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Lipid Raft Major Protein, Flotillin-2 in Gastric Cancer

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Introduction

Gastric Cancer (G.C) is one of the common malignant tumors which seriously dangerous to human life and health. At present, tumor invasion and metastasis are the main causes of death in gastric cancer. There has been a tremendous improvement in the diagnosis and treatment of gastric cancer but majority of patients still get recurrences and suffer death [1]. This needs to find new diagnostic and therapeutic approaches that will increase the survival rates. This can only be achieved by studying the molecular mechanisms of progression of the disease.

Lipid rafts like Flotillin-2 (Flot2) play big roles in the proliferation and progression of many human cancers. High Flot2 expression has been found in cell lung cancer [2], head and neck cancer [3], renal cell carcinoma [4], cervical and breast cancer [5,6]. Its importance has been associated with poor survival rates, metastasis, and tumor genesis. Interestingly, Cao K et al. [7], found the expression of flot2 is associated with histological grade, depth of invasion, lymphatic metastasis, and TNM stage in gastric cancer, small interfering RNA (siRNA) mediated Flot2 downregulation is reported to suppress proliferation and invasion in gastric cancer cell [7], it may suggest that Flot2 will be regarded as a new target of treatment and prognosis in G.C.

Though the molecular mechanisms of Flot2 are not well known in the progression of G.C, most studies are linking it to progression of various cancers. Both up-regulated and down-regulated miRNAs have been reported to contribute to gastric cancer development and progression [8]. Of those in G.C studies, miR-449a targets Flot2 by suppressing its expression. Flot2 is also thought to be beneficial in the expression of transforming growth factor β TGF-β)induced Epithelial-Mesenchymal Transition (EMT) in G.C cells. On the other hand, miR-499a reduces the expression of EMT markers but promoting epithelial cell markers expression in G.C cells. It inhibits proliferation and induces apoptosis by repressing E2F transcription factor 3 (E2F3) [9]. However, its molecular mechanism in the invasion of G.C is unknown and hence the study by Li et al. [9] focused on identifying Flot2 as a target of miR-449a and their role as diagnostic and therapeutic markers in G.C.

To achieve the above, the authors used both qRT-PCR and western blotting to achieve their results. The researchers used both normal human Gastric Epithelial Cell Lines (GES-1) and Gastric Cancer Cell lines (SGC-7901, NCI-N87, MGC-803). The levels of expressed miR-449a were consistent with those by a study by Li X et al. [9]. MiR-449a was down-regulated in G.C cell lines as compared to GES-1. This according to the researchers indicated that miR-449a is a tumor suppressor whereas Flot2 was found to be up-regulated in G.C cell lines showing that FLOT2 is an oncogene in gastric cancer. These results are supported by studies that found that deregulation of Flot2 is associated with progression and poor survival in numerous cancers [4,6,8].

Using a luciferase reporter vector containing the wild-type or mutant miR-449a, the researchers showed that overexpression of miR-449a inhibited the activity of the wild-type 3'-UTR of Flot2 but not the mutant reporter genes. Also, expression of Flot2 was down regulated by Flot2 siRNA. Also, the expression of miR-449a reduces the expression of Flot2 but silenced Flot2 didn't affect the expression of miR-449a. With these results, the authors show that Flot2 is a direct target of miR-449a. These results were consistent with the findings of Gong et al. [10] and Han et al. [11], who associated altered miRNAs expression with gastric cancer development and prognosis [10,11], by targeting different markers: for example, miRNA-506 targets Yap1 [12] and miRNA-29C targeting integrin beta 1 (ITGB1) [11]. They are able to do this by binding to the 3'-UTRs of the cancer-related genes RNA thereby controlling its expression.

By transferring MG-803 cells with Flot2 siRNA or miR-449a mimic cells, the authors showed the role of Flot2 and miR-449a in gastric vancer cell invasion. The researchers tell us that, the knockdown of Flot2 suppresses cell invasion because of miR-449a. Therefore, Li X et al. [9] concluded that miR-449a suppresses cell invasion by repressing Flot2 expression.

Using three EMT proteins, (E-cadherin, N-Cadherin, and Vimentin), Li et al. [9] were able to prove that miR-449a reduces EMT of gastric cancer cells by suppressing Flot2. The expression of E-cadherin was found to be higher in miR-449a mimics group and siRNA group. Also, N-cadherin and vimentin expression in Flot2 were higher as compared to the control groups. The authors concluded that this was because miR-449a repressed Flot2 expression reduces EMT, elevates E-cadherin expression and reduces N-cadherin and vimentin expression. This is because activation of EMT in cancer cells results in driving cancer cell migration, invasion and metastasis [13] since the epithelial protein levels become down-regulated whereas the mesenchymal proteins become up-regulated [14].

