PREFACE

In this book, the current advances on the functional role of molecular chaperones in protozoan's mechanisms of response to stressful conditions, as well as an overview of studies focusing on molecular chaperones as potential targets for designing novel anti-parasitic drugs, are examined. In the second chapter, the current progress regarding the structure-function relationship as well as its association with the chaperone-like activity of the mammalian PDIA1/P4HB protein are discussed. The final chapter focuses on the cytoplasmic and nuclear functions of URI/Bud27 in different organisms.

Chapter 1 – *In vivo*, proteins are synthesized as linear chains by ribosomes. To be functional, must fold and get their three-dimensional structure (native conformation). Interestingly, some proteins can get the native conformation spontaneously; however, many others cannot and are likely to get a misfolded conformation. Therefore, to facilitate the folding process, the endoplasmic reticulum contains a molecular machinery that includes a set of chaperones, which prevents protein aggregation and promotes correct folding, thereby controlling cellular proteostasis. Despite this, some proteins fail to adopt a native conformation and are more likely to form aggregates, which represent a constant threat to cell function and viability. For instance, human amyloid diseases are characterized by the accumulation of unfolded proteins which form insoluble aggregates. Parasitic infections are a major public health issue in tropical and subtropical regions. Several studies focusing on the biology of medically-important protozoan parasites, such as Leishmania, Trypanosoma, and Plasmodium, have revealed processes related to their particular lifestyle. As they endure harsh environment conditions during its life cycle (e.g., dealing with at least four types of cellular stress: thermal, nutritional, osmotic, and oxidative), protozoan parasites have developed a response mechanism, which includes activation of molecular chaperones, to

avoid unfolding of proteins. Consequently, molecular chaperones play a key role in both maintaining protein homeostasis and promoting correct folding of virulence-related proteins. This chapter reviews the current advances on the functional role of molecular chaperones and foldases from medically-important protozoan parasites in their mechanisms of response to stressful conditions, as well as an overview of studies focusing on these key molecules as potential targets for designing novel anti-parasitic drugs.

Chapter 2 – Protein folding is a sensitive process that can be affected by several factors, among which pH and temperature are notable (environmental factors). Protein misfolding is an important issue in some human disorders, e.g., Alzheimer's disease. Molecular chaperones are multi-domain proteins with a specific function in folding, unfolding, and remodeling of proteins. *In vivo*, molecular chaperones assist nascent polypeptides throughout the folding process until the native conformation has been attained. Furthermore, they can regulate unfolding and aggregation, protecting the cell from a proteotoxic stress. Protein disulfide isomerase (PDI, EC 5.3.4.1) enzymes are oxidoreductases that catalyze the oxidation and rearrangement of disulfide bonds in polypeptide substrates. PDI enzymes share as a common feature an active domain that folds similar to the bacterial protein thioredoxin (thus named thioredoxin domain), which has the conserved CXXC motif at its active site. The protein disulfide isomerase A1 (PDIA1), also named beta subunit of prolyl-4-hydroxylase (P4HB), is a multifunctional enzyme that plays a key role in the dithiol-disulfide equilibrium of the secretory pathway. Interestingly, a chaperone-like activity has been observed at high concentration, inhibiting aggregation of misfolded proteins. Conversely, anti-chaperone activity has been noted at low concentrations, promoting aggregation. This chapter reviews the current progress regarding the structure-function relationship as well as its association with the chaperone-like activity of the human PDIA1/P4HB protein.

Chapter 3 – The unconventional prefoldin Rpb5 interactor (URI/RMP), and its ortholog in yeast, Bud27, are members of the prefoldin (PFD) family of ATP-independent molecular chaperones. URI was originally identified as a protein binding the Rpb5 subunit of all three nuclear RNA polymerases (RNA pol) and is considered to function as a scaffold protein able to assemble additional members of the PFD family in both human and yeast.

URI and Bud27 have been linked to essential cellular processes both in the nucleus and the cytoplasm, such as RNA polymerases assembly, translation initiation, genome stability, DNA damage response, and viability. Furthermore, URI has been shown to be involved in several types of cancer

processes and to regulate the TOR pathway, not only in humans, but also in yeast.

Taken together, this data points to a role for URI/Bud27 as a global molecular chaperone participating in multiple essential cellular processes.

In this review, the authors focus on the cytoplasmic and nuclear functions of URI/Bud27 in different organisms.