Empowering normal cells against cancer with Par-4 secretagogues

Prostate apoptosis response-4 (Par-4) is a tumor suppressor protein that is ubiquitously expressed. Par-4 exhibits both intracellular and extracellular pro-apoptotic functions selectively against cancer cells. Transgenic mice overexpressing Par-4 are resistant to the growth of tumors. Par-4 is inactivated, down-regulated or mutated in several types of cancers. Par-4 is secreted by normal and cancer cells and it binds to its receptor GRP78 on the cancer cell surface to induce apoptosis by a caspase-8/caspase-3 pathway. Par-4-null mice develop spontaneous as well as inducible tumors at a higher frequency than wild type (Par-4+/+) mice implying that basal levels of Par-4 are effective in regulating tumor growth. We undertook a chemical biology approach to elevate the secretion of Par-4 from normal cells. Our recent studies identified novel compounds as potent Par-4 secretagogues in normal cell cultures and mouse models. The secreted Par-4 induced the paracrine apoptosis of diverse cancer cells and inhibits tumor growth in mouse models. Our studies focus on the mechanisms dependent on tumor suppressor p53 for Par-4 secretion and on the drug development of Par-4 secretagogues. As Par-4 is a generic tumor suppressor that is secreted, Par-4 secretagogues have broad translational relevance.

Biography

Vivek M Rangnekar is a Professor and Alfred Cohen Endowed Chair in the Department of Radiation Medicine and serves as Associate Director at the Markey Cancer Center, University of Kentucky. He received his PhD from the University of Bombay and completed Postdoctoral Training at the University of Chicago. He first identified the pro-apoptotic tumor suppressor gene Par-4/PAWR and characterized its mechanism of action. He currently serves as Senior Editor of Cancer Biology and Therapy and on the Editorial Board of Genes and Cancer. He has published over 100 research articles and edited two volumes of a book on Programmed Cell Death.

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