The authors also treated MGC-803 cells with TGF-β. TGF-β led to increased induction of mesenchymal markers, Vimentin and N-cadherin while decreasing the expression of E-cadherin. When the researcher added Flot2 siRNA into TGF-β cultures, there was an increase in the expression of TGF-β induced mesenchymal markers and a reduction of in the expression of the TGF-β induced epithelial marker. Also, TGF-β did not have any significant effects on Flot2 expression. This can be due to the ability of the growth factor (TGF-β)

to induce EMT by the signals the epithelial cells receive from the microenvironment.

The study demonstrates that miR-449a suppressed Flot2 expression lead to decreased cell invasion through suppressing TGF-β-mediated EMT. The provocative study raises several important questions for future research. FLOT2 is an oncogene in GC cells, and its molecular mechanism regulating the proliferation of gastric cancer cells is still unclear. Previous studies have shown that the expression of Flot2 is closely related to the progression and prognosis in gastric cancer. Its mechanism is related to the regulation of Flot2 in cancer cell proliferation, metastasis, and invasion. Liu et al. [15] found that in nasopharyngeal carcinoma cells, NF-κB and phosphatidylinositol 3-kinase (PI3K)/Akt3 signaling pathways are activated in Flot2 overexpressing cell lines, and NF-κB signaling pathways are activated by the up-regulation of p-p65, glycogen synthase kinase-3βGSK3and Matrx Metallo-Proteinases (MMPs), down-regulation of downstream p53, activated PI3K/Akt3 signaling pathway changes the downstream signals, such as up-regulation of p-FoxO1 and CC-NA1, down-regulation of forkhead box transcription factor O1(FoxO1), p21 and E-cadherin. Thus, Flot2 may stimulate tumor proliferation, migration, and invasion through NF-κB and PI3K/Akt3 signaling pathways. Mou et al. [16] showed that miR-485 repress the expression of Flot2 by decreasing the phosphorylation of PI3K in the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway results in decreased invasion, metastasis and EMT in lung adenocarcinoma cells. Liu et al. [17] revealed that Flot2 is a direct target of miR-34a, and overexpressed miR-34a inhibits the proliferation and metastasis in malignant melanoma cells by suppressing the expression of Flot2. Investigations have shown that in hepatocellular carcinoma, Flot2 promotes hepatoma cell proliferation through positive regulation of cyclin, such as up regulation of cyclin D3, CDK2 and CDK4 and down-regulation of P27, P21 and P18 [18]. However, whether the performance in gastric cancer cells and other cancer cells is the same is still to be further studied.

Cisplatin is one of the most commonly used drugs for chemotherapy in gastric cancer. Its anti-tumor toxicity and effectiveness have been affirmed, but the emergence of cisplatin resistance this year has reduced the actual efficacy of cisplatin, limiting the clinical application of cisplatin. Studies have shown that the sensitivity of cisplatin in gastric cancer is negatively correlated with the expression of mutant p53 [19]. The decreased expression of Flot2 promotes the expression of early growth response protein 1 (Egr1) and foes in the downstream of extracellular regulated protein kinases1 (ERK1)/ERK2, increased expression of the transcription factor EGR can enhance the activity of the target gene p53 [20]. We hypothesized that decreased Flot2 leads to an increase in EGR expression, which promotes the expression of p53 and increases the sensitivity of cisplatin in the treatment of gastric cancer. Whether this hypothesis is established or not is still waiting our follow-up research. Sasaki et al. [21] uncovered Flot2, a direct transcriptional target of p53 family members (p73 and p63), is regulated by p73 and p63, not p53. Silencing endogenous p73 abolished FLOT2 transcription after cisplatin treatment, knocking out FLOT2 inhibited p63-mediated activation of signal transducer and activator of transcription 3 (STAT3) and affected tumor differentiation, proliferation, and angiogenesis. Zhu et al. [22] illuminated a positive correlation between Flot2 and human epidermal growth factor receptor 2 (erbB2) levels in gastric cancer cells and tissues, overexpressing erbB2 tumor are more likely to be resistant to trastuzumab. Thus, as a new strategy, inhibiting Flot2 expression may increase the effectiveness of trastuzumab.

Recent studies have shown Flot2 affects the proliferation, invasion, and metastasis of tumor cells in multiple signaling pathways such as Wnt/β-catenin, NF-κB, PI3K/Akt3, TGF-β, and p53 family, and is also affected by various microRNAs. However, the specific functions and exact mechanisms of Flot2 in gastric cancer remain to be further studied and explored. As the thorough exploration of Flot2 and mechanisms in GC cell proliferation and metastasis, Flot2 as a new target for the treatment and diagnosis in GC provides a promising therapy in gastric cancer.

