

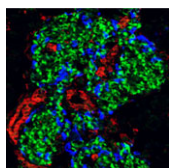
New moves in haematopoiesis: rumba and samba

Vertebrate haematopoiesis relies on a pool of haematopoietic stem/progenitor cells (HSPCs) that can self-renew and differentiate into all haematopoietic lineages. But what are the molecular mechanisms that regulate this process? Here, Zilong Wen and co-workers (p. 619) identify two novel factors that regulate zebrafish HSPC maintenance. During zebrafish development, HSPCs originate from the ventral wall of the dorsal aorta (VDA), migrate to the caudal haematopoietic tissue (CHT) and finally colonise the kidney. The researchers isolated and characterised two haematopoiesis-deficient mutants, *rumba*^{hkz1} and *samba*^{hkz2}. In these mutants, HSPC specification in the VDA and subsequent homing to the CHT are normal, but further HSPC development within the CHT is compromised. Using positional cloning, they show that Rumba is a novel nuclear C2H2 zinc-finger protein and that *samba* encodes a protein that is homologous to human augmin complex subunit 3 (Haus3). Both factors, they report, act independently and cell-autonomously to regulate cell cycle progression in HSPCs, and thus are essential regulators of zebrafish haematopoiesis.



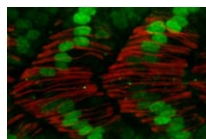
Pancreatic Hh signalling: a play in two acts

In amniotes, inhibition of hedgehog (Hh) signalling in the early embryonic endoderm is a prerequisite for pancreatic specification. By contrast, loss of Hh signalling in zebrafish severely disrupts pancreas development, suggesting opposite roles for Hh signalling in fish versus mammalian pancreas organogenesis. Zahra Tehrani and Shuo Lin (p. 631) now reconcile these contrasting functions by showing that the Hh pathway plays distinct roles during various stages of zebrafish pancreas development. Using genetic and pharmacological approaches to temporally modulate Hh activity, they show that Hh activity during early gastrulation is essential for the subsequent migration and differentiation of pancreatic precursors. This positive role of Hh acts to restrict Bmp signalling and to promote β -cell differentiation. By the end of gastrulation, they report, Hh signalling adopts a negative role by antagonizing retinoic acid (RA)-mediated induction of endocrine pancreatic precursors. These findings highlight sequential roles for Hh signalling in pancreas development and uncover antagonistic relationships between the Hh, Bmp and RA pathways during pancreas organogenesis.



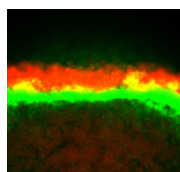
Sox9⁺ progenitors make β -cells in embryo but not in adult

All pancreatic cell types, including insulin-producing β -cells, arise from pancreatic progenitors during embryonic development, but whether the adult pancreas contains β -cell progenitors remains a controversial issue. Using fate-mapping studies in mice, Maïke Sander and colleagues (p. 653) now demonstrate that cells positive for Sox9 give rise to β -cells during embryogenesis, but not in the normal or injured adult pancreas. They generated *Sox9CreER^{T2}* mice in which Sox9-expressing cells can be accurately and temporally labelled. Lineage tracing shows that these cells can generate all pancreatic lineages during embryogenesis. By contrast, they report, endocrine and acinar cell neogenesis from Sox9-positive cells does not occur in the adult pancreas. Using partial duct ligation (PDL) to induce pancreatic injury, they also show that Sox9-positive cells do not generate β -cells following injury; PDL initiates pre-endocrine programs but not complete β -cell differentiation. Given the increasing use of PDL as a model to study β -cell regeneration, these studies provide important insights into the specification and regeneration of β -cells.



engrailed links Hh and Bmp muscle development signals

Myotome morphogenesis requires the specification of distinct muscle cell types. In zebrafish, the specification of medial fast-twitch fibres (MFFs) and slow-twitch muscle pioneers (MPs), both of which express *engrailed* (*eng*) genes, is regulated by hedgehog (Hh) signalling but the mechanistic basis of this regulation is unclear. On p. 755, Philip Ingham and co-workers demonstrate that the *eng2a* promoter integrates repressive and activating signals from the Bmp and Hh pathways, respectively, to limit its expression to MFFs and MPs during zebrafish myotome development. The researchers identified a minimal element in the *eng2a* promoter that can drive reporter gene expression specifically in MFFs and MPs. This element binds both Gli2, a mediator of Hh signalling, and activated Smads, mediators of Bmp signalling. They demonstrate that Hh activity antagonises Smad activation in myotomal cells and, conversely, that aberrant Smad activation suppresses *eng2a* expression. Their studies identify novel crosstalk between the Hh and Bmp pathways that may be mediated by direct interactions between Gli and Smad proteins.



Non-embryonic Nodals orchestrate early development

Vertebrate development and patterning require Nodal signalling. However, the upstream inducers of Nodal expression and the relative contributions of Nodal ligands from embryonic, extraembryonic and maternal sources to embryogenesis are unclear. Now, Benjamin Feldman and co-workers show that non-embryonic sources of Nodal-related ligands, activated in part by the transcription factor Mtx2, account for the spectrum of zebrafish early Nodal signalling events (p. 787). They report that Mtx2 activates and is required for the expression of *nodal-related 2* (*ndr2*) in the yolk syncytial layer, an extraembryonic tissue, thus identifying a novel upstream component of Nodal signalling. They further demonstrate that the co-disruption of extraembryonic *ndr2*, extraembryonic *nodal-related 1* (*ndr1*) and maternal *ndr1* recapitulates Nodal mutant phenotypes: embryos show a loss of endoderm and anterior mesoderm specification. Based on their findings, the authors propose that endoderm and anterior mesoderm specification during zebrafish development is executed by a failsafe mechanism involving the combined action of non-embryonic Nodal-related ligands, and that this mechanism may be relevant to higher vertebrates.

IN DISEASE MODELS & MECHANISMS

Mapping mutations in a mouse model of Meckel-Gruber syndrome

Meckel-Gruber syndrome (MKS) is a lethal recessive disorder characterised by multiple severe birth defects. The disease is associated with mutations in genes that are required for the generation of cilia, which are cellular structures with multiple roles ranging from motility to sensation. In a recent *Disease Models & Mechanisms* article, Cecilia Lo and colleagues recover a mouse mutant with developmental defects similar to those seen in humans with MKS, including polycystic kidneys and laterality defects. The authors map the mutation in these mice to a previously uncharacterised, highly conserved domain of a centrosome-localised protein called Mks1. They show that the mutation disrupts Mks1's function in late-stage ciliogenesis. These results clarify mechanisms underlying birth defects in MKS and provide molecular insight into how ciliogenesis occurs.

Cui, C. et al. (2011). Disruption of Mks1 localization to the mother centriole causes cilia defects and developmental malformations in Meckel-Gruber syndrome. *Dis. Model. Mech.* 4, 43-56.