How angioblasts form veins and arteries

Blood vessels are formed from capillaries sprouting from existing vessels or *de novo*. A third way of forming new blood vessels is now described in *Science* (*Science* **326,** 294–298; 2009). Stainier and colleagues show that in zebrafish embryos, the first artery (the dorsal aorta) and vein (the caudal vein) are derived from the same precursor vessel. Imaging of embryos with GFP-labelled endothelial cells revealed that angioblasts sprout ventrally from the precursor vessel, after which sprouts are terminated and an unconnected caudal vein is formed. The dorsal aorta is formed subsequent to dorsal sprouting by classic vasculogenesis. Knockdown of known vascular sprouting regulators of vascular sprouting, such as vascular endothelial growth factor (Vegfa) and Notch, revealed that Vegf restrains ventral sprouting through Notch signalling, while promoting dorsal sprouting. Ephrins are tethered to the plasma membrane and possess reverse signalling properties, mediating bidirectional signalling in various developmental contexts. Here, the authors demonstrate that the sorting of angioblasts towards ventral or dorsal migration is achieved through Ephrin signalling; Ephrin B2a is induced by Vegfa in arterial-fated angioblasts and limits their ventral migration, while its ligand, Ephrin B4a, promotes ventral migration of venous-fated angioblasts. These experiments elegantly demonstrate how angioblasts are directed towards different fates, and are likely to be relevant for vascular development in other systems. CKR

Traffic jam in the piRNA world

Germline-specific PIWI-interacting RNAs (piRNAs) are produced either through a primary pathway, which loads them onto the argonaute protein Piwi, or through an amplification loop, which involves additional activities of the Piwi-related proteins Aubergine and AGO3. Whereas the amplification loop is fairly well understood, far less is known about the primary production of piRNAs. Siomi and colleagues uncover a new locus, traffic jam (TJ), which produces piRNA in the somatic lineage of gonads through this primary route (*Nature*, doi: 10.1038/nature08501). The authors derived an ovarian somatic cell line (OSC) from *Drosophila* that expressed Piwi, but neither Aubergine nor AGO3. They found that in OSC cells, Piwi associated with piRNAs that were mostly antisense to retrotransposons. Several piRNAs in OSC cells do not exhibit the characteristics of amplification loop products shown by those derived from the known flamenco piRNA locus and 3′UTR of the gene encoding the transcription factor TJ. Somatic cells mutant for TJ or Piwi fail to envelop germline stem cells, and the adhesion molecule Fasciclin III, known to be involved in this process, is upregulated in these cells. Piwi is absent from TJ-mutant gonadal somatic cells and TJ can bind the Piwi promoter. Thus TJ regulates primary piRNA production in the somatic lineage by acting on Piwi, possibly at the transcriptional level, and by providing a source of piRNAs. In turn, the Piwi pathway can regulate gonadal features, perhaps through piRNA-mediated control of adhesion molecules. NLB

The importance of being asymmetric

Stem cells (SCs) self-renew and generate differentiating progenitors through asymmetric cell division. Progenitors proliferate actively, whereas undifferentiated SCs remain mostly quiescent, except for undergoing transient bursts of symmetric division whenever the SC pool needs to expand, as during development or following tissue injuries. Do cancer SCs behave differently?

Using an *ErbB2* transgenic model of breast cancer and tumour-derived mammospheres, Pelicci and colleagues (*Cell* **138**, 1083–1095; 2009) show that, compared with their normal counterparts, tumour mammary SCs exhibit a higher frequency of symmetric divisions and increased self-renewal, higher replicative potential and the ability to grow indefinitely. Interestingly, mammary SCs isolated from *p53*-null mice also showed increased symmetric divisions and higher replicative potential both *in vitro* and *in vivo;* indeed, p53 stability was reduced in Erb2B tumour samples. Stabilization of p53 with Nutlin3, a small molecule that inhibits p53 degradation, correlated with the restoration of asymmetric divisions in cancer SCs and a reduction in tumour growth. Thus, one mechanism of tumour suppression by p53 might involve maintenance of tissue homeostasis through regulation of SC division polarity. While further studies will elucidate how p53 inactivation leads to increased symmetric divisions, these findings support the hypothesis that polarity loss may contribute causally to cancer. SG

Synaptic development: autophagy weighs in

During autophagy, cellular components are sequestered in autophagosomes that deliver them to the lysosome for degradation. Shen and Ganetzky describe a new role for autophagy in regulating synapse development in the fruit fly (*J.Cell Biol.* **187,** 71–79; 2009).

The authors found that mutations in genes that function at various points along the autophagy pathway result in reduced neuromuscular junction (NMJ) size. Inducing high levels of autophagy leads to NMJ overgrowth, similar to that observed in *highwire* (*hiw*) mutants, which encode a defective ubiquitin E3 ligase. As in *hiw* mutants, NMJ overgrowth induced by autophagy was suppressed by mutations in *wallenda*, a MAPK kinase kinase, or a dominant-negative form of the c-Jun N-terminal kinase (JNK) *bsk*. Moreover, Hiw overexpression suppressed the effects of autophagy on NMJ overgrowth and, conversely, reducing Hiw levels enhanced NMJ overgrowth. Hiw levels were higher in autophagy pathway mutants, suggesting that autophagy controls NMJ development by downregulating Hiw levels. *hiw* is epistatic to *atg* mutants and increasing Hiw levels resulted in NMJ undergrowth, suggesting that Hiw is a key effector of NMJ development, downstream of autophagy.

Whether autophagy targets Hiw directly and the details of how autophagy results in specific degradation of Hiw remain to be determined. SS

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