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Opinion

GPC3 as a Target to Focus Efforts to Develop a New Theranostic Agent for Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, currently ranking fourth cancer in deaths globally. Conventional imaging techniques represent the standard for the diagnosis and follow-up of these patients. The role of ^{18}F-FDG PET/CT so far is usually complementary because FDG avidity in HCC is very variable and unpredictable; although it has been roughly described that well and moderately differentiated tumors have less FDG uptake than poorly differentiated ones [1]. Many researchers have wondered why HCC, being an aggressive and fast-growing tumor, which would indicate a high glucose metabolism, does not generally have a significant FDG uptake, and this is where Glypican-3 (GPC3) has attracted so much attention. GPC3 is a cell surface proteoglycan which is overexpressed in most HCC, but not expressed in normal liver cells or liver with other disease conditions such as fibrosis or cirrhosis. Its expression has been demonstrated in up to 63.7-74.8% of patients with HCC and this expression is greater in well and moderately differentiated tumors than in poorly differentiated ones [2,3].

It was always thought that this glycoprotein acted on glucose metabolism as an up regulator since it may increase the expression of hypoxia-inducible factor 1-alpha (HIF-1α) protein and with this the expression of Glucose Transporter (GLUT) and Hexokinase (HK) activity, which would have as a result in terms of imaging, an increase in the uptake of FDG [4].

This upregulation was studied and confirmed by [5]. Adipocytes, where they observed that in the presence of GPC3, glucose metabolism was increased due to a greater expression of GLUT4 transporter [5]. However, when studying this phenomenon in HCC cells with immunohistochemical staining of pathologic samples and correlation with tumor glucose uptake in ^{18}F-FDG PET/CT, You-Cai Li et al. demonstrated that particularly in HCC with positive expression of GPC3, low glucose metabolism was also a constant, and they confirmed the inverse relationship between GPC3 and SUV_{max} value [6]. Although a clear explanation for this phenomenon was not found, the findings raised the interest in this glycoprotein to explain the complexity in the FDG uptake of this type of tumors and probably other similar ones of the gastrointestinal tract. Some years ago, Cho et al. had similar results showing that glucose uptake in HCC cells was decreased in the presence of c terminal of GPC3 protein treatment, and identified a specific interaction between GLUT1 and GPC3 as a possible explanation; However, these findings were not further studied later [7]. Other important factor that contributes to the low FDG uptake in HCC, and that may be or not linked to GPC3 expression, is the glucose-6-phosohatase (G-6-P) activity which decreases progressively during carcinogenesis

and is almost null in HCC, but the exact mechanism or relation is yet not studied [8].

The findings of these studies, and few others, not only led to the belief that the low uptake in HCC could actually be related to the expression of GPC3, but also focused attention on this glycoprotein as a possible target for diagnosis and new therapies [9]. As some authors have mentioned, GPC3 is an interesting target to build a theranostic proposal in HCC. New GPC3 binding peptides radio labelled with ^{18}F [10] and GPC3-specific antibodies for immunoPET imaging have been developed, finding strong affinity and specificity [11,12] and suggesting more specific imaging agent. Therefore, we strongly recommend continuing to study GPC3 and try to clarify exactly its role in the glucose metabolism of HCC to better understand the findings in PET images, but more importantly to focus efforts and develop a new theranostic agent.

References

1. Lu R, She B, Gao WT, Ji YH, Xu DD, et al. (2019) Positron-emission tomography for hepatocellular carcinoma: Current status and future prospects. World J Gastroenterol 25(32): 4682-4695.
2. Cheng W, Tseng CJ, Lin T, Cheng I, Pan HW, et al. (2008) Glypican-3-mediated oncogenesis involves the Insulin-like growth factor-signaling pathway. Carcinogenesis 29(7): 1319-1326.
3. Chen R, Bai Y, Liu T, Zhang G, Han Y, et al. (2021) Evaluation of glypican-3 expression in hepatocellular carcinoma by using IDEAL IQ magnetic resonance imaging. Academic Radiology 28(8): 227-234.
4. Mossenta M, Busato D, Bo M, Toffoli G (2020) Glucose metabolism and oxidative stress in hepatocellular carcinoma: Role and possible implications in novel therapeutic strategies. Cancers 2(6): 1668.
5. Taguchia A, Emotoa M, Okuyaa S, Fukudaa N, Nakamoria Y, et al. (2008) Identification of Glypican3 as a novel GLUT4-binding protein. Biochemical and Biophysical Research Communications 369(4): 1204-1208.
6. Li YC, Yang CS, Zhou WL, Li HS, Han YJ, et al. (2018) Low glucose metabolism in hepatocellular carcinoma with GPC3 expression. World J Gastroenterol 24(4): 494-503.
7. Cho HS, Ahn JM, Han HJ, Cho JY (2010) Glypican 3 binds to GLUT1 and decreases glucose transport activity in hepatocellular carcinoma cells. Journal of Cellular Biochemistry 111(5): 1252-1259.
8. Weber G, Cantero A (1955) Glucose-6-phosphatase activity in normal, precancerous, and neoplastic tissues. Cancer Res 15: 105-108.
9. Zheng X, Liu X, Lei Y, Wang G, Liu M (2022) Glypican-3: A novel and promising target for the treatment of hepatocellular carcinoma. Frontiers 12: 1-11.
10. Qin Y, Cheng S, Li Y, Zou S, Chen M, et al. (2020) The development of a Glypican-3-specific binding peptide using *in vivo* and *in vitro* two-step phage display screening for the PET imaging of hepatocellular carcinoma. Biomater Sci 8: 5656-5665.
11. Kelada O, Gutsche N, Bell M, Berman R, Baidoo K, et al. International Journal of Radiation Oncology Biology Physics
12. Labadie KP, Ludwig AD, Lehnert AL, Donald KH, Aimee LK et al. (2021) Glypican-3 targeted delivery of ^{89}Zr and ^{90}Y as a theranostic radionuclide platform for hepatocellular carcinoma. Sci Rep 11: 3731.