Title: Epigenetic deregulation in cancer: the case of histone acetyltransferase Naa40

Abstract: Epigenetic modifications such as those occurring on histone proteins are important regulators of chromatin structure and gene expression. Deregulation of these histone marks has been implicated in the development of cancer. Due to the fact that epigenetic modifications are reversible, understanding their cellular function and role in cancer offers new opportunities for therapeutic interventions. N-alpha-acetyltransferase 40 (NAA40) is an epigenetic enzyme, which catalyzes histone H4 N-terminal acetylation (N-acH4) and its role in oncogenesis is poorly understood. In this study, we show that NAA40 protein and mRNA levels are commonly increased in colorectal cancer (CRC) primary tissues compared to non-malignant specimens. Importantly, depletion of NAA40 inhibits cell proliferation and survival of CRC cell lines and delays the growth of human CRC xenograft tumors. Intriguingly, we found that NAA40 knockdown and loss of N-acH4 reduce the levels of an adjacent histone modification, namely symmetric dimethylation of histone H4 (H4R3me2s), through transcriptional downregulation of protein arginine methyltransferase 5 (*PRMT5*). NAA40 depletion and subsequent repression of PRMT5 results in altered expression of key oncogenes and tumor suppressor genes leading to inhibition of CRC cell growth. Consistent with this, *NAA40* mRNA levels correlate with those of *PRMT5* in CRC patient tissues. Taken together, our results demonstrate a deregulated epigenetic mechanism in colon cancer cells and establish the oncogenic function of the epigenetic enzyme NAA40.

Antonis Kirmizis biosketch:

Antonis Kirmizis is an associate professor at the Department of Biological Sciences at the University of Cyprus. He received his PhD in Molecular and Cellular Biology at the University of Wisconsin-Madison, USA. He then completed his post-doctoral work in the field of Epigenetics as an EMBO and Marie Curie fellow at the Gurdon Institute of Cambridge University, UK. In 2010, Antonis has established a research lab in Epigenetics and Gene Regulation (www.kirmizislab.com), which focuses on deciphering functional and regulatory mechanisms of histone modifications in the context of health and disease. His lab was the first to define the cellular role of the previously uncharacterised histone N-terminal acetylation and of its associated enzyme in transcription and cell growth. In general, his studies are driven by the fact that deregulation of epigenetic mechanisms lead to diseases like cancer and the overall goal of his research is to identify new targets and strategies for cancer therapy. Since the launch of his group, Antonis has attracted considerable funding including a prestigious ERC-starting grant. He is also involved in various other collaborative projects and networks such as the EpiGene2Sys network of excellence, the COST action EpiChemBio and LifeTime initiative. Finally, Antonis interacts with many scientists and has important ongoing collaborations with various laboratories nationally and internationally.