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Novel roles for sirtuin deacetylases as regulators of cancer cell motility, aromatase expression and cancer epigenetics

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The sirtuin deacetylases and most notably, SIRT1, regulate multiple hallmarks of cancer. Recently, we were the first to demonstrate that sirtuins are key positive regulators of Wnt signaling and that they positively regulate Dishevelled protein levels (PNAS, 107(20):9216-21). We further explored this novel connection and found that SIRT1 was significantly upregulated in primary colon tumors and was associated with an increased risk of cancer recurrence. Additionally, we found that pharmacologic inhibition of SIRT-1 & -2 lead to a marked reduction in active Rac-1, its downstream effectors, and that the most robust link occurs within the context of KRAS-mutant cancer cells.

In breast cancer, CYP19A1 transcription is upregulated, resulting in an overexpression of the aromatase enzyme and a substantial increase in intratumoral estradiol levels. Aromatase inhibitors have proven to be highly effective in treating hormone-dependent post-menopausal breast cancer. Aromatase transcription in normal breast tissue is tightly controlled by one of 10 tissue-specific promoters. In breast cancer, however, aromatase transcription is driven by multiple promoters that somehow override the normal tissue-specific regulation. For the first time, we demonstrate that inhibition of SIRT1/2 reduces the levels of aromatase. Additionally, we demonstrate that SIRT1 occupies specific tissue-specific promoters and positively regulates aromatase expression. This work demonstrates a novel mechanism for the regulation of aromatase and provides rationale for further investigation of how sirtuin inhibition may provide a unique strategy for inhibiting aromatase in a promoter-specific manner. Together, these data suggest that SIRT1 may be an important biomarker for colon and breast cancer.

Biography

Kevin Pruitt received a B.S. in Chemical Engineering from UT-Austin and completed his Ph.D. training in Pharmacology as an N.S.F. Predoctoral Fellow under the direction of Channing Der, Ph.D., at UNC-Chapel Hill. He then continued postdoctoral studies as an American Cancer Society Postdoctoral Fellow at the Johns Hopkins School of Medicine under Stephen Baylin, M.D. Dr. Pruitt became an assistant professor at the LSU Health Sciences Center – Shreveport in 2006 and currently directs a very successful research program for which he has secured NIH/NCI funding (R01). The Pruitt laboratory has made major contributions in the study of sirtuin proteins and cancer epigenetics and has published papers in high impact science journals. Dr. Pruitt serves as an Ad hoc reviewer for the Cancer Genetics Study Section, the DOD Breast Cancer Research Program Programmatic Review, and the Clinical Integrative and Molecular Gastroenterology Study Sections.

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