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Topic of Research: Investigating the role of micro-RNAs in lung cancer metabolism

Keywords: microRNAs, aerobic glycolysis, Non small cell lung cancer (NSCLC), sphingolipid metabolism, macrophage polarization

Finding

Lung cancer (LC) is a leading cause of cancer associated worldwide deaths. Although numerous studies have demonstrated the correlation between micro-RNA (miRNA) dysregulation and metabolic reprogramming in LC, existential knowledge gaps at biochemical and cellular levels remains to be understood. We show that miR-16-5p targets Lactate Dehydrogenase-A (LDH-A), eventually causing reduction in aerobic glycolysis and inhibition of NF-κB pathway, leading to cell cycle arrest and apoptosis. Thus, miR-16-5p regulates aerobic glycolysis via LDH-A/Lactate/NF-κB, acting as a critical link between metabolism and LC tumorigenesis. We also demonstrated the role of miR-495-3p in sphingolipid reprogramming towards ceramide via targeting Sphingosine kinase-1 (Sphk1). Ceramide accumulation provide nutritional signals to foster metabolic adaptations via inhibition of nutrient uptake, induction of lethal mitophagy and apoptosis of NSCLC cells. Furthermore, miR-34a-5p mediates the cross talk between metabolic alterations and macrophage polarization in microenvironment of NSCLC. Here, lactate act as the oncometabolite and signaling molecule to fervor macrophages to acquire M2 phenotype, via activation of STAT3/ERK/KLF4 signaling pathways, thereby promoting tumorigenesis. Moreover, miR-34a-5p mediated inhibition of these pathways mediates the reversion of macrophage polarization towards M1 phenotype, and inhibiting tumorigenesis. These findings suggest that miRNA mediated targeting of metabolic cues in LC may have cogent therapeutic potential.