



## Channing J. Der

### Molecular Therapeutics

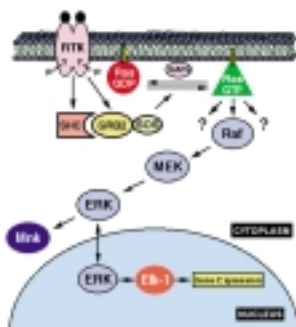
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RAS signals through multiple downstream effector pathways.

Our broad research interests center on understanding the molecular basis of human carcinogenesis.

Particularly, our research studies have dealt with three distinct aspects of the Ras oncogene proteins and one on the discovery of novel oncogenes involved in specific human cancers. First, we are interested in deciphering the increasingly complex nature of signal transduction pathways that mediate the oncogenic actions of Ras. It has become quite apparent that Ras regulates a multitude of signaling pathways via its interaction with a surprisingly diverse spectrum

of downstream effector targets, which include the Raf serine/threonine kinases. To date, at least a dozen distinct Ras effector targets have been identified. Whether the biology of Ras differs as a consequence of its interaction with different effectors is an important question that we are asking in our studies. Second, we now know that the three Ras proteins represent but a mere subset of a large superfamily of Ras-related proteins. Mammalian members of this family number over 60, with more likely to be discovered. Since Ras-related proteins share strong sequence and biochemical similarities with Ras proteins, a logical question is whether the aberrant function of any other members of this superfamily are also oncogene proteins involved in cancer development. Much of our current interest has centered on members of the Rho family of Ras-related proteins, which function as regulators of a wide spectrum of cellular processes that include actin cytoskeletal organization, gene expression and cell cycle progression. Recent studies by us and others have revealed that quite a diverse collection of oncogene proteins (including Ras) cause transformation, in part, by deregulating the function of Rho family proteins. It is generally believed that Rho family proteins may serve as key players in promoting the invasive and malignant properties of tumor cells. How Rho proteins contribute to Ras transformation, and what signaling pathways connect Ras with Rho, are questions that we are pursuing in our studies. Third, we are involved in drug discovery efforts to target Ras for cancer treatment. For example, we are engaged in studies to determine if farnesyltransferase inhibitors, which block Ras function by blocking its association with the plasma membrane, will be useful as anti-Ras and anti-cancer drugs. Finally, we have developed biological screens to search for novel oncogenes that are activated in a variety of human cancers, including carcinomas of the breast, colon, prostate and pancreas. We are using RNA isolated from tissues derived from these tumors to generate retrovirus cDNA expression libraries to screen for activated oncogenes using cell-based transformation assays. In summary, our studies span the broad range from gene discovery to drug discovery, with the long range goal of identifying better diagnostic and therapeutic approaches for cancer treatment.

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