DEVELOPMENTAL BIOLOGY

Nodal signalling gets foxy

Key morphogenetic events during vertebrate embryogenesis require the signalling molecule Nodal. These events include establishing and maintaining the embryonic organizer, inducing mesoderm formation, and specifying the left–right axis. As a result, vertebrate *nodal* genes, and their down-stream targets, have been well studied, and it has been found that *nodal* expression is controlled by both positive and negative auto-regulatory feedback loops. The recent identification of the zebra-fish *foxH1* gene has added a new component to these regulatory pathways.

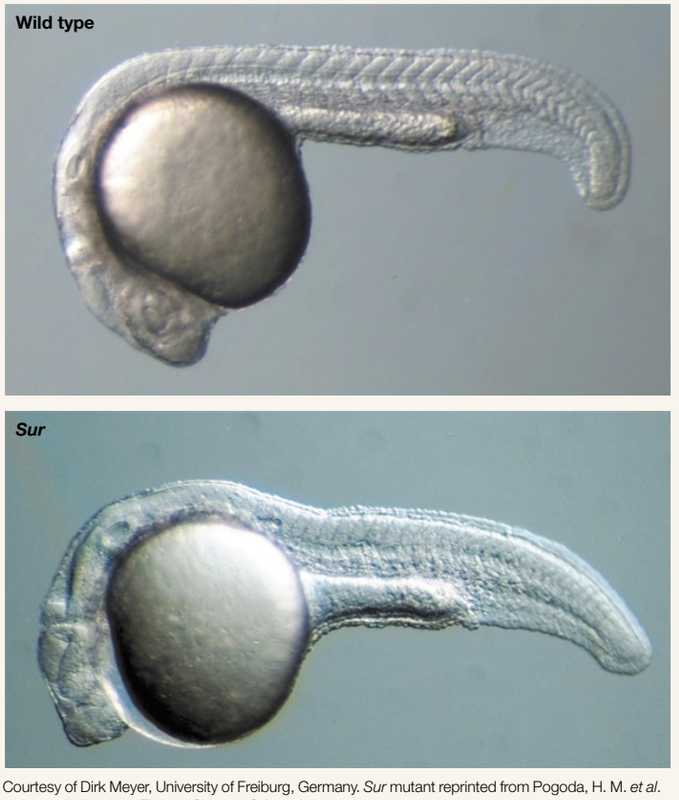
Foxh1 (or Fast1) is a forkhead (Fkh) transcription factor that has been shown to transmit inductive Nodal signals in frogs. However, in the absence of a *foxH1* mutant, the relevance of this data remained unconfirmed. This problem was solved when two research groups recently tested *foxH1* as a candidate gene for the zebrafish mutant, *schmalspur* (*sur*), which shares certain phenotypic features with other nodal-pathway mutants. Both groups identified *foxH1* mutations in *sur* zebrafish — Pogoda *et al.* also identified *foxH1* mutations in another allele, called *uncle freddy* — and subsequently showed them to be loss-of-function mutations in the conserved Fkh domain.

FoxH1 partly functions through its Fkh domain, which probably mediates its DNA-binding activity and nuclear localization. With the *sur* mutations to hand, Pogoda and colleagues investigated the biological activity of FoxH1 by making FoxH1 chimeric proteins that could repress or activate FoxH1 target genes — when introduced into zebrafish embryos, these proteins antagonized Nodal signalling or rescued Nodal-pathway mutant phenotypes, respectively. When Fkh-domain mutations from *sur* mutants were introduced into these chimeric proteins, they produced no phenotypic effect in zebrafish embryos, showing that these mutations abolish the function of the Fkh domain and the chimeric proteins' effect on Nodal signalling.

Pogoda and colleagues next investigated where in the nodal pathway FoxH1 acts by examining the expression of two zebrafish *nodal*-related genes, *squint* (*sqt*) and *cyclops* (*cyc*) in *sur* embryos. In early *sur* embryos, *sqt* and *cyc* were initially expressed — although at reduced levels — and their expression was rapidly lost with development. Compared to embryos that lack Nodal signals, *sur* mutants have only mildly affected mesodermal and endodermal development, suggesting that mesoderm formation and differentiation is initiated, as supported by these findings. These results also indicate that *foxH1* is unlikely to transmit inductive *nodal* signals but rather maintains and regulates *nodal*'s expression. The expression of the Nodal antagonist *antivin* is also rapidly lost in *sur* mutants, suggesting that FoxH1 functions in both positive and negative *nodal* regulatory pathways.

Future work should reveal how FoxH1, and its related proteins, function to modulate and amplify *nodal* gene expression to determine its intensity, range and duration.

Jane Alfred



Courtesy of Dirk Meyer, University of Freiburg, Germany. *Sur* mutant reprinted from Pogoda, H. M. *et al.* with permission from Elsevier Science © (2000).

References and links

ORIGINAL RESEARCH PAPER Pogoda, H. M. *et al*. The zebrafish forkhead transcription factor FoxH1/Fast1 is a modulator of Nodal signalling required for organizer formation. *Curr. Biol.* **10**, 1041–1049 (2000) | Sirotkin, H. I. *et al*. *fast1* is required for the development of dorsal axial structures in zebrafish. *Curr. Biol.* **10**, 1051–1054 (2000)

FURTHER READING Schier, A.F. & Shen, M. M. Nodal signalling in vertebrate development. *Nature* **403**, 385–389 (2000)

WEB SITE The zebrafish information network

WEB WATCH

Golden path to genome

If you are after access to the draft human genome sequence, then go to The Golden Path for a searchable, zoomable, scrollable view.

Searching for genomic loci is easy — several types of search term can be used, including gene names, clone identity numbers or keywords. Once found, a genomic location appears in a display window where zoom functions can take you from its chromosomal setting to its detailed exon–intron structure.

The main window provides several types of genomic information, and finding your way to more detailed data just requires a click on the displayed graphics. The fragment track, for example, shows clone assembly in the region and any gaps between clones. Genes in the genomic region are displayed from data processed by either Genie or Ensembl. Clicking on a displayed mRNA takes you through to a brief description of it and onto further, more detailed, links, such as its Genbank record. Information on ESTs, repeats, G+C content and puffer fish homologues can also be selected.

The browser displays draft sequence that was annotated and assembled as of July 2000, but links are available to a data set from September 2000. This assembled data is currently being annotated, and Jim Kent, the browser's developer, hopes to have it available at The Golden Path in the next month or so.

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Take a look online

Highlights are enhanced with hyperlinks, including:

- References — linked to PubMed.
- Genes, proteins, and diseases — linked to databases such as LocusLink and OMIM.
- Links to sites featured in Webwatch.
- Links to related online resources.

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