OMICS Group Conferences
Accelerating Scientific Discovery

International Conference and Exhibition on
Surgery, Anesthesia & Trichology

November 26-28, 2012 Hilton San Antonio Airport, USA

Antihypertensives as novel antineoplastics

Hwyda A. Arafat
Jefferson Medical College, Thomas Jefferson University, USA

Pancreatic ductal adenocarcinoma (PDA) is one of the most fatal malignancies that is characterized by metabolic alterations and increased rates of glycolysis and lipogenesis. Deregulation of the AMP-activated protein kinase (AMPK) and overexpression of the lipogenesis promoting enzyme fatty acid synthase (FAS) are key metabolic alterations in PDA. FAS, an oncogene that is regulated by AMPK, provides constant supply of lipids and lipid precursors to fuel membrane production during cancer cell proliferation. Activation of AMPK and subsequent inhibition of FAS have been shown to suppress tumor growth in several animal models of human cancer. We have previously shown that angiotensin II (AngII), the principal hormone of the renin angiotensin system (RAS), is actively generated in the pancreas. In PDA, all RAS members, including AngII receptors type 1 and type 2 (AT1R and AT2R) and angiotensin converting enzyme (ACE) are highly upregulated in the malignant ducts. We show here that AngII significantly increases the production of FAS in PDA cells and that its blockade by ACE inhibitors or by ATR blockers (ARBs) inhibits endogenous FAS production through regulating its transcription. Interestingly, AngII blockers activate AMPK and induce phosphorylation-inhibition of acetyl CoA carboxylase (ACC). In vivo, in a xenograft model of human PDA, AngII blockade induces significant reduction of tumor size and decreases FAS production. Furthermore, we show that hypertensive PDA patients who receive AngII blockade therapies enjoy a significant survival advantage ($P<0.02$). Our data have a considerable impact on both the understanding of pancreatic carcinogenesis and its treatment as targeting AngII maybe an attractive means to modulate pancreatic cancer progression. Our results also shed new light on the ' lipogenesis-cancer' paradigm as our data suggest that AngII may be a central component in the sequence of metabolic changes leading to cancer by down regulating AMPK activity and driving oncogenic FAS production.

Biography

Arafat completed residency and a fellowship in Clinical Pathology at Ain Shams University Hospital, Cairo, Egypt. She received a master degree in Anatomy and Biochemistry. In 1996, she received her doctorate in Cell Biology and Immunology from the University of Medicine and Dentistry of New Jersey. Dr. Arafat completed her postdoctoral training at the University of Pennsylvania. She joined the faculty at Jefferson Medical College in 2002 and in 2007 she was nominated the Associate Professor of Surgery, Pathology Anatomy and Cell Biology. In 2011, she was nominated the Professor Surgery. Dr. Arafat research is focused on investigating the molecular mechanisms involved in the regulation of oxidative stress and inflammation signaling in pancreatic diseases. She received multiple honors and awards from several funding agencies in the fields of diabetes and cancer research, such as the prestigious Junior Faculty Award from the American Diabetes Association, the Research Scholar Award from the American Cancer Society, and from the National Institutes of Health. Dr. Arafat is a member of the Diabetes and Obesity Center at the University of Pennsylvania and the Kimmel Cancer Center at Thomas Jefferson University. He serves on the advisory boards of many funding agencies. She serves on the editorial boards and as a reviewer to different scientific journals. Dr. Arafat became the co-director of the Jefferson Pancreatic, Biliary & related Cancer Center in 2009.

Hwyda.Arafat@jefferson.edu