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How Bacteria Handle Copper

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Abstract Copper in biological systems presents a formidable problem: it is essential for life, yet highly reactive and a potential source of cell damage. Tight control of copper is thus a cellular necessity. To meet this challenge, cells have evolved pumps for transmembranous transport, chaperones for intracellular routing, oxidases and reductases to change the oxidation state of copper, and regulators to control gene expression in response to copper. These systems are complemented by specific mechanisms for the insertion of copper into enzymes. Copper homeostasis has evolved early in evolution and some components have been conserved from bacteria to humans. This has allowed researchers to apply knowledge across phyla and even involving human copper homeostatic diseases to elucidate the fundamental mechanism of cellular copper homeostasis. After an introduction to the properties of copper and its role in biological systems, some of the best studied bacterial systems for copper homeostasis will be discussed.

1 Introduction: Copper and Life

Copper has been known since prehistoric times. Metallic copper was available in the Middle East around 3500 B.C. It was obtained by reduction of its ores with charcoal. The discovery, some 500 years later, that the addition of tin to copper produced a much harder metal, established the Bronze Age. Copper has continued to this day to be an important metal to human kind. The abundance of copper in the earth's crust amounts to 68 ppm. It occurs mainly as the sulfide, oxide, or carbonate. Its major ores are copper pyrite (chalcopyrite, $CuFeS_2$), copper glance (chalcocite, Cu_2S), cuprite (Cu_2O), and malachite ($Cu_2CO_3(OH)_2$) (Tylecote 1992).

In the primordial, anaerobic word, copper was in the Cu(I) state in the form of water-insoluble sulphides. The ensuing oxygen evolution by microorganisms, a process which started less than 3×10^9 years ago, was a dramatic event for most living organisms. It could be considered to be an early, irreversible pollution of the earth, to which most living organisms adapted by acquiring an oxidative metabolism. While enzymes involved in anaerobic metabolism were designed to operate in the lower portion of the redox spectrum, the arrival of dioxygen created the need for a new redox active metal that could attain higher redox potentials. The oxidation of insoluble Cu(I) led to soluble and thus more bioavailable Cu(II), which was ideally suited to exploit the oxidizing power of dioxygen (Crichton and Pierre 2001). Copper is thus a modern bioelement (Kaim and Rall 1996). Concomitant with the arrival of oxygen, multi-cellular organisms developed.

Today, over 30 types of copper-containing proteins are known, prominent examples being lysyl oxidase (involved in the crosslinking of collagen) tyrosinase (required for melanin synthesis) dopamine β-hydroxylase of the catecholamine pathway, cytochrome *c* oxidase, the terminal electron acceptor of the respiratory chain, and superoxide dismutase, required for defense against oxidative damage. Another class of copper proteins, such as plastocyanins or azurines, act as electron carriers. In redox enzymes, copper serves as an electron acceptor/donor by alternating between the redox states Cu(I) and Cu(II) (Karlin 1993). Depending on the type of coordination of the copper to the protein, the redox potential can vary over the range + 200 to + 800 mV.

The redox properties of copper can, on the other hand, also cause cellular damage. A number or mechanisms have been suggested. Reactive hydroxyl radicals can be generated in a Fenton-type reaction:

$$Cu^+ + H_2O_2 = Cu^{2+} + OH^- + OH^\cdot . \quad (1)$$

The extremely reactive hydroxyl radical can participate in a number of reactions detrimental to cellular molecules, such as the oxidation of proteins and lipids (Yoshida et al. 1993). Copper can also lead to depletion of sulfhydryls,