



Outside the gonad: a story of p53 and cell death

In animal embryos, primordial germ cells (PGCs) migrate long distances to the developing gonads. During this journey, programmed cell death removes abnormal, misplaced or excess cells. The regulation of this process, which ensures germline integrity, is poorly understood. Now, Clark Coffman and co-workers report that the tumour suppressor p53 and Outsiders (a monocarboxylate transporter) regulate programmed cell death during PGC development in *Drosophila* (see p. 207). They show that in loss-of-function p53 and outsiders embryos, the programmed cell death (but not migration) of PGCs is abnormal, resulting in the persistence of ectopic PGCs outside of the gonads. This p53 phenotype (the first developmental phenotype seen for loss of *Drosophila* p53 function) closely resembles that of outsiders mutants, not the researchers. Furthermore, overexpression of p53 in the PGCs of outside embryos partly suppresses the cell death phenotype. Thus, p53 and Outsiders may function in a common pathway to eliminate a subset of PGCs during oogenesis.



Wnt-Shh neural tube patterning crosstalk

In the developing spinal cord, morphogenetic signals secreted from dorsal and ventral signalling centres control dorsoventral (DV) patterning. The Shh/Gli pathway plays a major role in patterning the ventral neural tube but what restricts its activity to specific domains? On p. 237, Alvarez-Medina and colleagues propose that the Wnt canonical pathway fulfils this role. Wnt1 and Wnt3a, which signal through the canonical β -catenin pathway, are expressed in the dorsal midline region of chick embryos. Their misexpression along the DV axis by *in ovo* electroporation, the authors report, expands dorsal marker gene expression in the developing neural tube, whereas their inhibition suppresses the dorsal programme and expands ventral gene expression. These phenotypes, the authors show, depend on the Wnt-controlled expression of Gli3, which in its repressor form (Gli3R) acts as the main transcriptional repressor of the Shh/Gli pathway. Together, these observations suggest that the Wnt canonical pathway indirectly restricts graded Shh/Gli ventral patterning activity by regulating the dorsal expression of Gli3 to ensure proper spinal cord patterning.



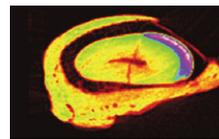
Heads down with Hox

Conserved Hox transcription factors direct the formation of distinct structures along the anteroposterior axis of bilaterian animals. Given that Hox genes probably all derive from a single unique gene by duplication, might they also share a common function? On p. 291, Coiffier and co-workers propose that this is the case by showing that all *Drosophila* central and posterior (CP) Hox genes repress head formation in the fly's trunk, in addition to their well-known roles in segment identity. Hox genes of many species fall into CP and anterior classes based on their expression pattern and sequence similarities. The researchers report that, in *Drosophila*, the central Hox proteins (including Antennapedia and Ultrabithorax) and the posterior Hox protein Abdominal B prevent the expression of the head-specific gene *optix* in the trunk. Furthermore, several non-Hox genes, including *Teashirt* and *Wingless/Wn* contribute to this repression. The researchers propose, therefore, that an early function of Hox genes was to repress the head and that novel Hox functions that specialise the trunk appeared later.



Network theory unravels patterning

Pattern formation during development depends on combinatorial interactions between signalling pathways, but the strategies for pathway integration and coordination are still poorly understood. Now Yakoby and colleagues have developed a new model based on network theory to explain how the *Drosophila* eggshell is patterned (see p. 343). During *Drosophila* oogenesis, the EGFR and Dpp pathways specify the follicle cells that give rise to dorsal eggshell structures. Follicle cells that express the transcription factor Broad (Br), whose expression is regulated by both EGFR and Dpp signalling, form the roof of these structures. From their observations of signalling patterns during eggshell formation and from published data, the researchers propose that EGFR signalling determines the spatial pattern of Br by inducing the expression of both *br* and its transcriptional repressor Pointed (a feedforward loop). Later, a feedback loop activated by Br controls Dpp, which terminates Br expression. Future work will explore how other feedback loops interact with the simple regulatory network motifs described in this new model to generate complex gene expression patterns.



Sprouty free and long in tooth

Unusually for mammals, rodent incisors grow continuously, fuelled by stem cells in their mesenchymal and epithelial compartments. Constant abrasion of the incisor's lingual side (the side facing the tongue), which unlike the opposite side has no hard enamel covering, maintains its length and shape. But why is enamel produced asymmetrically? On p. 377, Gail Martin and co-workers report that sprouty (*Spry*) genes, which encode FGF signalling antagonists, ensure this asymmetrical enamel deposition and prevent the growth of tusk-like incisors. The researchers show that enamel-producing ameloblasts develop from stem cells on both sides of the incisors of *Spry4*^{-/-} mouse embryos and that an ectopic epithelial-mesenchymal FGF signalling loop on the lingual side of the incisors causes this phenotype. Interestingly, ectopic ameloblast formation is maintained after birth only if the dosage of *Spry1* or *Spry2* is also reduced. Thus, the researchers suggest, the generation of differentiated progeny (such as ameloblasts) from stem cell populations can be differentially regulated in embryos and adults.



Vesicle trafficking: transported into development and disease

Several inherited human diseases [such as arthrogryposis-renal dysfunction-cholestasis and Hermansky-Pudlak (HP) syndromes] are associated with defective vesicle transport, which is an essential process for many cellular events. Now, Neuhauss, Dahm and colleagues identify the zebrafish mutant *leberknödel* (*lbk*) as a model for such disorders (see p. 387). These mutants, like individuals with HP syndrome and similar disorders, have hypopigmented skin melanocytes and a hypopigmented retinal pigment epithelium (RPE). The mutant fish also have visual and immunological defects and defects in various internal organs. The researchers identify the mutation in *lbk* as a loss-of-function mutation in the gene encoding Vam6p/Vps39p, which is required for the trafficking of lysosomes and lysosome-related vesicles, such as melanosomes. They also report that macrophages and cells in the RPE, liver and intestines of *lbk* mutants contain increased numbers of enlarged intracellular vesicles compared with wild-type cells. Overall, these results highlight *vam6* as a novel candidate disease gene and reveal its requirement for normal development for future research to explore.

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