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References

1. Khatami F, Karbakhsh M (2015) Socioeconomic position and incidence of gastric cancer: A systematic review and meta-analysis. J Epidemiol Community Health 69: 818-819.
2. Wang YL, Yao WJ, Guo L, Xi HF, Li SY, et al. (2015) Expression of flotillin-2 in human non-small cell lung cancer and its correlation with tumor progression and patient survival. Int J Clin Exp Pathol 8: 601-607.
3. Rickman DS, Millon R, De Reynies A, Thomas E, Wasylyk C, et al. (2008) Prediction of future metastasis and molecular characterization of head and neck squamous cell carcinoma based on transcriptome and genome analysis by microarrays. Oncogene 27: 6607-6622.
4. Yan Y, Yang FQ, Zhang HM, Che J, Zheng JH (2014) Up-regulation of flotillin-2 is associated with renal cell carcinoma progression. Tumour Biol 35: 10479-10486.
5. Liu Y, Lin L, Huang Z, Ji B, Mei S, et al. (2015) High expression of flotillin-2 is associated with poor clinical survival in cervical carcinoma. Int J Clin Exp Pathol. 8: 622-628.
6. Wang X, Yang Q, Guo L, Li XH, Zhao XH, et al. (2013) Flotillin-2 is associated with breast cancer progression and poor survival outcomes. J Transl Med 11: 190.
7. Cao K, Xie D, Cao P, Zou Q, Lu C, et al. (2014) siRNA-mediated flotillin-2 (Flot2) downregulation inhibits cell proliferation, migration, and invasion in gastric carcinoma cells. Oncol Res 21: 271-279.
8. Xie J, Chen M, Zhou J, Mo MS, Zhu LH, et al. (2014) miR-7 inhibits the invasion and metastasis of gastric cancer cells by suppressing epidermal growth factor receptor expression. Oncol Rep 31: 1715-1722.
9. Li X, Li H, Zhang R, Liu J, Liu J (2015) MicroRNA-449a inhibits proliferation and induces apoptosis by directly repressing E2F3 in gastric cancer. Cell Physiol Biochem 35: 2033-2042.
10. Gong Y, Ren J, Liu K, Tang LM (2015) Tumor suppressor role of miR-133a in gastric cancer by repressing IGF1R. World J Gastroenterol 21: 2949-2958.
11. Han TS, Hur K, Xu G, Choi B, Okugawa Y, et al. (2015) MicroRNA-29c mediates initiation of gastric carcinogenesis by directly targeting ITGB1. Gut 64: 203-214.
12. Deng J, Lei W, Xiang X, Zhang L, Yu F, et al. (2015) MicroRNA-506 inhibits gastric cancer proliferation and invasion by directly targeting Yap1. Tumour Biol 36: 6823-6831.
13. Kalluri R, Weinberg RA (2009) The basics of epithelial-mesenchymal transition. J Clin Invest 119: 1420-1428.
14. Yang J, Mani SA, Donaher JL, Ramaswamy S, Itzykson RA, et al. (2004) Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis. Cell 117: 927-939.
15. Liu J, Huang W, Ren C, Wen Q, Liu W, et al. (2015) Flotillin-2 promotes metastasis of nasopharyngeal carcinoma by activating NF-κB and PI3K/Akt3 signaling pathways. Sci Rep 5: 11614.

16. Mou X, Liu S (2016) MiR-485 inhibits metastasis and EMT of lung adenocarcinoma by targeting Flot2. Biochem Biophys Res Commun 477: 521-526.
17. Liu R, Xie H, Luo C, Chen Z, Zhou X, et al. (2015) Identification of FLOT2 as a novel target for microRNA-34a in melanoma. J Cancer Res Clin Oncol 141: 993-1006.
18. Wang CH, Zhu XD, Ma DN, Sun HC, Gao DM, et al. (2017) Flot2 promotes tumor growth and metastasis through modulating cell cycle and inducing epithelial-mesenchymal transition of hepatocellular carcinoma. Am J Cancer Res 7: 1068-1083.
19. Nakamura Y (2004) Isolation of p53-target genes and their functional analysis. Cancer Sci 95: 7-11.
20. Banning A, Kurrle N, Meister M, Tikkanen R (2014) Flotillins in receptor tyrosine kinase signaling and cancer. Cells 3: 129-149.
21. Sasaki Y, Oshima Y, Koyama R, Maruyama R, Akashi H, et al. (2008) Identification of flotillin-2, a major protein on lipid rafts, as a novel target of p53 family members. Mol Cancer Res 6: 395-406.
22. Zhu Z, Wang J, Sun Z, Sun X, Wang Z, et al. (2013) Flotillin2 expression correlates with HER2 levels and poor prognosis in gastric cancer. PloS one 8: e62365.