Physica A 463 (2016) 1–11

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Oxygen channels and fractal wave–particle duality in the evolution of myoglobin and neuroglobin

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HIGHLIGHTS

- Amino acid sequences alone describe many functional differences between globins.
- Dynamics involve allosteric balance, quantified by hydrodynamic level sets.
- Differences between the two oxidation channels are seen in hydropathic waves.

ARTICLE INFO

Article history:
Received 10 March 2016
Received in revised form 9 May 2016
Available online 15 July 2016

Keywords:
Globin
Allometric
Hydropathic
Level set
Scaling

ABSTRACT

The evolution of terrestrial and aquatic globins is dominated by changes in two proximate–distal His channels, here monitored quantitatively by hydropathic waves. These waves reveal allometric functional features inaccessible to single amino acid stereochemical contact models, and even very large all-atom Newtonian simulations. The evolutionary differences between these features between myoglobin and neuroglobin are related to the two oxidation channels through hydropathic wave analysis, which identifies subtle interspecies functional differences inaccessible to traditional size and metabolic scaling studies. Level set analysis involves dynamic synchronization of allometric interactions across entire globins. Amino acid sequences alone show functional differences between species, which reflect basic metabolic differences (for instance, between temperate and tropical fresh water fish, or differing escape strategies of mice and rabbits).

1. Introduction

Here we discuss the evolution of myoglobin (Mb) and neuroglobin (Ngb) in functional terms, connecting hydropathic allometric globular properties and oxidation kinetics. Our analysis assumes that globins have evolved from aquatic predecessors to take nearly optimal advantage of the 28 times larger oxygen concentration available terrestrially. Mb stores O_2 in tissues, was the first protein whose structure was determined [1], and is the best understood globin. Ngb is concentrated in the neural network and the retina, and it exhibits instructive differences from Mb, and substantial sequence differences (similar overall length, but only 24% identity, 39% similarity). Features of Mb and Ngb evolution are largely hidden from structural studies, which generally show little difference between human and chicken protein backbones. Phylogenetic trees explore evolution in terms of single-site amino acid (aa) identities or similarities; more complex overall evolutionary scenarios are poorly described by such one-dimensional models [2].

It was first suggested that short-range hydrogen bond donation by the neutral NϵH tautomer of distal His(E7) regulates Mb oxygen affinity, a small energy change [3]. Later structural studies showed that ligand entry into Mb occurs by swinging

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http://dx.doi.org/10.1016/j.physa.2016.07.007

