Preface to Volume 5
Metallothioneins and Related Chelators

Metallothioneins are cysteine-rich low molecular mass (5 to 10 kDa) proteins, occurring from bacteria to humans, having, in the case of vertebrates, commonly 7 metal ions incorporated. This wide distribution already emphasizes the importance of these proteins, which are in the focus of this book. Relevant research is going on now for more than 50 years and its historical development, concentrating on mammalian metallothioneins (MTs) and their role in cadmium toxicology, is summarized in Chapter 1. Chapter 2 provides an overview of our current knowledge on the expression and regulation of MT genes: The intracellular concentration of MTs is adjusted to cellular demand. Upon heavy metal load, metallothionein gene transcription is often strongly induced. Indeed, all organisms use elaborate systems to regulate the levels of bioavailable zinc, copper, and other essential metal ions. Thus, MTs play pivotal roles in metal homeostasis as well as in detoxification reactions. Their high cysteine content enables MTs to avidly bind toxic metal ions and also to influence the cellular redox balance and radical scavenging. These points are further highlighted throughout the volume.

Chapters 3 to 5 give an account of bacterial MTs, MTs in yeast and fungi, and MTs in plants. Most astonishingly, the MTs of bacteria and plants contain next to cysteine also histidine residues and thus, metal ions are not only sulfur- but also imidazole-coordinated which gives rise to zinc finger-like structures. Remarkably, most yeast and fungal MTs are Cu(I) rather than Zn(II) or Cd(II) binding proteins. Next, Chapters 6 through 9 discuss the MTs of dipteran insects, including the model organism *Drosophila*

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melanogaster, earthworms and nematodes, as well as echinoderms, crustaceans, molluscs, and fish. Actually, aquatic animals, both vertebrates and invertebrates, have the potential to be used for monitoring metal contamination in aquatic ecosystems. Interestingly, in Chapter 9 the remarkable speculation is presented that under chronic natural exposure conditions the animals establish a trade-off between the "cost" of detoxifying non-essential metal ions and the "cost" of allowing some of these metal ions to spill over onto metal-sensitive sites. This contrasts with laboratory experiments involving aquatic animals, where the toxicity of non-essential metal ions normally exhibits a threshold response: at low exposure concentrations the organisms can detoxify the incoming metal ion and thus, tolerate the exposure, whereas at concentrations above the threshold, the detoxification mechanism is no longer able to protect the organism completely.

The structure and function of vertebrate MTs is detailed in Chapter 10, centering on MT-1 and MT-2. MT-3, discovered in 1991 and also known as the neuronal growth inhibitory factor, is dealt with in Chapter 11: it plays a vital role in zinc and copper homeostasis in the brain. Furthermore, MT-3 is involved in the protection against copper-mediated toxicity in Alzheimer's disease and the control of abnormal metal-protein interactions in other neurodegenerative disorders. The next two chapters address the role of MTs in protecting cells from injury due to toxic metal ions, oxidants, and electrophiles. In fact, a poor ability to produce MT in response to metal ion exposure may predispose certain individuals to carcinogenesis by some, though not all, inorganic carcinogens.

The final two chapters deal with "relatives" of metallothioneins. Chapter 14 is devoted to thioredoxins and glutaredoxins, which represent the major cellular systems for the reduction of protein disulfides and protein deglutathionylation, respectively. They take part in many aspects of human health, e.g., by controlling and maintaining the cellular redox state, and accumulating evidence suggests a close relationship between the redoxins and the cellular iron pool. Phytochelatins, which are dealt with in the terminating Chapter 15, are produced by plants, fungi, and algae (as well as nematodes) to maintain the homeostasis of essential metal ions in different cellular compartments and to regulate metal tolerance and detoxification mechanisms.

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