**MOLECULAR BIOLOGY
INTELLIGENCE
UNIT**

Networking of Chaperones by Co-Chaperones

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GREGORY L. BLATCH is Professor of Biochemistry at Rhodes University, Grahamstown, South Africa. His research interests fall within the broad field of cell stress and chaperones, with a focus on the role of co-chaperones in the regulation and networking of the major molecular chaperones, Hsp70 and Hsp90. He was recently awarded a Wellcome Trust International Senior Research Fellowship for his research on the biomedical aspects of chaperones and co-chaperones. He received his Ph.D. from the University of Cape Town (UCT), South Africa, and did his Postdoctoral at Harvard University Medical School, U.S.A.

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PREFACE

There are a number of books dedicated to the cellular and molecular biology of chaperones and their important role in facilitating protein folding; however, this is the first book dedicated to the co-chaperones that regulate them. This book is perhaps long overdue, as the concept of co-chaperones has been in place for more than a decade. The chapters reflect many of the emerging themes in the field of co-chaperone-chaperone biology, with a particular emphasis on the co-chaperones of the major molecular chaperones, Hsp70 and Hsp90.

What constitutes a co-chaperone? In formal terms, a co-chaperone may be defined as any non-substrate protein that interacts specifically with a molecular chaperone and is important for efficient chaperone function. Many co-chaperones are dedicated to a specific chaperone and play a regulatory role (e.g., Hsp40 regulates the nucleotide-bound state of Hsp70). This regulatory role is highly substrate-sensitive, with some co-chaperones having the ability to directly interact with the substrate protein and target it to the chaperone. Indeed, some co-chaperones have the capacity to carry out some of the functions of a chaperone, such as the prevention of protein aggregation (e.g., some Hsp40s, UNC-45 and Cdc37). However, co-chaperones do not always have the ability to interact with substrate or to act as true chaperones in their own right. Nevertheless, whether they directly bind the substrate or indirectly “sense” its presence, in many cases co-chaperones provide specificity to their somewhat promiscuous chaperone partner.

The structure of co-chaperones suggests that they have evolved through domain recruitment, manifesting as highly sophisticated protein scaffolds for the efficient spatial orientation of protein-protein interaction domains (e.g., J domain) and motifs (e.g., tetratricopeptide repeat [TPR] motif). A number of the chapters document the rapidly emerging structural data on domains and motifs, giving us insight into the elegant manner in which these structural features are the functional engines driving the optimal docking and regulation of chaperones by co-chaperones. Interestingly, evidence has also emerged for “fractured” co-chaperones (e.g., Zim17 in yeast), which represent the evolution of physically uncoupled, yet functionally linked, partner domains, allowing for the flexibility of multiple roles.

Contrary to the perception that co-chaperones are merely auxiliary components of the cell’s molecular chaperone machinery, a number of chapters suggest that co-chaperones are core components of, and can sometimes transcend, the chaperone machinery (e.g., the role of GrpE as a thermosensor; and Hop may not be dedicated to Hsp70 and Hsp90). Furthermore, co-chaperones not only play an important role in the regulation of Hsp70 and Hsp90 protein folding pathways, but also integrate these folding pathways with protein degradation pathways so as to maintain

cellular homeostasis. Therefore, co-chaperones can be broadly viewed as quality control factors enabling the major molecular chaperones to integrate diverse cellular signals and make the correct decision on whether to hold, fold, or degrade; the global safety of the cell being paramount. Finally, the dogma that chaperones interact only with misfolded or denatured substrate proteins is being challenged by mounting evidence to indicate that co-chaperones are able to target chaperones to act with near native proteins to facilitate conformational change (e.g., targeting of clathrin to Hsp70 by auxilin). The name co-chaperone is perhaps limiting, and as more details on the global cellular roles of co-chaperones are revealed, we will no doubt have to re-evaluate the co-chaperone paradigm.

Gregory L. Blatch, Ph.D.

Acknowledgments

I have been very privileged to have had the opportunity to edit the first book dedicated to co-chaperones. Privileged, firstly because it has given me many new and exciting insights into this fascinating field of research, and secondly because it has allowed me to enter into a thoroughly enriching process of interacting with a highly professional network of biologists. Like any typical network, there were many weak links (the email conversations) and a few strong links (the book chapters) in the network of interactions between editor and authors! And so it was that this book on the “Networking of Chaperones by Co-chaperones” was born. I hope that each of the contributors to this book enjoyed the process as much as I have; thank you for your immense creative input. I am also very grateful to the Rhodes University Chaperone Research Group for so eagerly assisting me at the whole book proofing stage: Dr. Aileen Boshoff, Melissa Botha, Sheril Daniel, Dr. Linda Stephens, Dr. Victoria Longshaw, Michael Ludewig, Dr. Eva-Rachele Pesce, Mokgadi Setati and Addmore Shonhai. I went to many people for advice; thanks to all of you for your valuable time, but especially Dr. Graeme Bradley (Rhodes University), Dr. Peter Lund (Birmingham University, U.K.) and my wife Heather Yule.