

Review

Hemoproteins in the cold

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ABSTRACT

This review highlights some aspects of the biochemistry of cold-adapted hemoproteins in fish and bacteria, without claiming to be exhaustive. Heme hexacoordination where the sixth ligand is provided by an internal amino-acid residue, in cold-adapted hemoproteins will be discussed.

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1. Introduction

Few proteins have been studied in such a wide array of organisms as hemoglobin (Hb), and recent discoveries on its structure–function relationship keep stimulating interest. Hbs are very ancient proteins; they probably evolved from enzymes that used to protect the tissues against toxic oxygen levels. Hbs have been found in bacteria, protists, fungi, plants and animals; they serve a wide array of physiological roles, from oxygen transport in vertebrates to catalysis of redox reactions (Gardner et al., 1998; Minning et al., 1999). These different functions suggest the acquisition of new roles, by changes not only in

the coding regions, but also in the regulatory elements in the pre-existing structural gene (Hardison, 1998).

Hbs share a common structure comprising 5–8 helices. Thanks to genome sequencing, the evolutionary tree of globins went back to 1800 million years at the time when the oxygen began to accumulate in the atmosphere (Wajcman and Kiger, 2002). It is generally accepted that during the first 2000 million years of existence of the Earth, the oxygen levels in the atmosphere were very low until the advent of the “Great Oxidation” (Holland, 2006). The atmospheric oxygen content reached the present levels about 540 million years ago (mya) (Holland, 2006). At those times, the Hb-like ancestor was likely to have adapted to locally scavenge excessive oxygen concentration and/or, similar to bacterial flavoHbs to be involved in detoxification of nitrogen monoxide (Poole, 2005). The evolution of simple oxygen-binding proteins into multi-subunit proteins, in combination with the

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development of the circulatory system, made the transport of oxygen from the blood to metabolising cells possible on a significant scale (Wajcman and Kiger, 2002).

Thus, the familiar vertebrate Hb, a tetramer of two identical α and β globin chains, developed relatively recent adaptation to widely different environmental conditions (Vinogradov and Moens, 2008). The amino-acid sequences of the α and β globins are about 50% identical, suggesting a common ancestor (Hardison, 1998). The specialised function in higher vertebrates imposes severe structural constraints on the Hb molecule. Hence, it is not surprising that only a small fraction of the residues of the polypeptide chains are allowed to be replaced during evolution. According to the species-adaptation theory of Perutz (1983), the replacement of few key residues may produce functional modulation. The first protein crystal structures of myoglobin (Mb), present in cytoplasm of skeletal and cardiac myocytes, and Hb provided the basis to understand the relationship between changes in amino-acid sequence and protein overall structure (Kendrew et al., 1958; Perutz et al., 1965). During the following four decades, studies of protein structure and function have led to a detailed understanding of these hemoproteins.

The quaternary structure, assembling the four globin subunits, also provided classical source of theories on allosteric conformational transitions (Monod et al., 1965; Perutz et al., 1987). The main concept of the two-state allosteric model of Monod, Wyman and Changeux (MWC) was that the Hb molecule can only exist in two quaternary states, corresponding to a low-affinity structure T (Tense) and a high-affinity structure R (Relaxed) (Monod et al., 1965). According to the MWC model, cooperative oxygen binding arises from a shift in the population from the T to R structure as binding increases. This model further postulates that the heterotropic effects, such as the Bohr effect, are due to shifts of the allosteric equilibrium.

In addition to tetrameric Hbs and monomeric Mbs, four vertebrate hemoproteins have been recently discovered. These are cytoglobin (Cyg) which is widely expressed in vertebrate tissues (Trent and Hargrove, 2002; Burmester et al., 2002), globin E (GbE) (Kugelstadt et al., 2004) in the chicken eye (absent in mammals), globin X (GbX) recently found in fish and amphibians (Roesner et al., 2005) and neuroglobin (Ngb) (Burmester et al., 2000). The latter has received

the most attention for its hypothetical role in protecting neurons from several injuries (Greenberg et al., 2008).

