Redox reactivity of non-classical copper-protein complexes: Implications in physiological and pathological processes

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Due to its reactivity and catalytic functions, copper is an essential cofactor in metalloproteins. Copper proteins are classified by their function and spectroscopic features, e.g. type 1 Cu and Cu\textsubscript{A} sites are electron transfer centers, binuclear and trinuclear Cu sites for oxygen activation and reduction, and tetranuclear Cu\textsubscript{2} sites for N\textsubscript{2}O reduction [1]. However, several proteins associated with neurodegenerative and degenerative diseases, such as prion (PrP\textsuperscript{C}), alpha-synuclein (AS) and \(\gamma\)-crystallin proteins, can coordinate Cu ions, but the resulting complexes are not classical sites with specific electron transfer or reactivity functions [2-4]. This presentation will discuss and contrast the biophysical details of copper coordination to PrP\textsuperscript{C}, AS and \(\gamma\)-crystallin proteins and their impact on reactivity, providing critical insights to understand the physiological and pathological implications of these proteins.

PrP\textsuperscript{C} is a 209 amino acids cell-surface glycoprotein that is anchored to the cell membrane by a glycosylphosphatidylinositol. The misfolded isoform of PrP\textsuperscript{C} is named prion scrapie (PrP\textsuperscript{Sc}) and is associated with a set of rare and fatal neurodegenerative disorders affecting humans and other mammalian species. PrP\textsuperscript{C} is expressed primarily in the central nervous system (CNS) and has been associated with a role in metal homeostasis [5]. PrP\textsuperscript{C} coordinates up to six Cu\textsuperscript{2+} ions in the N-terminal region, whose anchor sites are the histidine residues at positions 61, 69, 77, 85, 96 and 111; its Cu\textsuperscript{2+} coordination is highly dependent on Cu concentration and pH. Interestingly, the His111 site contains two adjacent methionine residues at positions 109 and 112, where the thioether groups of these methionines act as ligands in Cu\textsuperscript{+} coordination and promote redox reactivity at this site (Figure 1).

On the other hand, AS is a 140 amino acids protein that is predominantly expressed in the presynaptic terminals of CNS neurons. AS aggregation is associated with synucleinopathies, a group of neurodegenerative disorders whose hallmark is cytoplasmic inclusions known as Lewy bodies. The proposed physiological functions of AS include uptake, storage and recycling of neurotransmitter vesicles, auxiliary chaperone at synapses as well as maintenance of dopamine levels [5]. AS can coordinate copper ions with high affinity, the binding sites are located at the N-terminal region, a site involving the first six residues of AS (MDVFMK); and the other site around the only His residue of AS, His50. The first site contains two methionine residues involving in the Cu\textsuperscript{+} coordination (Figure 1).
Figure 1. Comparison of Cu$^{2+}$ and Cu$^+$ coordination between the complex formed at pH 6.5 at the His111 site of PrP$^C$ and the N-terminal site of AS protein.

Finally, γ-crystallins, proteins found mainly in the lens, are among the more stable proteins in the human body. The formation of nonamyloid aggregates of γ-crystallins contributes to light-scattering in a cataractous lens. Cu$^{2+}$ ions can cause nonamyloid aggregation of human γ-crystallins in vitro. The mechanism for Cu-induced aggregation of γ-crystallins involves metal-bridging, formation of disulfide-bridged dimers and oligomers, protein unfolding, and Cu$^{2+}$ reduction to Cu$^+$ at expense of protein oxidation [4].

These proteins linked to various neurodegenerative and degenerative diseases can coordinate copper ions and exhibit a coordination and reactivity that differs from the classical Cu metalloprotein sites. A discussion and comparison of these three systems will be presented, contributing to the understanding of the physiological and pathological aspects of these proteins.

References: