Preface

Proteins, the major functional macromolecules of life, are composed of long chains of L-α-amino acids linked by amide bonds between the α-caboxyl group of one residue and the α-amino group of the next. Although proteins contain several dozens to thousands of amino acid residues, only the 20 canonical coded amino acids, including two that contain sulfur—cysteine and methionine—are involved. Many diseases originate from mutations or modifications in proteins that affect their structure and cause a loss of function.

Recent studies provide evidence that in humans and animals, the noncoded sulfur-containing amino acid homocysteine (Hcy) becomes a constituent of proteins via two mechanisms: (a) protein *N*-homocysteinylation by Hcy-thiolactone and (b) protein *S*-thiolation in thiol–disulfide exchange reactions. Protein *N*-homocysteinylation is absolutely specific for Hcy because Hcy-thiolactone, the actual agent creating the modification, can only arise from Hcy in any cell type. In contrast, protein *S*-thiolation is not limited to Hcy but occurs with other thiols as well, generating a variety of *S*-thiolated proteins such as *S*-glutathionyl-protein, *S*-cysteinyl-protein, and *S*-cysteinyl-glycyl-protein, in addition to *S*-Hcy-protein. Thus, while *N*-Hcy-protein is unique, *S*-Hcy-protein is a quantitatively minor component of the total *S*-thiolated-protein species. Furthermore, as described in this book, physiological responses to *N*-Hcy-protein are also unique and distinct from the responses to *S*-Hcy-protein.

In the first sections of this book, I have described fundamental aspects of protein-related chemical biology of Hcy and emphasized the importance of Hcy-thiolactone-mediated protein *N*-homocysteinylation in Hcy pathobiology. Of many known naturally occurring Hcy species, only the thioester Hcy-thiolactone, a product of an error-correcting reaction in protein biosynthesis, can mediate the incorporation of Hcy into proteins via stable isopeptide bonds. Protein *N*-homocysteinylation creates altered proteins with newly acquired interactions. With the development of novel analytical methods within the last few years, studies of the role of Hcy-thiolactone and protein *N*-linked Hcy in humans and experimental animals became possible. So far, these studies have identified about three dozens of individual *N*-Hcy-proteins and specific sites of *N*-homocysteinylation in some of them. These studies also show

that the genetic or dietary hyperhomocysteinemia greatly elevates levels of Hcy-thiolactone and protein *N*-linked Hcy in humans and mice. Other studies provide evidence that *N*-Hcy-proteins are immunogenic in humans and experimental animals. In humans, *N*-homocysteinylation causes the formation of neo-self *Nε*-Hcy-Lys epitopes in proteins, which induce an adaptive immune response, manifested by the generation of anti-*N*-Hcy-protein IgG autoantibodies. Levels of these autoantibodies are elevated in stroke and coronary artery disease (CAD) patients and thus may play an important role in atherosclerosis. Other data show that *N*-homocysteinylation of fibrinogen by Hcy-thiolactone contributes to thrombogenic effects of elevated plasma tHcy levels in humans. Furthermore, these studies also show that primary Hcy lowering by B-vitamin therapy is beneficial in that it improves fibrin clot properties and lowers the levels of anti-*N*-Hcy-protein autoantibodies in healthy individuals. In contrast, secondary B-vitamin intervention appears to be ineffective: although it lowers plasma tHcy, *it does not affect anti-N-Hcy-protein autoantibody titers in CAD patients*. Finally, roles of Hcy-thiolactone-detoxifying enzymes, paraoxonase 1 and bleomycin hydrolase, as well as urinary Hcy-thiolactone elimination are discussed.

The final sections of this book are devoted to protein *S*-homocysteinylation. About a dozen of individual proteins are described that have been shown to be susceptible to *S*-homocysteinylation in vitro, and some of them are also found to be *S*-homocysteinylated in vivo. *S*-homocysteinylation, or more generally *S*-thiolation, causes profound changes in protein structure and function, but the physiological significance of these changes is not fully understood. The function of several proteins has been shown to be affected by Hcy and other thiols in vitro, and some of them are also affected in cultured cells and in vivo.

West Orange, NJ Hieronim Jakubowski
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Jakubowski, H.

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