FUNCTIONAL ROLE OF circHIPK3 IN GASTROINTESTINAL TUMORS

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Introduction

Circular RNA circHIPK3 can act as a sponge for miRNAs blocking their modulatory function on their target genes (circHIPK3/miRNA/mRNA). Studies have revealed that this interaction plays an important role in colorectal (CRC), cholangiocarcinoma (CHOL), esophageal (ESC), gallbladder (GALC), gastric (GC), hepatocellular (HCC) and pancreatic (PC) cancers. However, the functional role of this interaction network in the gastrointestinal tumors' (GIT) development remains unclear.

Methods

Thus, we selected sponged miRNAs by circHIPK3 in GIT, for search, gene enrichment and functional analysis of their target genes, so that we could identify the biological pathways and processes that they can regulate via the circHIPK3/miRNA/mRNA-tar The miRNAs were selected from experimentally validated studies (EVS) deposited in PubMed, BioMedCentral and Google Scholar databases. Only EVS (e.g., RT-qPCR, cell assay, and/or luciferase reporter) were included for circHIPK3/miRNA-target interaction in TGI. miRTargetLink 2.0 tool, which uses information from the miRTarBase 7.0 database (the main repository of EVS about the miRNA/mRNA-target interaction), was used to search for target genes of the selected miRNAs. The STRING v.11.0 tool was used for gene enrichment of target genes in pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) databases (**Figure 1**). These platforms are repositories of experimentally validated biological pathways and processes that map the main genes involved in each pathway. The data were plotted in graphs using the R software (v.4.1).

Results

Figure 1 shows the flowchart developed in this study. Eighteen studies reported that circHIPK3 (upregulated) acts as a sponge for 15 miRNAs **(Figure 1 and 2)** in CRC (miR-7, miR-637 and miR-1207-5p), CHOL (miR-637 and miR-148a-3p), ESC (miR-599), GALC (miR-124-3p), GC (miR-107, miR-637, miR-124-3p, miR-29b, miR-653-5p; miR-338-3p and miR-876-5p), HCC (miR-124-3p, miR-338-3p, miR-582-3p, miR-4524-5p and miR-506), and PC (miR-330-5p) cancers **(Figure 2)**. Deregulation of circHIPK3/miR-124-3p (GALC, GC and HCC), circHIPK3/miR-637 (CRC, CHOL and GC), and circHIPK3/miR-338-3p (GC and HCC) occurred in more than one tumor type **(Figure 2)**. These miRNAs together can regulate 314 target genes, several of which are involved in EGFR tyrosine kinase inhibitor (28 genes), antifolate (5 genes) and platinum (11 genes) resistance **(Figures 1 and 3)**. They may also control the PD-L1 and PD-1 pathway (20 genes), apoptosis (15 genes) and cell cycle (18 genes), important therapeutic targets in GIT **(Figure 3)**. Finally, they may control or compose ATP-binding (53 genes) and modulate antitumor molecules efflux in cancer cells **(Figure 1)**.

Conclusions

Thus, 15 miRNAs are regulated by circHIPK3 in seven GIT types. circHIPK3/miR-124-3p, circHIPK3/miR-637 and circHIPK3/miR-338-3p were deregulated in more than one tumor type, suggesting that they may be important for the GIT pathogenesis. Sponged miRNAs regulate important genes associated with resistance to different types of therapeutic agents. Therefore, circHIPK3 can be controlling specific miRNAs related to modulation of chemoresistance and may be a potential therapeutic target in GIT.
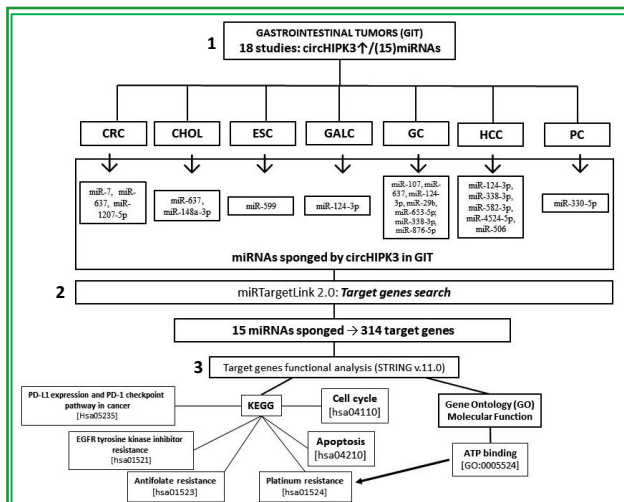
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Figure 1: Study Flowchart. **(1)** Eighteen studies reported that circHIPK3 is upregulated and acts as a sponge for 15 miRNAs in GIT; **(2)** These miRNAs can regulate 314 target genes; **(3)** These target genes are involved in resistance to therapeutic agents and pathways that induce tumorigenesis.
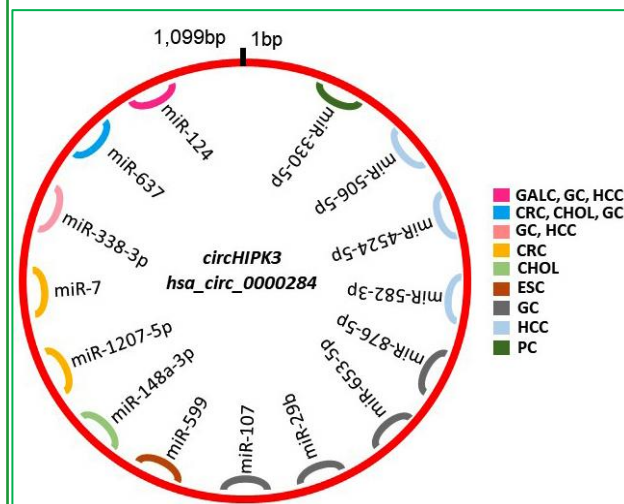

Figure 2: circHIPK3 structure and sponged miRNAs in GIT. **CRC:** Colorectal cancer; **CHOL:** Cholangiocarcinoma; **ESC:** esophageal cancer; **GALC:** gallbladder cancer; **GC:** Gastric cancer; **HCC:** hepatocellular carcinoma; **PC:** Pancreatic cancer.
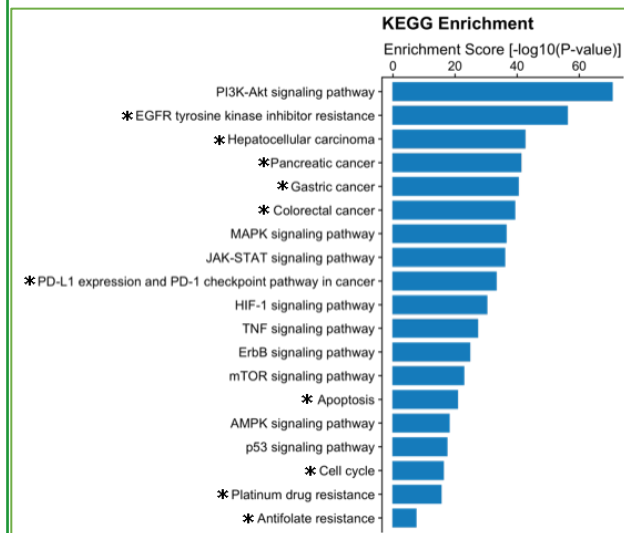

Figure 3: Gene enrichment of the 314 target genes in important pathways for GI tumorigenesis. (*) Important pathways for the resistance and establishment of TGI.

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