MECHANISM OF DISEASE

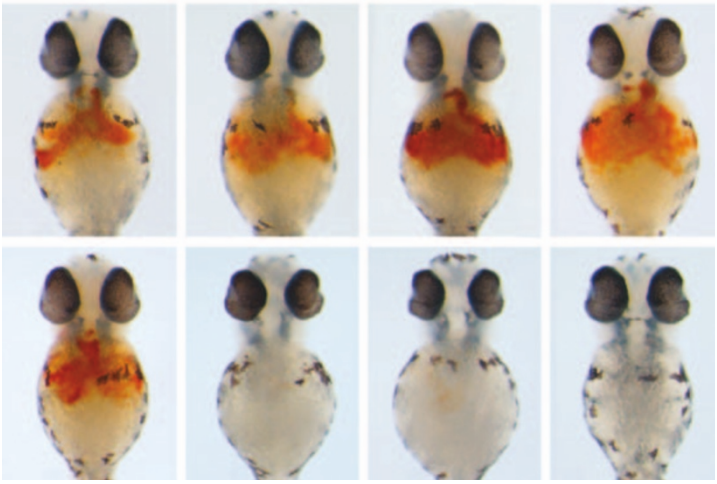
Portrait of anaemia in *sir* zebrafish

A group of scientists studying a zebrafish mutant, the *shiraz* (*sir*) mutant, have uncovered a link between two important pathways — the formation of Fe–S clusters and the production of haem. Reporting in *Nature*, Leonard Zon and colleagues describe how the Fe–S pathway controls haem synthesis and suggest that these findings have unveiled an unrecognized cause of anaemia in humans.

The authors first showed that the *sir* mutant has a deletion of the *glutaredoxin 5* (*grx5*) gene and that the profound anaemia that characterizes *sir* embryos is a direct result of Grx deficiency. Further analysis indicated that, similar to yeast, zebrafish *grx5* is required for the assembly of Fe–S clusters — complexes of iron and sulphur atoms that are incorporated into catalytic proteins in the mitochondria.

But how does defective Fe–S-cluster formation impair red-blood-cell production? The *sir* mutants have pale (or hypochromic) red blood cells, indicating that defective production of the oxygen-carrying pigment haemoglobin might be the cause of anaemia. So Zon and his team reviewed the intricate pathways that control the production of haemoglobin in eukaryotes and pinpointed a possible link with Fe–S-cluster assembly — the haem biosynthesis pathway.

The genes that are involved in the synthesis of the iron-rich haem molecule are tightly regulated. For instance, when cellular iron is depleted, the iron-regulatory protein-1 (IRP1) binds to and inhibits the translation of aminolaevulinate synthase-2 (*ALAS2*) mRNA, which encodes the enzyme that catalyses the first step in haem production. By contrast, when cellular iron is plentiful, IRP1 is sequestered by a 4Fe–4S-cluster protein and cannot bind to *ALAS2*. This allows haem synthesis to proceed unfettered.



Wild-type and *sir* zebrafish embryos have provided a clearer picture of the control of haem synthesis. Modified with permission from Wingert *et al*. © (2005) Macmillan Magazines Ltd.

Zon and colleagues proposed that, in the *sir* mutants, defective Fe–S assembly liberates active IRP1. Just as in iron deficiency, active IRP1 inhibits *ALAS2* translation and blocks haem production. Indeed, the overexpression of *ALAS2* RNA without the IRP1 regulatory region, but not unmodified *ALAS2*, rescued haemoglobin production in *sir* embryos. And antisense knockdown of IRP1 restored *sir*-embryo haemoglobin synthesis, providing conclusive proof for this model.

These studies are the first to show that vertebrate haemoglobin production is regulated by Fe–S-cluster assembly. Notably, a yeast model of a complex human anaemia syndrome (X-linked sideroblastic anaemia and ataxia) is deficient in cytosolic Fe–S clusters, which indicates that disrupted Fe–S-cluster synthesis underlies the hypochromic anaemia seen in these patients. So, the anaemic profile of *sir* zebrafish might well have revealed a novel therapeutic target for human anaemia.

Shannon Amoils

References and links

ORIGINAL RESEARCH PAPER Wingert, R. A. *et al*. Deficiency of *glutaredoxin 5* reveals Fe–S clusters are required for vertebrate haem synthesis. *Nature* **436**, 1035–1039 (2005)