# Preface

The Ras superfamily (>150 human members) encompasses Ras GTPases involved in cell proliferation, Rho GTPases involved in regulating the cytoskeleton, Rab GTPases involved in membrane targeting/fusion, and a group of GTPases including Sar1, Arf, Arl, and dynamin involved in vesicle budding/fission. These GTPases act as molecular switches, and their activities are controlled by a large number of regulatory molecules that affect either GTP loading (guanine nucleotide exchange factors or GEFs) or GTP hydrolysis (GTPase-activating proteins or GAPs). In their active state, they interact with a continually increasing, functionally complex array of downstream effectors.

In this new series of *Methods in Enzymology*, we have strived to bring together the latest thinking, approaches, and techniques in this area. Two volumes (403 and 404) focus on membrane regulating GTPases, with the first dedicated to those that function in budding and fission (Sar1, Arf, Arl, and dynamin) and the second focused on those that control targeting and fusion (Rabs). Volumes 406 and 407 focus on the Rho and Ras families, respectively. It is important to emphasize that, while each of these volumes deals with a different GTPase family, they contain a wealth of common methodologies. As such, the techniques and approaches pioneered with respect to one class of GTPase are likely to be equally applicable to other classes. Furthermore, the functional distinctions that have been classically associated with the distinct branches of the superfamily are beginning to blur. There is now considerable evidence for biological and biochemical interplay and cross-talk among seemingly divergent family members. The compilation of a database of regulators and effectors of the whole superfamily by Bernards (Vol. 407) reflects some of these complex interrelationships. In addition to fostering cross-talk among investigators who study different GTPases, these volumes will also aid the entry of new investigators into the field.

Since the last *Methods in Enzymology* volume on this topic in 2000, the study of Ras family GTPases has witnessed a plethora of new directions and trends. With regards to the founding member of the Ras superfamily, the study of Ras in oncogenesis has seen the development and application of more advanced model cell culture and animal systems. The discovery of mutationally activated B-Raf in human cancers has injected renewed interest in this classical effector pathway of Ras. New regulators and effectors of Ras that further diversify the signaling inputs and outputs of the already complex Ras signaling networks

continue to be identified. Other members of the family continue to enter the spotlight. In particular, with the identification of tumor suppressor Tsc2 as a GAP for Rheb, this previously understudied Ras family GTPase has received considerable research attention. Additionally, Ras family proteins that function more as tumor suppressors than oncogenes continue to emphasize the importance of many Ras family proteins in human disease. The interplay between the Ras family and other branches of the Ras superfamily continues to emerge, with GEFs such as Tiam1 and Rin leading the way and linking Ras with Rho and Rab GTPases, respectively. New technological developments such as fluorescence imaging and interfering RNA, together with the continued emergence of yet more "omics" applications, have advanced our ability to study old questions in new ways, as well as to address many new questions. Finally, the database for Ras family proteins and their effectors and regulators by Bernards in chapter one highlights the fact that much remains unknown, and hence, progress and new discoveries for the Ras family will surely continue at a rapid pace for many years to come.

We are extremely grateful to the many investigators who have generously contributed their time and expertise to bring this wealth of technical knowledge into this and other volumes comprising the Ras superfamily series.

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