt signaling targets common transcription factors to lineage-specific genes via shared mechanisms. In the context of in vivo or in vitro stem cell biology, Bmp and Wnt synergies might suggest protracted lineage flexibility during the early commitment to mesoderm, PGC, or blood. Similarly, the requirement of T for PGC gene expression could explain the inefficiency of differentiation from mouse ESCs and may guide strategies for improving human PGC derivation. As exemplified by Saitou and colleagues, interweaving approaches in the embryo and the dish toward understanding and recapitulating developmentally relevant intermediates is likely to be a successful strategy for in vitro differentiation in many tissues.

A broader implication from this work concerns the link between PGC specification and lineage determination in the embryo. Although modes of germ cell specification differ, both rely upon mechanisms of embryonic axis patterning. In PGC preformation, polarization of RNAs and proteins in the early embryo or oocyte ensures cytoplasmic inheritance of germ cell determinants in the correct cells at the proper end of the embryo. Reliance of PGC induction upon a conserved primary axis determinant such as Wnt3 may arise as economical use of signals in the early embryo or may represent a strategy for evolvability. Following the argument that germ cell formation by induction may be advantageous with changing body plans through evolution, a functional connection between early patterning and PGC formation allows portability of the germline. Invoking mesoderm transcription factors such as T in germ cell specification is hardly new: salamanders and crickets also induce PGCs from mesoderm (Ewen-Campen et al., 2013). Although highly conserved through evolution, shifting T expression and function could suggest a primary role in promoting cell motility. Indeed, in T mouse chimeras, a pileup of mutant cells in the primitive streak suggested T function in nascent mesoderm cell movement during gastrulation (Wilson et al., 1995). By extension, T targets in PGCs may include motility, adhesion, or cytoskeletal genes, thus eliciting a broader migratory gene program to equip newly minted germ cells for the next steps in their development: a multiday migration to the gonads. Whether by borrowing T from the mesoderm or through something more ancient, Bmp and Wnt create the perfect neighborhood for raising the cells of the next generation.

REFERENCES


