Preface

The present volume of *Current Topics in Microbiology and Immunology* contains seven chapters that illuminate various aspects of a protein's genesis and terminal fate in the endoplasmic reticulum (ER). This area is of immediate medical relevance and has blossomed, to no small extent, because of the study of molecules central to the function of the immune system [immunoglobulins, T cell receptors, major histocompatibility complex (MHC)-encoded products]. Similarly, the clever strategies used by bacteria or viruses to gain a foothold in the host and ensure their continued survival have uncovered altogether new cell biological principles. It is therefore fitting that a special volume be devoted to the interplay between pathways of protein degradation in the ER and a wide variety of pathogens. The concept of quality control emerged with the appreciation that, in the case of multimeric glycoproteins, any unpaired glycoprotein subunit had great difficulties leaving its site of synthesis—the ER—and was destroyed instead. Free immunoglobulin heavy chains were probably the earliest documented example of this kind, and were long known to cause pathology when their accumulation went unchecked.

Increased knowledge of the biosynthetic pathways of glycoproteins allowed the identification of the ER as an important site where such quality control decisions were made. The T cell receptor for antigen, long considered the paradigm of this mode of degradation, led the way in these early explorations. A major puzzle remained: if the ER is indeed the compartment where nascent chains make their first appearance, begin to fold, and assemble with partner subunits, how then is the distinction made between terminally misfolded proteins and those on the way to a functional end-product? Part of the solution, surely, was the appreciation that the synthetic and degradative functions of the ER might be topologically distinct: by exercising quality control in the lumen of the ER, but relegating proteolysis to the cytosol, this paradox might be solved. There is now ample evidence that such separation indeed occurs, although it is unlikely to be the only solution.

It is the study of viruses and bacteria that has helped identify some of these escape hatches from the ER. Intoxication with cholera toxin or the dislocation

reaction used by herpes viruses to dispose of class I MHC products are but two examples, dealt with in this volume (chapters by Lord et al. and Kikkert et al.). Especially the latter studies would have been impossible, were it not for the detailed insights into the biosynthesis of glycoproteins in general, and of MHC products in particular. Two chapters in this volume, by Molinari and Sitia and Groothuis and Neefjes, deal with the general and MHC-specific aspects of glycoprotein synthesis, assembly, and intracellular transport. Yeast geneticists have pursued a parallel route: the wonderful toolbox of Sec mutants has been the key ingredient to a dissection of the eukaryotic secretory pathway. Surely the rules that operate in the ER to ensure delivery of the proper products apply across the eukaryotic kingdom. Using genetics, a host of genes were identified in yeast that could be linked to the disposal of misfolded proteins. It is gratifying to see how the studies initiated in yeast converge with the more biochemically inspired experimental systems in higher eukaryotes, again exemplified by three chapters in the present volume, those by McCracken and Brodsky, Wolf and Schäfer, and Bar-Nun. Given the involvement of the cytoplasmic compartment in disposal of unwanted ER proteins, it is perhaps not surprising to see the ubiquitin-proteasome system make its obligatory appearance: the multitude of Ub ligases required for recognition of an extremely heterogeneous set of substrates is only now beginning to be unraveled. A helicopter view of these pathways is provided in the chapter by Kikkert et al. It would be misleading to suggest that there is now uniformity for pathways of quality control in the ER, and a consensus has yet to emerge. What about the unfolding requirements, so as to be able to deal with partially folded proteins? What about the identity of the channels via which proteins escape from a membrane-delimited compartment? What about the routes used by soluble versus membrane proteins? Polytopic membrane proteins? How many different pathways for such escape exist? The continued examination of viruses, bacteria, and their products is required to answer these questions, as pathogens rely on the exploitation of these cellular pathways for their survival. The chapter by Lord et al. provides an overview of our understanding of the routes traveled by cholera toxin. While certain commonalities with ER degradative pathways are apparent, there are also important differences. It stands to reason that the final picture will be even more complex.

It is perhaps equally important to point out which areas have not been covered in this volume, for lack of reliable information. The most successful approaches in the field of protein quality control have relied on the tried and trusted methods of genetics and biochemistry. Many aspects of cellular physiology are under the control of processes that are not template-encoded, and cannot be manipulated simply by introduction of a mutant cDNA or a siRNA vector. Glycosylation, lipid modifications, and other post-translational modi-

fications must surely be superimposed on the basic toolbox of the host and its pathogens. Continued improvements in analytical methodology coupled with the development of new chemistry-based tools to interfere in these processes should be a high priority to illuminate the many different functions of the ER.

Boston, MA, USA, October 2005 *Hidde L. Ploegh*