

Preface

Most naturally evolved proteins are only marginally stable, always on the verge of losing their structure. But this is what most exciting biology is about: flexible molecular machines that undergo large conformational changes in addition to small fluctuations and adjustments, together conferring functionality. Nature has developed a means to reconcile these controversies: the disulfide bond. Strategically placed, this covalent crosslink of two cysteine residues can drive folding, inhibit unfolding and stabilize oligomeric protein assemblies. But it comes with a cost: owing to the intrinsic reactivity of cysteines, disulfide bonds may form erroneously, may need to be isomerized or broken for a protein to fold correctly, or for a protein to be degraded. Furthermore, reactions that form or break disulfide bonds are redox reactions – which means that the cell has to handle potentially harmful oxidative species.

Despite these odds, the intricate machinery that cells have developed to make, break and isomerize disulfide bonds speaks to the importance of this covalent modification in proteins. Disulfide bonds are particularly abundant in extracellular proteins, where they confer stability to the structure of individual polypeptide chains and their oligomeric assemblies. As such, unpaired cysteines are an important feature recognized by the secretory protein quality control machinery as a signature of incomplete protein folding and assembly.

However, beyond these structural roles, it is becoming increasingly evident that cysteines and disulfide bonds can do more: they serve regulatory roles, can stabilize protein conformations with different functions, and signal changes in the redox environment of a protein. The intimate connection between cysteines, disulfide bonds and protein folding and function also explains their prominent role in human disease, where cysteine mutations are common.

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Oxidative Folding of Proteins: Basic Principles, Cellular Regulation and Engineering

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Apart from these basic biological considerations, the rise of recombinant proteins and biopharmaceuticals depends on proper ways to form disulfide bonds – and techniques to analyze them. But it also depends on approaches to introduce covalent modifications into proteins for the purpose of their stabilization without disrupting functionality.

Both the basis of and recent developments in our understanding of these various facets of disulfide bonds are covered in this volume by leading experts in their field. The 18 individual contributions are combined in five sections: the first section is dedicated to the principles and analysis of disulfide bond formation – from single molecules to biopharmaceuticals. The second section covers structural and functional roles of disulfide bonds, from evolutionary, biotechnological and mechanistic perspectives. The third section traces the question of how disulfide bonds form, are isomerized and are broken – with a view to revealing common principles between different kingdoms of life and between different mammalian organelles. Based on these insights, the fourth section addresses the question of how oxidative folding and cellular homeostasis are coupled and how cells avoid and deal with oxidative stress. Lastly, the fifth section provides insights into how covalent linkages in proteins can be engineered for structural and functional purposes.

Covering such a broad scope of topics depends on the commitment of many people: my gratitude goes to all the authors of chapters in this volume and also to Rowan Frame, Drew Gwilliams and Robin Driscoll at the RSC, who made it possible to develop this comprehensive and in-depth overview of the principles, the biology, the analysis and the design of oxidative protein folding.

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