Phylogenetic analyses of vertebrate globins suggest a common ancestor, but confirm an ancient evolutionary relationship between GbX and Ngb, suggesting the existence of two distinct globin types in the last common ancestor of Protostomia and Deuterostomia (700 mya) (Roesner et al., 2005) as shown in Fig. 1. In fact, GbX sequences are distinct from vertebrate Hb, Mb, Ngb, and Cygb, but display the highest identity scores with Ngb (26% to 35%). For the first time in vertebrate globins, analysis of the gene structure showed an intron in helix E of Ngb and GbX, supporting the assignment of Ngb and GbX to a gene family different from that including Mb, Hb and Cygb. Only two introns, positioned at B12.2 and G7.0, are present in most vertebrate genes and are phylogenetically ancient ((Wajcman and Kiger, 2002; Roesner et al., 2005).

The variety of recently discovered bacterial Hbs has dramatically changed our view of the globin family. Bacterial Hbs highlight that oxygen transport in vertebrate Hbs is a relatively recent evolutionary acquisition and that the early Hb functions have been enzymatic and oxygen sensing (Vinogradov and Moens, 2008). The bacterial superfamily comprises three families distributed in two structural classes (Fig. 2). Within each family a given globin may occur in a chimeric or in a single-domain structure (Vinogradov and Moens, 2008). The first class, including the two families of flavoHbs and sensor Hbs, respectively involved in nitrosative stress and in adaptive responses to fluctuations of gaseous physiological messengers, displays the “3-on-3” classical Mb-like folding (3/3 Hbs). Historically, the first members of the two families were found to be chimeric. Single-domain flavoHbs are present in eukaryotic globins unlike single-domain sensor globins. The second class includes the third family of “2-on-2” Hbs (2/2 Hbs), and is widely distributed in bacteria, microbial eukaryotes and plants. Currently, there are still some uncertainties about the evolutionary relationship between the three families. The 2/2 Hbs and the sensor globins seem to have kept their original enzymatic functions in prokaryotes, plants and some unicellular eukaryotes. Therefore, the flavoHb family has been the only one able to adapt to different functions more extensively than the other two families (Vinogradov and Moens, 2008).

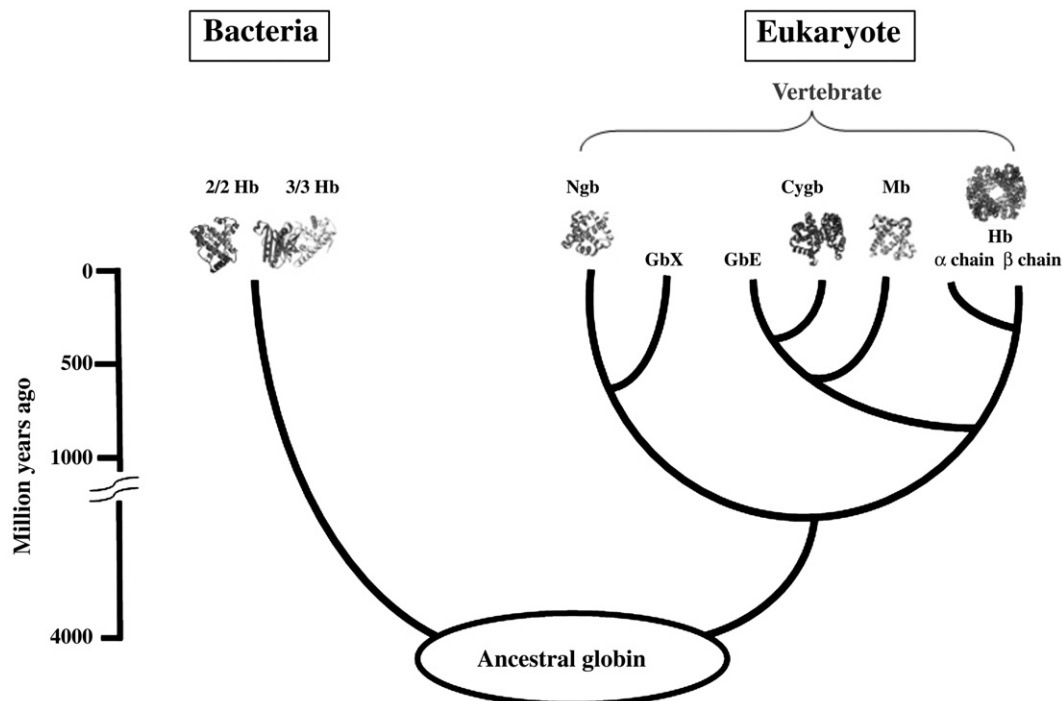


Fig. 1. A simplified phylogenetic tree of vertebrate globins. After Brunori and Vallone, 2007; Vinogradov et al., 2005.

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