Dr. Herbert and Nicole Wertheim Leadership in Healthcare and Medicine Lectureship

Presents

The Paracrine Hormone Hypothesis of Colorectal Cancer

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Venue: AHC4 101

Biography

Dr. Scott Waldman obtained his PhD degree from Thomas Jefferson University, and his MD degree from Stanford University. He was a postdoctoral fellow at the University of Virginia and Stanford University in the Division of Clinical Pharmacology in the laboratory of Ferid Murad, MD, PhD, who won the 1998 Noble Prize in Physiology or Medicine. He is the Samuel MV Hamilton Professor of Medicine, Director of the Gastrointestinal Cancer Program of the Kimmel Cancer Center, and Chairman of the Department of Pharmacology and Experimental Therapeutics of the Sidney Kimmel Medical College of Thomas Jefferson University. Also, he directs the MD-PhD Program, the NIH-sponsored Postdoctoral Training Program in Clinical Pharmacology, and the Training Program in Human Investigation (former NIH K30 Program) at Jefferson. He is a past member of the American Board of Clinical Pharmacology, a past Regent of the American College of Clinical Pharmacology (ACCP), a past-President of the American Society for Clinical Pharmacology and Therapeutics, and Chair of the Scientific Program Committee and Council Member of the American Society for Pharmacology and Experimental Therapeutics. He is a Fellow of the ACCP (FCP) and American Heart Association (FAHA). He is the Editor-in-Chief for Clinical Pharmacology and Therapeutics and Biomarkers in Medicine, and co-Editor for Waldman and Terzic's Pharmacology: Principles to Practice. Dr. Waldman's research interests focus on clinical pharmacology and translational medicine in the context of gastrointestinal malignancies and obesity.

Abstract

Colorectal cancer is the 4th most common cancer and the 2nd leading cause of cancer death. Transformation begins with activation of Wnt signaling through mutations in APC (80%) or its degradation target β-catenin (15%), producing a gain-of-function in TCF-dependent nuclear transcription underlying epithelial dysfunction and tumorigenesis. While a role for APC and β-catenin in colorectal cancer is well-established, steps leading from gene mutation to tumorigenesis, and their reversibility, remain incompletely defined. Guanylin is the paracrine hormone in colorectum for the receptor GUCY2C. This hormone is the most commonly lost gene product in colorectal cancer, and its universal suppression and associated silencing of GUCY2C at the earliest step in neoplasia contributes to tumorigenesis in a mechanism that is conserved across species. GUCY2C regulates homeostatic mechanisms organizing the intestinal crypt-surface axis, and its silencing through guanylin suppression drives hyperproliferation, DNA damage, metabolic reprogramming and desmoplasia contributing to tumorigenesis. Beyond this dysregulation of homeostatic mechanisms contributing to transformation, we recently discovered that guanylin suppression is required for tumorigenesis induced by mutant APC-β-catenin, reflecting a role for GUCY2C in β-catenin degradation that blocks tumorigenesis. Thus, inactivation of APC, or activation of β-catenin, induces TCF-dependent elimination of guanylin transcription and translation in human intestinal cells in vitro and in conditional genetic mouse models in vivo. Conversely, activation of GUCY2C induces elimination of β-catenin, even in the context of mutations which inactivate the APC degradation complex. Importantly, enforced genetic expression of guanylin in intestinal epithelial cells eliminated tumorigenesis in mouse models of colorectal cancer. These observations reveal a pathophysiologic model in which mutant APC-β-catenin signaling eliminates guanylin expression as an obligatory step in tumorigenesis. In turn, silencing GUCY2C reversibly disrupts epithelial homeostatic processes corrupted in tumorigenesis, and removes an essential block to transformation, creating a circuit which amplifies mutant APC-β-catenin signaling. These studies shift the prevailing paradigm for colorectal tumorigenesis from an irreversible oncogenomic mechanism to a reversible functional mechanism whose reconstitution abrogates those mutational defects. Indeed, they define a novel molecular pathway that is obligatory for tumorigenesis, to which the transformation process is addicted. In that context, they highlight how this addiction creates a unique disease-specific vulnerability that can be leveraged to eliminate tumorigenesis by GUCY2C hormone replacement. We have translated these observations to an NCI-funded clinical program exploring the utility of oral GUCY2C ligands to prevent colorectal cancer.

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