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Targeting the neurotransmitter receptor-driven regulation of pancreatic cancer

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Pancreatic Ductal AdenoCarcinoma (PDAC), is the leading histological type of pancreatic cancer with incidence rising and a very high mortality within one year of diagnosis. We have pioneered the concept that the highly coordinated hyperactivity of pancreatic cancer stem cell self-renewal, cell proliferation, angiogenesis, metastatic potential and drug resistance is regulated by neurotransmitter receptors that are the recipients of signals from the autonomic nervous system. We as well as others have thus shown that either stress or drug-induced hyperactivity of the sympathetic branch of the autonomic nervous system, resulting in systemic increases of the catecholamine neurotransmitters epinephrine and norepinephrine, significantly stimulated the growth of PDAC in mouse xenografts via hyperactive cAMP-dependent signaling downstream of Gs-coupled beta-adrenergic receptors. Treatment of the animals with γ-Amino Butyric Acid (GABA) completely reversed this effect via inhibition of cAMP formation in response to binding of GABA to Gi-coupled GABAB receptors. The general beta-blocker propranolol had similar effects via inhibition of cAMP formation downstream of Gs-coupled beta-adrenergic receptors. Using a hamster model of pancreatitis-associated PDAC, we additionally showed that treatment of the animals with GABA effectively prevented the development of PDAC. Stress reduction via environmental enrichment also significantly reduced the development and progression of PDAC xenografts in mice. In each of these animal models, the observed inhibition of PDAC growth and progression was accompanied by decreases in cAMP-dependent signaling of multiple proteins associated with cell proliferation, cell migration, stem cell self-renewal and angiogenesis. *In vitro* investigations with human PDAC cell lines confirmed the central role of cAMP hyperactivity downstream of Gs-coupled receptors as the driving force of PDAC growth suggested by the animal experiments. Collectively, these findings identify the opposing roles of PDAC stimulating Gs-coupled neurotransmitter receptors and PDAC inhibiting Gi-coupled neurotransmitter receptors as promising novel targets that can be successfully used for the prevention and therapy of PDAC by restoration of cAMP homeostasis via psychological as well as pharmacological agents that are already widely used for the therapy of several non-neoplastic diseases.

Biography

Hildegard M Schuller is a Distinguished Professor Emeritus, College of Veterinary Medicine, The University of Tennessee Knoxville, USA. She has held positions at the Medical School Hannover, Germany, the Frederick Cancer Research Center and National Cancer Institute before joining the University of Tennessee Knoxville TN in 1985 as the Director, Experimental Oncology Laboratory and was promoted to Distinguished Professor in 1994. Her research has pioneered the concept that neurotransmitter receptors regulate lung cancer and pancreatic cancer and are promising targets for the prevention and therapy of these cancers. She has published 248 articles in national and international professional journals.

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