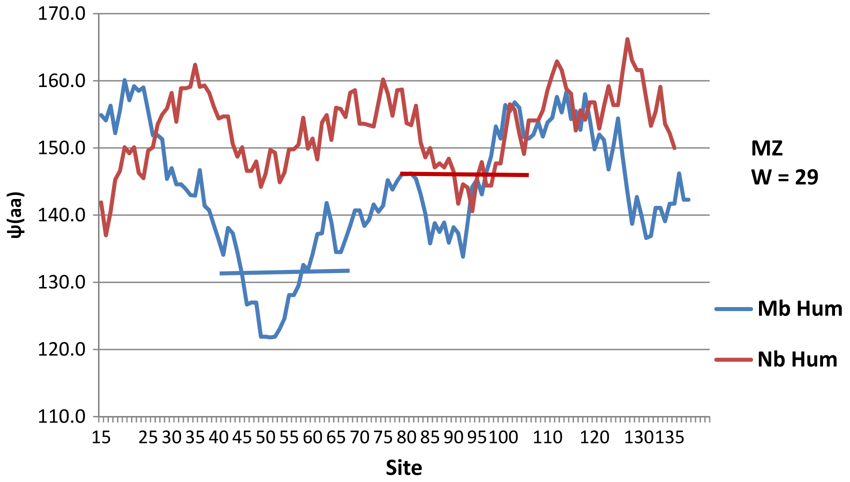

Fig. 1. The Ψ (aa, $W = 29$) hydropathic profiles for human Myoglobin and Neuroglobin. Also shown is the ψ (aa) averages for the elastic region spanning 29 amino acids between the Mb heme contact points 42–71 discussed in the text. The much lower elastic blue value for Mb enables the E8 His (64) gate to open and function as a small gas molecule channel. The much larger red elastic value for Ngb stiffens this region, so that the functional channel is switched from Mb. In Ngb the channel goes from E8 (64) to the C-terminal ends of the E and H helices [7,8]. Note that in Mb the deepest hydrophilic minimum is centered near the distal His 64, while in Ngb the deepest minimum is centered near the proximate His 96. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

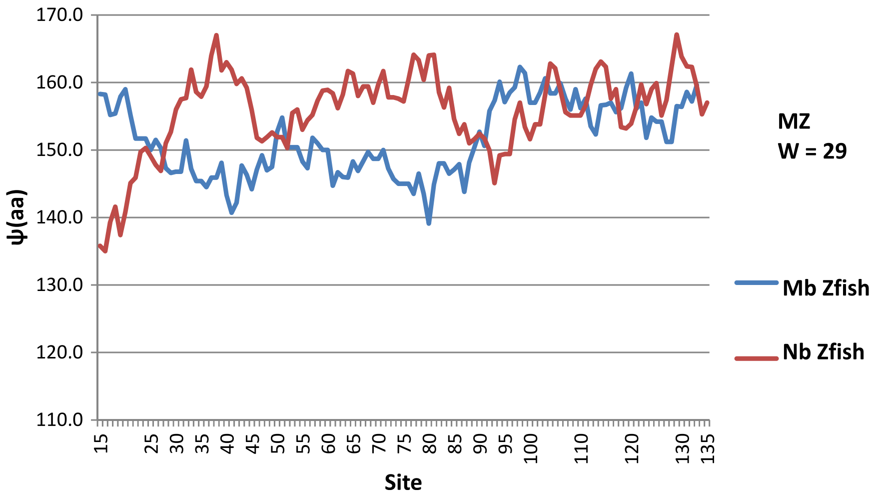

Fig. 2. The zebrafish profiles here should be compared to the human profiles of Fig. 1. The largest difference is the upward (hydrophobic) shift of the Mb hinge near 50 from human to zebrafish. The Ngb profile is little changed from fish to human in the 50–110 central region, which is shifted downwards in human by only 4 (about 10% of the overall range) in Ψ (aa, $W = 29$).

the distal His E7 imidazole gate near the solvent edge of the Fe-binding porphyrin ring [4], a medium-range interaction (a still smaller energy) that also plays a key role in discrimination between O_2 and CO binding [5]. While the separation of the proximate and distal His in Euclidean space on opposite sides of the porphyrin ring is small, their separation tangentially along globin chains looping around the porphyrin ring is large, and in Mb and Hemoglobin (α, β) it is usually 29 aa. This fixed chain spacing is not so surprising for Mb (∼75% aa conservation between human and chicken), or for Hb (∼70% conservation), yet their functions (storage or transport) are different. Moreover, the recent discovery of Ngb, which appears to resemble Mb [6], has shown a dis-his Ngb spacing of 32 aa in all species sequenced so far. This could be related to a different oxidation channel opposite to the standard Mb channel, as shown by detailed structural comparisons ([7], esp. Figs. 2 and 3, and [8]). Here we are involved with still smaller energies.

The proximate–distal His channel aa spacing in Mb has oscillated from 32 (ultraprimitive vertebrates, lamprey and hogfish) to 25 (amphibian bullfrog), and finally settled at 29 in Mb and Hb α and β, across many species, including even primitive pufferfish Mb and lungfish Hb. The mechanics of channel opening and closing involve long-range interactions (network strain), not just medium range channel unblocking near His 64. Only recently has it become possible to show the existence of a single Mb oxidation channel spanning so many aa side groups, and involving long diffusion times, with a single escape pathway, using Newtonian mechanical models [9–11].