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Clinicopathological Features of Glypican 4 in Cancer: From Laboratory to Clinic

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Short Communication

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DESCRIPTION

Glypicans have been subjected to extensive investigations in the area of oncology and hold substantial amount of preclinical and clinical data implying their clinicopathological implications. While some glypicans have been more thoroughly studied, a growing body of evidence reveal pivotal role of Glypican 4 (GPC4) in various cancers, particularly in terms of their prognostic value and therapeutic applications. This short communication presents an overview of recent developments on the impact of GPC4 in various human cancer types and its molecular involvements in mitogenic signaling.

Key words: Glypican 4; Cancer; Mitogenic signaling; Oncogenes; Biomarker.

Impact of GPC4 in cancer

Albeit limited, existing clinical and animal *in vivo* studies show promising results regarding the potential role of GPC4 in cancer development. Mutations in GPC3 and GPC4 has been shown to be the cause of Simpson-Golabi-Behmel Syndrome Type 1 (SGBS1), a genetic congenital overgrowth disorder with increased risk to develop different cancerous or noncancerous tumors in early childhood, including hepatoblastoma, hepatocellular carcinoma, wilms tumor, adrenal neuroblastoma, medulloblastoma and gonadoblastoma [1]. In mice, decreased tumor volume has been shown for tumors derived from breast cancer cells overexpressing GPC4 compared to control. Further, analyzing breast cancer tissue from clinical patients for GPC4 expression has shown significantly lower expression in tissue samples from metastatic tumors compared to non-metastatic tumors [2]. Studying polymorphism of the GPC4 gene in tissue samples from patients with gastric carcinoma has yielded results indicating a significant association between Epstein-Barr virus (EBV) associated gastric carcinoma and mutated alleles of GPC4, compared to gastric carcinoma not associated with EBV or control samples [3]. Regarding cancer prognosis and patient survival, augmented levels of GPC4 in plasma

has been shown to correlate with increased cancer progression and poor 12-month survival in metastatic colorectal cancer and to be negatively correlated with 24-month overall survival in metastatic breast cancer, indicating a high prognostic value for plasma levels of GPC4 in these cancers [4, 5]. These results conflict with the findings of Munir and co-authors [2] which showed lower expression of GPC4 in tissue samples from metastatic breast tumor tissues, but none the less elucidate the importance of further investigation of this glypican and its potential as a prognostic biomarker and therapeutic agent in cancer. The multifaceted role of GPC4 in cancer has been demonstrated through *in vitro* studies on glioma and Non-Small Cell Lung Adenocarcinoma (NSCLC) cell lines, with the removal of GPC4 expression yielding tumor suppressing effects in glioblastoma and tumor promoting effects in NSCLC. Conversely, GPC4 overexpression showed an increased proliferative rate in glioblastoma and decreased proliferation in NSCLC. These results emphasize the cancer dependent dichotomous effects of GPC4 on cancer development [6].

GPC4 associated signaling pathways

Exact mechanisms by which GPC4 operates in cancer remains largely elusive. Emerging data indicates that GPC4 influences a myriad of mitogenic signaling pathways. However, the available data are not limited to the context of cancer but mostly pertain to other biological processes. Several studies show that GPC4 modulates cell proliferation and survival signaling pathways such as FGF an FGF2 [7, 8] and the Wnt/β-catenin pathway [9-14]. Additionally, it has been shown that GPC4 and MMP 14 act synergistically and modulate extracellular matrix deposition and regulate cellular migration [15], an important feature for tumor invasiveness and metastatic behavior. GPC4 has also been shown to be a key enhancer of the TLR4/NF-κB pathway [16], indicating its involvement in inflammation and cancer detection. Moreover, overexpression of GPC4 has been shown to result in hyperactivation of the master regulator of cell growth control mTOR in the dentate gyrus of the brain [17]. Systematic analysis of mechanism of action of GPC4 using clinical cancer patient data in The Cancer Genome Atlas (TCGA) has revealed alterations in expression of genes involved in cell cycle control (S100 family and E2F) and oncogenes including FGF5, TGF-β superfamily members and molecules involved in cancer invasiveness affecting cell adhesion and EMT transformation, including ITGA-5 integrin as well as IL-12 signaling and production of macrophages [6]. The influence of GPC4 on these signaling pathways collectively underscore its critical role in regulating cancer cell proliferation, invasive behavior, and immune system detection.

CONCLUSION

Understanding the role of GPC4 in cancer biology holds promise for the development of novel therapeutic strategies, including targeted therapies aimed at inhibiting GPC4 mediated signaling pathways or exploiting GPC4 as a diagnostic or prognostic biomarker. Further research is needed to fully elucidate the molecular mechanisms underlying the involvement of GPC4 in cancer and to explore its potential as a therapeutic target.

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