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Targeting a lncRNA – epigenetic factor complex to inhibit colon cancer metabolism

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L ncRNAs (long non-coding RNAs) have recently occurred as new epigenetic regulators contributing to human diseases. We found that the lncRNA HOTAIR is up-regulated in colon cancer and associates with poor patient survival. HOTAIR directly interacts with the histone acetyltransferase PCAF (KAT2B) to regulate H3K27 acetylation and transcriptional activation. Hence, the HOTAIR/PCAF complex induces cell metabolic reprogramming and oncogenic transformation of colon epithelial cells. We have characterized the interface of HOTAIR/PCAF complex and developed a specific inhibitor (CPDI-1) that disrupts their interaction. This inhibitor reverses the HOTAIR/PCAF-induced metabolic rewiring and inhibits tumorigenesis *in vivo*. Disruption of an lncRNA/epigenetic factor interaction may offer an alternative approach to target cancer metabolism and progression.

Recent Publications

- 1. Vorvis C, Hatziapostolou M, Mahurkar Joshi S, Koutsioumpa M, Williams J, Donahue TR, Poultsides G A, Eibl G and Iliopoulos D (2016) Transcriptomic and CRISPR/Cas9 technologies reveal FOXA2 as a tumor suppressor gene in pancreatic cancer. Am. J. Physiol. Gastrointest. Liver Physiol. 310(11):G1124-37.
- 2. Polytarchou C, Hommes D W, Palumbo T, Hatziapostolou M, Koukos G, van der Meulen de Jong A E, Oikonomopoulos A, van Deen W K, Vorvis C, Koutsioumpa M, Birli E, Choi J, Chang L, Anton P A, Pothoulakis C, Verspaget H W and Iliopoulos D (2015) Therapeutically targeting miR-214 circuit in ulcerative colitis and colitis-associated colon cancer. Gastroenterology 149(4):981-992.
- 3. Chen X, Iliopoulos D, Zhang Q, Tang Q, Greenblatt M B, Hatziapostolou M, Lim E, Tam W L, Ni M, Chen Y, Mai J, Shen H, Hu D Z, Adoro S, Hu B, Song M, Tan C, Landis M D, Ferrari M, Shin S J, Brown M, Chang J C, Liu X S and Glimcher L H (2014) XBP1 promotes triple negative breast cancer by controlling the HIF1A pathway. Nature 508(7494):103-7.
- Sanidas I, Polytarchou C, Hatziapostolou M, Ezell S A, Kottakis F, Hu L, Guo A, Xie J, Comb M, Iliopoulos D and Tsichlis P N (2014) Phosphoproteomics screen reveals Akt isoform-specific signals linking RNA processing to lung cancer. Mol. Cell. 53(4):577-90.
- 5. Hatziapostolou M, Polytarchou C, Aggelidou E, Drakaki A, Poultsides G A, Jaeger S A, Ogata H, Karin M, Struhl K, Hadzopoulou Cladaras M and Iliopoulos D (2011) An HNF4A-microRNA inflammatory feedback circuit regulates hepatocellular oncogenesis. Cell 147(6):1233-47.

Biography

Maria Hatziapostolou explores novel areas of basic research and specifically works on projects that span from tumour-stroma interactions, to the implications of epigenetic machinery and non-coding RNAs in oncogenesis and chemoresistance. She uses high-throughput approaches, sophisticated molecular techniques, and functional *in vitro* and *in vivo* approaches focusing on basic research outcomes that can be translated in potential clinical applications. Her research in Hatziapostolou laboratory focuses on the molecular interplay between the genome and the epigenome during oncogenic transformation, cancer growth and metastasis. She has her interest in cancers of those of the gastrointestinal tract with an emphasis on pancreatic, liver and colon cancer.

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