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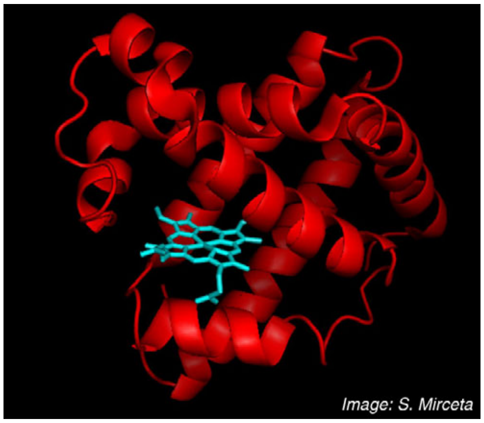
Editorial

Myoglobin's old and new clothes: from molecular structure to integrated function and evolution

Myoglobin is a small, 17 kDa, monomeric, O_2-binding haemoprotein that typically occurs in cardiac and aerobic skeletal muscle of vertebrates. Its classic function is the short- and long-term buffering of muscle O_2 concentrations during bursts of exercise or breath-hold diving and the facilitated diffusion of O_2 from blood to mitochondria (Wittenberg and Wittenberg, 2003). Determination of the crystal structure and the amino acid sequence of sperm whale myoglobin are considered landmark discoveries in molecular and structural biology. Today, 50 years since sperm whale myoglobin was the first protein whose structure was revealed at the atomic level in Nobel-Prize-winning work (Kendrew et al., 1960), myoglobin is perhaps the best-understood protein in terms of molecular structure–function relationships.

However, studies on myoglobin continue to surprise and reveal novel fundamental biological concepts (Cossins and Berenbrink, 2008). Thus, just when one might have thought we knew everything there was to know about myoglobin, the apparent lack of any adverse effects in myoglobin knockout mice questioned its physiological importance (Garry et al., 1998) and sparked a renaissance in myoglobin research based on novel analytical and experimental techniques and animal model systems. The collection of six articles in this issue of *The Journal of Experimental Biology* highlights the resurgent interest in novel functions of this old protein and demonstrates the power of a comparative and integrative approach for obtaining a true understanding of biological function from the molecular to the whole-organism level of organisation.



Thus, on the cell and tissue level, new biophysical methods have refined our understanding about the factors that affect the intracellular diffusion coefficient of myoglobin and thereby its potential contribution to facilitated oxygen transport in cardiac and skeletal muscles of different vertebrates (Gros et al., 2010) (p. 2713).

Knockout mice have revealed novel roles for myoglobin in cardiac cytoprotection by scavenging nitric oxide and reactive oxygen species under oxygenated conditions (Flögel et al., 2010) (p. 2726) and by producing nitric oxide from nitrite under deoxygenated conditions (Hendgen-Cotta et al., 2010) (p. 2734).

The recently reported, widespread non-muscle expression of myoglobin in vertebrates (e.g. Cossins et al., 2009) suggests that these new roles may extend to other tissues and may be of general importance. It is therefore critically important to unravel the mechanisms regulating the level of myoglobin expression (Kanatous and Mammen, 2010) (p. 2741).

The discovery of duplicated, tissue-specific myoglobin isoforms in certain fishes (Fraser et al., 2006) offers unique opportunities to disentangle cell/tissue-specific functions of myoglobin. At the same time, comparative studies on myoglobin function in vertebrates from different environments (Pedersen et al., 2010) (p. 2755) and comparisons with 'natural' knockouts in some amphibians and Antarctic ice fishes are important for mapping out the scale of intraspecific functional diversity of this protein.

Myoglobin from diving mammals has been the key to the Nobel-Prize-winning work of Kendrew that elucidated the first atomic structure of a protein at high resolution (Kendrew, 1960). Since then, myoglobin is still *the* test bed for structural and functional studies aimed at understanding the general properties of proteins. These have been carried to new heights by the recent atomic-level, time-resolved visualisation of the gaseous ligand pathway from the myoglobin surface through the protein core to the buried haem binding site. How these pores in myoglobin affect physiological function poses yet another striking question at the frontier of biology (Tomita et al., 2010) (p. 2748).

Thus, the textbook function of myoglobin in storage and transport of oxygen in red muscle needs to be rewritten to include, for example, handling of biologically important nitric oxide in an oxygen-dependent manner and widespread non-muscle expression. The present collection of articles is the result of a session devoted to these novel aspects of myoglobin function, held at the 2nd International Congress of Respiratory Science (ICRS) in Bonn/Bad Honnef, Germany (Perry et al., 2009). The session brought together scientists from a wide range of biological subdisciplines, all united by their interest in the most famous protein, and provided the ideal environment for breaking boundaries between established disciplines, cross-fertilisation of ideas, novel insights and thereby future scientific breakthroughs.

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