New look haemoglobin

Despite their historical position as the first proteins whose three dimensional structure was determined, the members of the oxygen-binding globin family are far from a closed book. For example two papers in this issue of *Nature Structural Biology* throw new light on their ligand binding. While Franzen *et al.* (pp. 230–233) have used resonance Raman spectroscopy to elucidate the first picoseconds of ligand dissociation, Huang and Boxer (pp. 226–229) have performed a tour-de-force of mutagenesis to plot the route of these ligands from the haem binding site to the outside world.

The basic globin monomer can be combined in a myriad of quaternary structures, from dimers to large assemblies; not only the pathological aggregates of sickle-cell anaemia, but also complexes like the extracellular haemoglobin of the earthworm *Lumbricus terestris* which contains over two hundred polypeptides.

Even the standard tetramer of haemoglobin, much beloved of undergraduate examination questions, is not immune from revelations. The haemoglobin pictured here, from the marine worm *Urechis caupo* (top figure; Kolatkar, Hackert & Riggs, *J. molec. Biol.* **237**, 87–97), despite having the characteristic tertiary fold of the globin family has a dramatically different quaternary arrangement unique among all known haemoglobins. In vertebrate haemoglobin (an $(\alpha\beta)_2$ heterodimer; bottom figure) the inter subunit contacts formed by helices G and H (green in both figures; helices A and B are orange; helices C to F yellow) are responsible for the allosteric behaviour crucial for efficient oxygen transport. In this invertebrate haemoglobin however the subunits come together leaving the G and H helices exposed on the outside of the molecule.

It is unsurprising therefore that *Urechis* haemoglobin does not display the dramatic cooperativity of its vertebrate cousins. *Urechis* lives in marine sediment and uses its haemoglobin as an oxygen reserve for times of deficiency such as low tide. Cooperativity, so important for a transport protein, would thus convey no special advantage but, intriguingly, its occurrence has not been completely ruled out. Should this behaviour exist in *Urechis* the intersubunit contact involving the E helix may prove to be the basis for a completely new haem-haem signalling pathway. CS

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