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Novel combination of natural compounds GZ17-6.02 inhibits tumorigenesis in pancreatic cancer by suppressing SHH signaling

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Background & Aim: Novel therapeutic targets are needed to treat pancreatic cancer because nothing is available for this devastating disease. GZ17-06.02, combination of novel natural compounds, contains anti-cancer properties in several cancers. Therefore, we hypothesize that GZ17-06.02 can inhibit tumor progression and metastasis in PDAC by suppressing cancer stem cells (CSC) and sonic hedgehog (SHH) pathway.

Methods: We have determined cell proliferation, pancosphere formation and apoptosis following treatment of different doses GZ17-6.02 in human pancreatic cancer cells. Orthotopic pancreatic cancer model in athymic nude mice was developed and GZ17-6.02 was given orally for 20 days. Proliferative markers, pEGFR/pAkt and apoptotic markers, Bax- Bcl-2- Caspase3 and also metastatic markers, MMP-2 and MMP-9 were measured in primary and metastatic tumor tissues. SHH pathway was determined using western blot, immunohistochemistry and cellular thermal shift assay (CETSA). Bioavailability through oral delivery of GZ17-6.02 in mice demonstrated rapid clearance from circulation and showed significant absorption and distributed quickly in different tissues.

Results: GZ17-6.02 inhibits proliferation of pancreatic cancer cells in a dose and time-dependent manner. GZ17-6.02 induced apoptosis in both *in vitro* and *in vivo* pancreatic cancer. GZ17-6.02 significantly inhibited EGFR and Akt phosphorylation. Furthermore, GZ17-6.02 decreased the number and size of the pancospheres and inhibited CSCs markers such as DCLK1, Lgr5, EpCAM and Sox9. GZ17-6.02 inhibited SHH and the downstream signaling pathway including SUFU, Gli1 and Gli2. Significant interaction of GZ17-6.02 with SHH was found using CETSA assay. Metastatic markers, MMP-2 and MMP-9 activity increased in the tumors. GZ17-6.02 treatment showed down-regulation of proliferative and anti-apoptotic genes using RNAseq data. GZ17-6.02 has also been detected in different tissues particularly in liver when it is given orally.

Conclusion: GZ17-6.02 significantly reduces tumorigenesis and metastasis in both *in vitro* and *in vivo* pancreatic cancer models through impairment of CSCs and SHH pathway.

Biography

Animesh Dhar did his PhD from the University of Calcutta in Physiology in 1982. He did his Post-doctoral training from the University of Puerto Rico in Biochemistry and University of Missouri-Columbia in Pharmacology. He is now an Associate Professor in the Department of Cancer Biology at the University of Kansas Medical Center (KUMC). He has published more than 50 publications in the high impact journals and about more than 10 reviews in the area of his research. He is a member of several scientific society including American Association of Cancer Research, American Association of Advancement of Sciences, American Association of Biochemistry and Molecular Biology, etc. His research work is focused on the preventive and therapeutic approaches in pancreatic cancer. His research has been funded by NIH and Genzada Pharmaceuticals.

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