

# Preface

Molecular chaperones were first identified more than 30 years ago and have been the subject of considerable research ever since. Their importance in a wide range of different cellular processes has been recognised and in the past decade great strides have been made in understanding them from a structural and mechanistic perspective. This issue of *Topics in Current Chemistry* reviews work in the field over the past decade.

Numerous definitions for the term molecular chaperone exist – one long-standing definition is that they are a functional class of unrelated families of protein that assist the folding or assembly of other polypeptide-containing structures *in vivo*, but are not components of these assembled structures when they are performing their normal biological functions. Although many think of molecular chaperones in terms of how they affect protein folding, this class of proteins has a much wider role in the cell, and chaperones are involved in assembly and disassembly of macromolecular complexes, play essential roles in targeting and translocation of proteins to specific cellular locations and compartments, are central to many cellular degradation pathways, also regulate cell signalling and through heat shock factor 1 regulate the cellular stress response. Collectively, molecular chaperones in conjunction with other systems govern proteostasis *in vivo*.

So many families of molecular chaperones are now known it is not possible to discuss in detail the latest research for all of these. Instead, this issue is focussed on six key families for which there have been major advances in knowledge over the last 10 years.

The first two chapters focus on molecular chaperones which can perhaps be described as true protein folding catalysts, as they accelerate the rate of otherwise slow, rate-limiting steps in folding, that is, disulphide bond formation/rearrangement and peptidyl prolyl isomerisation. PDI, protein disulphide isomerase, is one of the most abundant proteins in the endoplasmic reticulum and plays a critical role in the oxidative folding of many ER and extracellular proteins. Chapter 1 describes recent advances in our understanding of the structure and function of PDI, as well as the Dsb family of chaperones which carry out similar functions in prokaryotes. The diversity of potential pathways and intermediates in the oxidative folding of proteins is illustrated using BPTI and detailed mechanistic studies on how PDI facilitates the folding of such systems are provided. The challenges in investigating a complex system in which the chaperone has multiple domains with differing

structures and functions but where high-resolution structural information can only be obtained on individual domains are nicely exemplified. Recent work establishing how the individual domains interact both structurally and functionally with each other to provide a holistic view of PDI's mechanism of action is described.

Chapter 2 describes all three families of known peptidyl prolyl isomerases (PPIases) including the FKBP, cyclophilins and parvulins. These chaperones catalyse conformational interconversions of peptide bonds which can be critical to the correct folding of many proteins. The structural and chemical features of PPIases and the catalytic cycle are described, and a discussion of chaperoning *versus* catalysis is also included.

One common feature of molecular chaperones is that many are multi-domain and/or oligomeric proteins. The intra-domain and inter-molecular dynamics of these systems can play a very important role in their function, and this is particularly true for the small heat shock proteins (sHsps). Chapter 3 describes the dynamic architecture of this class of chaperones and how their oligomeric state affects their chaperoning activity. Another common feature of many chaperones is that different classes cooperate together in chaperoning networks, some acting, as the small heat shock proteins do, as “holdases” in conjunction with other classes of chaperones that act as “foldases”. This is well illustrated in this chapter, the authors coining the phrase “paramedics of the cell” to describe the sHsps which effectively keep proteins alive until the medics (in this case other classes of chaperones) can treat them.

The Hsp70 family of molecular chaperones, which in bacteria comprises DnaK, DnaJ and a nucleotide exchange factor such as GrpE, has a central role in many cellular processes. Hsp70 is a classic chaperone with ATPase activity which is linked with conformational rearrangements in its multi-domain structure. Chapter 4 describes in detail the structure of the Hsp70 system and how ATP binding and hydrolysis linked with conformational changes create a functional cycle which binds and releases unfolded polypeptide chains in a controlled manner. This chapter highlights the importance of allostery in molecular chaperone machines and it goes on to demonstrate how allosteric effectors may act as drugs targeting cellular chaperones. This chapter introduces the idea that chaperones are closely associated with many disease states including neurodegenerative disorders and cancer, and this theme is continued in Chapter 5 on Hsp90s, which not only describes the importance of Hsp90 inhibitors as cancer therapeutics, but also recent work which has begun to establish that chaperones, in particular Hsp90, may also be important in the development of therapeutic agents against viral infection, protozoan parasites and other human pathogens as well as a large number of neurodegenerative disorders. Chapter 5 also describes the biological activity of this important chaperone and the many structural and functional studies that have generated considerable insight into the mechanism of its action. As with the chapter on the Hsp70 system, this section illustrates how ATP binding and hydrolysis, and the binding of co-chaperones, are linked with conformational changes in Hsp90 which results in activation of client (substrate) proteins.

The first five chapters are focussed on major classes of intracellular chaperones whilst the final chapter, Chapter 6, describes recent work in the increasingly important field of extracellular molecular chaperones. The function of a number of extracellular chaperones such as clusterin,  $\alpha 2$  microglobulin, haptoglobulin, apoE, serum amyloid P component, caseins and fibrinogens are all described, in addition to the link between these molecular chaperones and various disease states, in particular neurodegenerative diseases.

Together, it is hoped that this issue of *Topics in Current Chemistry* provides a useful resource for anyone coming into the field of molecular chaperones as well as those of us who have been working in this area for many years. I would like to take this opportunity to thank all the authors for their contributions and the staff at Springer for their patience.

Cambridge, UK

Sophie E. Jackson



<http://www.springer.com/978-3-642-34551-7>

Molecular Chaperones

Jackson, S. (Ed.)

2013, X, 274 p., Hardcover

ISBN: 978-3-642-34551-7