Preface

Cellular protein homeostasis is vital for cellular survival and requires a balance between the integrated processes of protein folding, degradation and translocation. Proteostasis is regulated by a diverse family of proteins known as molecular chaperones. Molecular chaperones act as catalysts for protein homeostasis by preventing protein aggregation, promoting protein folding and mediating appropriate protein degradation under both physiological and stressful conditions. These chaperones rely on a network of accessory proteins, termed co-chaperones, to fine-tune their function. As a consequence, co-chaperones are important mediators of the outcome of chaperone assisted protein homeostasis. Indeed, Hsp70 molecular chaperones cannot participate in productive protein folding without an Hsp40 co-chaperone. Equally, the co-chaperones Hop and CHIP interact with the Hsp70/Hsp90 chaperones to control triage of protein clients towards folding or degradation pathways. A co-chaperone can be defined as a non-client protein that interacts with a protein chaperone and/or its client protein to regulate chaperone function. Co-chaperones are evolutionarily conserved together with their chaperone counterparts (even being identified in the recently sequenced genome and transcriptome of the Coelacanth). Co-chaperones often outnumber their respective chaperones and are hence a way to induce specialisation of a relatively small number of chaperone isoforms. Co-chaperones may fulfil this function in a number of ways; by inducing conformational changes, delivering client proteins or regulating inherent enzymatic activities of chaperones. Many co-chaperones are modular proteins that combine the ability to bind client proteins with the capacity to interact with or modulate the activity of chaperones. Therefore, whilst co-chaperones are structurally diverse, there are conserved structural features within some families (such as the J domain of Hsp40 and the tetratricopepetide repeat (TPR) domain of some Hsp90/Hsp70 co-chaperones). Some co-chaperones (e.g. many Hsp40 isoforms) have chaperone-like activity in that they can bind and prevent aggregation of client proteins. However, most co-chaperones lack the inherent ATPase activity of chaperones and hence cannot actively refold proteins in the absence of chaperones. This second edition is timely since research in recent years has substantially expanded our understanding of co-chaperone function. For some co-chaperones, a number of new isoforms have been discovered, including FKBP immunophilin isoforms, virally encoded GroES

and the first putative co-chaperone for the organelle Hsp90, Gp96. However, the role of many of the numerous Hsp40 co-chaperones remains undefined. Our understanding and integration of the roles of known co-chaperones into cytosolic chaperone pathways has expanded. In particular, the roles of the structurally diverse Hsp90 co-chaperones during the ATP-dependent Hsp90 folding cycle have begun to emerge. We are beginning to appreciate that certain co-chaperones also function independently of chaperones and have features that are not normally associated with co-chaperone function. In particular, the established Hsp90/Hsp70 co-chaperone, Hop, is the first of this group to be shown to have independent ATPase activity; a characteristic not associated with co-chaperones. Does this suggest that it is time to reclassify Hop as a chaperone? Or will future analyses discover similar features of other co-chaperones, necessitating us to redefine the features of a co-chaperone? We have a new understanding of the role played by co-chaperones in human disease. Cell biological studies have demonstrated that some co-chaperones, like Hop and Cdc37, are expressed at higher levels in cancer, where they may contribute to maintenance of the malignant state and as such are now being considered as drug targets. We are starting to recognise that some co-chaperones are collaborative whilst others are mutually exclusive, although we perhaps don't fully appreciate the functional redundancy between co-chaperones yet. However, we still do not have a complete understanding of the spatial and temporal control of co-chaperone function. The mechanisms that control co-chaperone expression and subcellular localisation are poorly understood. Furthermore, the global control of co-chaperone and chaperone function through fluctuations of ATP levels ("energy" levels) in the cell, has not been studied in any detail. This represents a logical area to investigate towards understanding how the co-chaperone-chaperone network is tuned for different cellular states from normal through to stress and disease states. How do chaperones select their co-chaperones, particularly in cases of potential functional redundancy between certain isoforms? Likewise, while many co-chaperone isoforms (e.g. Hop) have been detected in the extracellular environment, we do not know whether these proteins function as co-chaperones outside of the cell. Indeed, many chaperones are now known to have extracellular functions and therefore it is likely that co-chaperones may too. Are there any co-chaperokines waiting to be identified? Are extracellular co-chaperones analogous to their intracellular counterparts? Our recent advances in analysis of co-chaperone function has demonstrated that there is still much to learn, and led to new questions that will ensure that research into our understanding of this important family of proteins continues.

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