Interactions of Metal Ions with Proteins

Interaction of Metal Ions with Proteins: an Overview

G. ROTILIO

Institute of Biological Chemistry and CNR Center for Molecular Biology, University of Rome, Rome, Italy

Coordination of metal ions by the amino acid side chains of proteins is an extensively studied solute–solute interaction, which usually occurst at a restricted number of binding sites and often gives rise to very strong and specific interactions (metalloproteins). Such interactions have structure, functional and physiological implications.

From the standpoint of molecular structure, metal binding usually induces local constraints of protein mobility which, in turn, may produce long-range conformational effects. Therefore a protein-bound metal may become a *conformational probe*, in relation to its spectroscopic properties. Substitution of the metal contained in the native protein by a metal having better spectroscopic properties (*e.g.*, Co^{2+}) is often permitted, because of similar coordination geometries of the metals involved and of structural flexibility of some binding sites.

From the standpoint of molecular function, interaction with metals is often fundamental for constitution of *active sites*, especially in the case of redox systems (*e.g.* Cu^{2+}, Fe^{2+}, Fe^{3+}). In this context oxidases are particularly interesting, because their mechanism involves the concerted action of more than one specific metal center (*e.g.* cytochrome oxidase, copper 'blue' oxidases). In other circumstances, metal ions play a *regulatory role* through conformational effects (*e.g.* Ca^{2+}, Zn^{2+}). *Coordination of functionally relevant water or solute molecules* is sometimes specifically sensed by the protein-bound metal-ion (*e.g.* Cu^{2+}, Tb^{3+}). Superoxide dismutase is a comprehensive example of all types of interactions ('active' Cu, 'regulatory' Zn, 'functional' metal-bound water). The reaction of superoxide dismutase with halide inhibitors is a clear model for similar reactions of metal centers in proteins.

From the physiological standpoint, metal binding by proteins was probably fundamental to the evolution of life, as indicated by the involvement of copper and iron in aerobic respiration. This involvement must have been preceded by ability of cells to manipulate these metal ions. In fact, *metal buffering and metal transport* are vital requirements for living systems to counteract the toxic effects of excessive amounts of metal ions, and are satisfied by specific proteins, which build up 'non-functional' types of binding sites. In such sites metals are stored in anticipation of demand and in a form that neutralizes toxicity. Transport to and from these metal 'sinks' is a new, intriguing aspect of metal–protein interaction.

Binding of Luminescent Metal Probes to Proteins: the Case of Terbium

A. FINAZZI AGRÒ

Istituto di Chimica Biologica, Facoltà di Farmacia, Università di Roma, Rome, Italy

Some lanthanides show room temperature phosphorescence related to f–f transitions. The excitation to the emitting state can be accomplished by either direct or indirect absorption of light by the rare earth ions. However, the low oscillatory strength of f–f transitions makes the direct excitation not very useful to probe dilute protein–metal complexes. Indirect (sensitized) emission occurs than a ligand or a nearest chromophore is able to transfer non radiatively the energy absorbed on the lanthanide. This process is particularly effective with protein Tb^{3+} complexes. The green Tb^{3+} phosphorescence can be increased more than 10^4 times upon binding of the metal to binding sites of proteins.

Terbium may exchange with ligands 6–9 bonds, which preferentially involve charged or uncharged oxygen atoms. Up to date Tb^{3+} has been shown to substitute more or less conservatively in proteins calcium, iron or manganese. The former substitution is particularly relevant since calcium is spectroscopically silent. The substitution of iron and manganese by Tb^{3+} may give very useful information on the environment of the metal site.

The Tb^{3+} substitution for Ca^{2+} in hemocyanin, a copper protein where Ca^{2+} plays an important regulatory role, and in concanavalin, a plant agglutinin containing both Mn^{2+} and Ca^{2+}, and for Fe^{2+} or Fe^{3+} in ferritin, a metal storage protein, will be discussed in detail.