PREFACE

Why write this book now? At first glance, the topic may seem esoteric and just about one more signaling pathway. Yet this is a most unusual mechanism which repurposes an intracellular protein, the Glucose Regulated Protein of molecular weight 78,000 (GRP78), as a cell surface signaling receptor. There are precedents for such behavior, for example cell surface ATP synthase as the angiostatin receptor. However, cell surface GRP78 has unique properties. The intracellular version of the protein exists in the endoplasmic reticulum (ER) where it is a key player in the unfolded protein response, essential for cell survival under conditions of stress. Cells may be stressed by many factors such as hypoxia, disregulation of glucose metabolism, or injury to tissues requiring rapid division of cells to repair the damage. Under these conditions, protein synthesis ramps up and there is a risk of piling up misfolded proteins in the ER. GRP78 is crucial for driving proper folding of such proteins, and its ATP binding domain is essential for these functions. When GRP78 reaches the cell surface, this ATP binding domain is essential, allowing GRP78 to autophosphorylate and function like a classic tyrosine kinase-type receptor. To our knowledge, this represents unique behavior for a repurposed intracellular protein. Of particular interest, GRP78 as a cell surface receptor is generally associated with disordered cell biology. Other than a small fraction of the population of "activated" macrophages, it does not demonstrate signal transduction properties in normal cells. Cancer cells are the main arena where cell surface GRP78 functions as a pro-proliferative, promigratory, and antiapoptotic receptor. But, similar biology is seen in synovial cells from rheumatoid arthritis patients, and in damaged endothelial cells such as are seen in atherosclerosis. On the cell surface, GRP78 associates with many other proteins playing a regulatory "dance." One such example to be discussed in detail in this book is its association with the procoagulant molecule tissue factor. Indeed,

regulation of these complexes is almost certainly critical with respect to the association of cancer and thrombotic events.

Thus, we feel that this is a good time for such a book and we thank Elsevier for the opportunity.

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