DEVELOPMENTAL BIOLOGY

Gridlock holds the key to vasculogenesis

The formation of the first artery and vein — vasculogenesis — is an important step in embryogenesis because a complete vascular loop is required to accommodate the output of the first heartbeat. Although arteries and veins are derived from the same embryonic precursor cells, called angioblasts, they differ functionally, morphologically and molecularly. How and when does an angioblast decide whether it will become part of an artery or a vein? Reporting in *Nature*, Zhong and colleagues show that, in zebrafish, the Gridlock (Grl) transcription factor controls the development of the first embryonic artery by mediating the arterial/venous cell-fate decision.

In vertebrates, angioblasts are initially found at the 'edge' of the embryo in the lateral posterior mesoderm (LPM) — they later migrate to the middle of the embryo where they aggregate to form the aorta and the first veins. By labelling angioblasts and following their progeny, Zhong *et al.* showed that individual angioblasts contribute to the artery or the vein, but not both.

This result indicated that the fate of an angioblast is determined long before it leaves the LPM, and that arterial and venous precursors are spatially mixed.

The *grl* gene is expressed in the LPM and along the aorta, and *grl* mutants have a specific defect in the dorsal part of the aorta, so the team tested the involvement of this gene in the cell-fate decision. When Zhong *et al.* decreased the levels of Grl using antisense constructs, the aorta shrank, whereas the adjacent vein increased in size. Conversely, overexpression of *grl* in embryos reduced vein size. Taken together, these results imply that angioblast expression of *grl* suppresses a default vein-specific pathway, allowing cells to take on arterial characteristics.

Grl is a member of the Hairy-related family of transcriptional repressors and, like repressors of its class, *grl* expression is affected by perturbing the Notch receptor or its signalling pathway. The authors also found that the ephrin B4 receptor — a vein-specific gene — is downregulated by Grl, consistent with it being downstream of

Grl. Zhong *et al.* propose that the Notch–Grl pathway is essential for the early distinction between artery and vein, a role that is in keeping with the function of Notch in deciding between alternative developmental fates in other tissues.

Sarah Cooney, Sub-Editor, Nature

References and links

ORIGINAL RESEARCH PAPER Zhong, T. P. *et al.* Gridlock signalling pathway fashions the first embryonic artery. *Nature* **414**, 216–220 (2001)

WEB SITE

Mark Fishman's lab:
<http://civrc.mgh.harvard.edu/research/fishman/>

GENOMICS

Journey to the CENTre of the X

The centromere has a key role in chromosome biology, but the genetic determinants that encode the centromere are difficult to pin down. In part, this is because in higher organisms centromeres comprise highly repetitive sequence, and have therefore been largely ignored by genome sequencers.

However, Mary Schueler and colleagues have shown that centromeric DNA can be characterized very successfully by physical mapping and sequencing, and their study of the X-chromosome centromere also provides the most in-depth view of a human centromere so far.

Although centromeres in higher primates are made up of megabase-long tandem arrays of 171-bp repeats — α -satellite DNA — the repeat array has a higher-level organization, with some sequence variation between the repeats. This variation was elegantly exploited by Schueler *et al.* to define STS markers within the array itself. Along with physical mapping techniques, these markers were used to construct a BAC contig that extended from the unique region on the short arm of the X that is very close to the centromere into the core of the centromeric repeats. DNA sequence was then generated from various parts of the contig.

There is a sharp transition from the unique region into the region containing α -satellite DNA. However, between this transition and the core of the centromere — where the α -satellite DNA is most homogeneous — there are stretches of α -satellite with distinct sequence characteristics. The closer they are to the core, the more similar these stretches are to the core α -satellite DNA. This observation fits very well with the idea that unequal crossing over is the mechanism that

maintains the overall integrity of the centromere: peripheral regions of the repeat array are predicted to be less strongly homogenized than more central regions.

Functional studies show that the core α -satellite DNA sequences form a key functional element of the centromere. Furthermore, on the basis of an analysis of the repeat content within the region, the core part of the X-chromosome centromere seems to have evolved quite recently in primate evolution.

Even though this work provides a clearer picture of the sequence organization of a human centromere, there are still many uncertainties about how the sequence encodes centromere function. The role of epigenetic mechanisms is but one puzzle. Nevertheless, the work lays a firm foundation for the analysis of other human and primate centromeres. A job that was written off as being too difficult has been shown to be possible, and we can expect some more fascinating insights into centromere evolution and function very soon.

Mark Patterson

References and links

ORIGINAL RESEARCH PAPER Schueler, M. G. *et al.* Genomic and genetic definition of a functional human centromere. *Science* **294**, 109–115 (2001)

FURTHER READING Sullivan, B. A. *et al.* Determining centromere identity: cyclical stories and forking paths. *Nature Rev. Genet.* **2**, 584–596 (2001)

WEB SITE

Hunt Willard's lab: <http://genetics.gene.cwru.edu/willard>