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Targeted Knockdown of IQGAP1 Fully Inhibits the Progression of Colorectal Carcinoma Cell In Vitro by Modulation of Ras and trails Genes Expression- Khairy M A Zoheir - National Research Centre

Khairy M A Zoheir
National Research Centre, Egypt

Abstract

For many years, the medical setting up has called the chronic or life- threatening diseases incurable But now, The gene therapy compromises hope for those looking for release from hundreds of different diseases. The objective of this application was to determine the outcome of inhibiting IQGAP1 and consequently Ras family genes and TRAIL-induced apoptosis in colorectal carcinoma cells (HCT166) and to delineated the mechanism of such modulation.

We investigated the impact of IQGAP1 silencing on the interactions of IQGAPs and RAS with several apoptotic, pre-apoptotic and anti- apoptotic genes, including caspase-3 (CASP3), BCL2-associated X protein (BAX), B-cell leukemia/lymphoma 2 (BCL2), TRAIL1, DR4, DR5, CXCR1, CXCR2, Dcoy receptor 1, Dcoy receptor 2, and Cxcr3 and programmed cell death 5 (Pdcd5),. Additionally, we investigated the effects of the interactions of these genes on cell viability, proliferation, apoptosis, and invasive capacity.

IQGAP1 siRNA-treated HCT166 cells showed very low invasive capacity than the control cells, and this stopping of invasive capacity was time- and vector concentration-dependent. In addition, IQGAP1 silencing resulted in highly significantly lower IQGAP1, HRAS, KRAS, NRAS, MRAS, and BCL2 level and, subsequently, higher IQGAP2 and IQGAP3 expression in HepG2 cells than in the control. Flow cytometry analyses indicated that the silencing of IQGAP1 can induce early and late apoptosis in HCT166 cells. Additionally, IQGAP2, IQGAP3, DR4, DR5, CXCR1, CXCR2, Dcoy receptor Dcoy receptor, Cxcr3 and programmed cell death 5 (Pdcd5), CASP-3, and BAX were up regulated whereas IQGAP1 and BCL2 were downregulated in the siRNA-treated cells. These findings indicated that IQGAP1 actually regulates the expression of IQGAP, RAS and TRAILs gene families, and demonstrate its regulatory role in the apoptotic network. RNAi is our way to wellness. One of the most alternative cancer therapies,

Now, in this study, gene therapy reveals even more on the powerful therapeutic effects of gene silencing. Not only can RNAi reverse the effects of many degenerative illnesses-it can save lives.

IQGAP1 is a scaffolding protein that can regulate several distinct signaling pathways. The accumulating evidence has demonstrated that IQGAP1 plays an important role in tumorigenesis and tumor progression. However, the function of IQGAP1 in esophageal squamous cell carcinoma (ESCC) has not been thoroughly investigated. In the present study, we showed that IQGAP1 was overexpressed in ESCC tumor tissues, and its overexpression was correlated with the invasion depth of ESCC. Importantly, by using RNA interference (RNAi) technology we successfully silenced IQGAP1 gene in two ESCC cell lines, EC9706 and KYSE150, and for the first time found that suppressing IQGAP1 expression not only obviously reduced the tumor cell growth, migration and invasion in vitro but also markedly inhibited the tumor growth, invasion, lymph node and lung metastasis in xenograft mice. Furthermore, Knockdown of IQGAP1 expression in ESCC cell lines led to a reversion of epithelial to mesenchymal transition (EMT) progress. These results suggest that IQGAP1 plays crucial roles in regulating ESCC occurrence and progression. IQGAP1 silencing may therefore develop into a promising novel anticancer therapy.

High IQGAP1 expression is found in thyroid cancer tissues and cells. Knockdown of IQGAP1 had inhibitory effects on cell proliferation and EMT, as well as on the Wnt/β-catenin pathway. Additionally, inactivation of the Wnt/β-catenin pathway by XAV939 or si-β-catenin suppressed cell proliferation and EMT. Furthermore, suppression of the Wnt/β-catenin pathway reversed the positive effects of pcDNA-IQGAP1 on cell proliferation and EMT in vitro. Moreover, downregulation of IQGAP1 suppressed tumor growth and EMT in SW579 tumor xenografts through the Wnt/β-catenin pathway in vivo.

IQGAPs are evolutionary conserved multi-domain scaffold proteins, including IQGAP1, IQGAP2 and IQGAP3. Among these, IQGAP1 has been proved to widely exist in human tissues and participate in many cellular processes, such as cell attachment, cell migration, extracellular signaling and division of cytoplasm. Previous studies indicated that IQGAP1 promoted cell proliferation through interacting with the MAP kinase and PI3K/Akt pathways in thyroid cancer cells. Moreover, IQGAP1 amplification was found to be associated with invasiveness of thyroid cancer cells, and coexistence of IQGAP1 copy-number gain and BRAF V600E mutation was particularly associated with a high tumor recurrence rate of 60% in PTC.

The metastatic spread of tumor cells to distant anatomical locations is a critical cause for disease progression and leads to more than 90 % of cancer-related deaths. IQ motif-containing GTPase-activating protein 1 (IQGAP1), a prominent regulator in the cancer metastasis process, is a scaffold protein that interacts with components of the cytoskeleton. As a critical node within the small GTPase network, IQGAP1 acts as a binding partner of several small GTPases, which in turn function as molecular switches to control most cellular processes, including cell migration and invasion. Given the significant interaction between IQGAP1 and small GTPases in cancer metastasis, we briefly elucidate the role of IQGAP1 in regulating cancer metastasis and the varied interactions existing between IQGAP1 and small GTPases. In addition, the potential regulators for IQGAP1 activity and its interaction with small GTPases are also incorporated in this review. Overall, we comprehensively summarize the role of IQGAP1 in cancer tumorigenicity and metastasis, which may be a potential anti-tumor target to restrain cancer progression.