Structural dynamics of neuroglobin: from ligand binding to signaling

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Neuroglobin, a heme protein expressed in the central nervous system of vertebrates, was shown *in vivo* and *in vitro* to counteract the effects of ischemia and the onset of Alzheimer disease [1]. Moreover association was shown between neuroglobin and the cellular prion protein (prPc) and between one of the subunits (G_{ai}) of heterorimeric G-proteins [2,3]. The overexpression of neuroglobin has beneficial effects also upon hypoxia of cardiac tissue [4].

The mechanism of neuroprotection by neuroglobin is still unclear, and its characterization may pave the way to novel strategies for the treatment and prevention of neuronal death due to ischemia and neurodenerative diseases. Our approach is to describe the structural dynamics of neuroglobin, therefore characterizing the structural transitions associated to ligand binding and how this information is transmitted to the protein regions involved in signalling of hypoxia and oxidative stress.

We have determined the three-dimensional structure of liganded and unliganded neuroglobin [5,6] and characterized its reaction with radicals such as NO [7]. The structural dynamics of neuroglobin was analysed by molecular dynamics and, experimentally, by microspectrophotometry in crystals, XANES [8], and stopped-flow kinetics.

Migration and docking of gaseous ligands within the protein matrix was simulated by MD [9] and by experimentally determining the structure of neuroglobin in the presence of Xe [10], carbon monoxide and dioxygen and at 15K under illumination (for the structure of the primary photoproduct).

The main goal is the determination of the molecular mechanism of neuroprotection exerted by neuroglobin by rigorous structural and biophysical characterization of the system and implementation of this information in cell biology experiments.

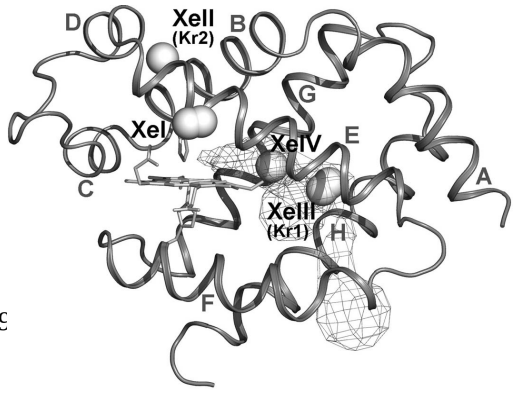

Fig. 1. The structure of neuroglobin with Xe atoms docked into cavities provides a putative ligand migration pathway.

References

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