

Preface

Many molecular changes within a tumor cell occur during cancer progression. Cell growth, survival, morphology, and invasive characteristics are altered and contribute to the formation of advanced disease that eventually disseminates from the primary tumor and establishes new tumors at distant sites. Nearly all aspects of cellular behavior are controlled by small guanosine triphosphatases (GTPases). The importance of these molecules is highlighted in nature, as a majority of bacterial toxins specifically target the small GTPases and thus exert their deleterious effects by inhibiting these proteins.

In the early 1980s activating mutations in the Ras proteins were found to occur in a number of human cancers and thus became a focus of cancer research. However, not all cancers contained mutant Ras; therefore, other Ras-like proteins were thought to exist and contribute to cancer formation and progression. The discovery of the Ras homology or Rho GTPases and other small GTP-binding proteins caused quite a bit of excitement in the cancer world and much work has ensued over the years demonstrating their roles in cancer progression.

Currently, the Ras superfamily of small GTP-binding proteins has more than 150 members in five major separate subfamilies: Ras, Rho, Rab, Ran, and Arf. Each of these subfamilies controls an aspect of cellular behavior: Ras is intimately involved in growth regulation, Rho regulates the cytoskeleton, Rab and Arf are primarily involved in vesicle fusion, and Ran is involved in nuclear transport.

Because of their intimate involvement with the cytoskeleton, the Rho GTPases are primarily implicated tumor cell progression from transformation to metastasis. Since their discovery in the mid-1980s, many of the Rho proteins have been analyzed for activating mutations similar to Ras. With very few exceptions, activating mutations have not been identified. Instead, aberrant expression and activation in the absence of mutations appears to be the rule in human cancers. This volume is intended to give a concise overview of the current knowledge of Rho GTPase biology in the context of cancer progression. The book is separated into four sections, each of which explores a different aspect of Rho biology and its contribution to cancer etiology.

The first section is an overview of the Rho proteins in both normal and cancer cells. Combined with an introduction from Alan Hall, one of the pioneers of Rho biology, and his colleagues, this section provides a comprehensive overview of Rho history, regulation, signal transduction, phenotype, and its role in cancer progression.

Channing Der and colleagues provide an encyclopedic overview of the Rho GTPases, providing enough detail to make any reader well-versed in the Rho field. Finally, Sofia Merajver's laboratory provides an overview, which details the roles of the Rho proteins in cancer progression. She provides us with the history of the study of the Rho GTPases, their regulatory and effector proteins in cancer and gives us a benchmark of where the field is today.

The second section of the book details the current knowledge of the Rho regulatory proteins in cancer progression: aberrant expression and activation of these proteins leads to dysfunctional Rho signaling and a cancer phenotype.

Gary Bokoch's laboratory has provided a detailed overview of the role of Rho guanine dissociation inhibitors (GDIs) in cancer. These molecules are involved in preventing the Rho protein from associating with the inner plasma membrane and exchanging GDP for GTP, and thus becoming active. Next, Tozu Kazasa's laboratory has worked on the link between heterotrimeric G proteins and Rho activation via the RGS-RhoGEFs. This aspect of Rho activation is particularly interesting in that heterotrimeric G proteins and their associated G-protein-coupled receptors are attractive and attainable therapeutic targets. Dan Billadeau's laboratory has worked extensively on the Vav RhoGEFs, which are potent oncogenes in their own right. The chapter that he offers here covers the ever-emerging details of how these specific GEFs contribute to cancer progression. Finally, Yi Zheng and colleagues describe the role of the RhoGAPs in cancer progression. Increasingly, it is becoming apparent that RhoGAPs have other functions in addition to catalyzing the hydrolysis of Rho-bound GTP and closing of the GTPase cycle.

The third section deals with the current understanding of the Rho GTPase proteins themselves in cancer. This section goes beyond an understanding of the three most studied Rho proteins: RhoA, Rac1, and Cdc42. Instead, the chapters explore some of the lesser known, but eminently important GTPases.

Harry Mellor begins this section by describing the biology and contribution of RhoBTB, one of the least studied Rho proteins, in breast cancer. My own laboratory has studied the role of RhoC GTPase in the metastatic phenotype of several cancers and this, along with the work of other laboratories, is summarized in the second chapter of this section. In collaboration with George Prendergast and his colleagues, we have shown interactions between RhoC and RhoB GTPases. The biology and functions of RhoB are highlighted in a chapter by George Prendergast and colleagues. Finally, we focus on a short overview of another potentially important, yet understudied mechanism of Rho GTPase activation and control, the concept of phosphorylation by protein kinases. This brief chapter gives an overview of some of the salient work performed by a number of laboratories on the control of Rho activation by a variety of protein kinases.

Finally, Michael Olsen provides us with a comprehensive overview of one of the apparently most important Rho effector proteins, Rho kinase, a.k.a. ROCK. Dr. Olsen's laboratory has significantly contributed to the understanding of these proteins and their contribution to cancer progression and metastases. His discussion of this extremely important effector is exhaustive and provides a great deal of detail of its role in cancer progression.

Together, these chapters not only provide a detailed overview of essential background Rho GTPase biology, but also provide a comprehensive and detailed description of the state of knowledge of the field as it stands today. These chapters provide insight into an ever-expanding field that has become increasingly recognized over the past decade as being key to the understanding of cancer progression. Without a doubt, the Rho proteins and their related signaling molecules will provide valuable therapeutic targets in the near future.

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