Thermally triggered theranostics for pancreatic cancer


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Conclusion: Our study shows that miR-625-3p induces oxalaplatin resistance by abrogating MAP2K6-p38 regulated apoptosis and cell cycle control networks, and corroborates the predictive power of miR-625-3p. This has significant clinical potential as the expression level of miR-625-3p, possibly combined with the expression level of MAP2K6, has the potential to serve as a predictive biomarker. Since ~20% of metastatic CRC patients have high miR-625-3p expression, the number of patients potentially benefiting from the use of miR-625-3p/MAP2K6 is substantial.

No conflict of interest.

595 Gli1/DNA interaction is a druggable target for Hedgehog-dependent tumors

P. Infante1, M. Mori1, R. Alfonsi2, C. Ingallina3, B. Botta3, L. Di Marcello1,2
1Istituto Italiano di Tecnologia, CNLSigSapienza, Rome, Italy, 2Sapienza University, Molecular Medicine, Rome, Italy, 3Sapienza University, Chimica e Tecnologie del Farmaco, Rome, Italy

Background: Hedgehog (Hh) pathway is essential for tissue development and stemness, and when deregulated leads to tumorigenesis. Although many Hedgehog-driven human cancers involve upstream pathway activation (i.e. either loss-of-function of the receptor Ptch1 or gain-of-function mutations of the transmembrane transducer Smo), Smo-independent hyperactivation of the downstream Gli transcription factor is responsible for the development of several tumors and resistance to therapy. This raises the need to identify novel Gli1 inhibitors, a challenging issue mostly due to the lack of information on the structural requirements of Gli1/DNA interaction. Molecular characterization of Gli1/DNA binding was performed by a mix of computational and experimental structure-based in vitro studies. Molecular dynamics simulations were carried out to identify the residues involved in DNA binding. The data obtained were then used to set up the docking-based virtual screening of a natural products library available in house, with the aim to discover pharmacological agents able to interfere with Gli1/DNA interaction. The molecules identified as potential Gli1 inhibitors were investigated for their functional activity through a Gli-dependent luciferase reporter screening assay. The most active was tested for its effectiveness to counteract Hh-dependent tumor growth by medulloblastoma and basal cell carcinoma allograft model from Ptch+/− mice and orthotopic medulloblastoma xenografts.

Results: We identified a small molecule, GlaBrescione B (GlaB), an isoflavone naturally found in the seeds of Derris glabrescens (Leguminosae), able to impair Gli1/DNA binding as revealed by Chip and EMSA assays. In agreement with these molecular results, GlaB revealed great anti-tumor efficacy. Indeed, we observed that GlaB strongly inhibited the growth of Hedgehog-dependent tumor cells in vitro and in vivo as well as the self-renewal ability and clonogenicity of tumor-derived stem cells.

Conclusions: Our study highlighted the relevance of structural details of Gli1/DNA interaction as a promising tool to discover small molecules able to inhibit Hh pathway by directly targeting Gli1. Here we identified GlaB as a potent and specific Gli1 inhibitor able to interfere with Gli1/DNA binding, resulting in the inhibition of Hh-dependent tumor cells and cancer stem cells growth, thus becoming a profitable pre-clinical candidate.

No conflict of interest.