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Targeting a lncRNA Ã¢?? Epigenetic factor complex to inhibit colon cancer metabolism

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Abstract

LncRNAs (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.

Cellular metabolism alterations have been recognized as one of the most predominant hallmarks of colorectal cancers (CRCs). It is precisely regulated by many oncogenic signalling pathways in all kinds of regulatory levels, including transcriptional, post-transcriptional, translational and post-translational levels. Among these regulatory factors, epigenetics play an essential role in the modulation of cellular metabolism. On the one hand, epigenetics can regulate cellular metabolism via directly controlling the transcription of genes encoding metabolic enzymes of transporters.

On the other hand, epigenetics can regulate major transcriptional factors and signaling pathways that control the transcription of genes encoding metabolic enzymes or transporters, or affecting the translation, activation, stabilization, or translocation of metabolic enzymes or transporters.

Interestingly, epigenetics can also be controlled by cellular metabolism. Metabolites not only directly influence epigenetic processes, but also affect the activity of epigenetic enzymes. Actually, both cellular metabolism pathways and epigenetic processes are controlled by enzymes. They are highly intertwined and are essential for oncogenesis and tumor development of CRCs. Therefore, they are potential therapeutic targets for the treatment of CRCs. In recent years, both epigenetic and metabolism inhibitors are studied for clinical use to treat CRCs. In this review, we depict the interplay between epigenetics and cellular metabolism in CRCs and summarize the underlying molecular mechanisms and their potential applications for clinical therapy.

Long non-coding RNAs (lncRNAs) represent a significant population of the human transcriptome. Many lncRNAs exhibit cell and/or tissue/tumor specific expression making them excellent candidates for therapeutic applications. In this review we discuss examples of lncRNAs that demonstrate the diversity of their function in various cancer types. We also discuss recent advances in nucleic acid drug development with a focus on oligonucleotide-based therapies as a novel approach to inhibit tumor progression. The increased success rates of nucleic acid therapeutics provides an outstanding opportunity to explore lncRNAs as viable therapeutic targets to impact various aspects of cancer progression.

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