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The Role of Glypican in Differentiating the Pancreatic from Hepatocellular Carcinoma

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Introduction

The Pancreatic Ductal Adenocarcinoma (PDAC), the most usual form of pancreatic neoplasia, is a tumour derived from ductal epithelia of the pancreas and is extremely malignant [1]. This cancer is commonly diagnosed at an advanced stage already with metastasis (in over 85% of the cases), due to the lack of specific symptoms or signs [2]. Early disease is frequently asymptomatic and the risk factors for PDAC, such as family history of tumours derived from pancreas, personal history of chronic pancreatitis or diabetes, smoking and obesity, are not sufficient to stratify the population to establish a disease screening.

When detected early, a pancreatico-duodenectomy (Whipple procedure) can be the definite treatment for PDAC patients [3]. However, the 5-year survival rate is lower than 5% because, when the cancer is found, it can no longer be resected by surgery due to local invasion and distant metastasis [2,4,5] In each year, the mortality rate of pancreatic cancer is equivalent to its incidence [6] For these reasons, pancreatic cancer is the fourth leading cause of cancer death and is expected to be the second leading cause of cancer death by 2020 [4].

PDAC carries an extensive variety of genetic and epigenetic alterations such as high frequency of activating *K*ras mutations (90-95%), homozygous deletion (85%), epigenetic silencing of the tumor suppressor genes (15%) and an abundance of Heparin Binding Growth Factors (HBGFs) [7].

The mechanisms behind the poor prognosis of PDAC have yet to be elucidated, so, it is of the utmost importance to identify biomarkers associated with PDAC which may allow early detection.

Hepatocellullar Carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer–related deaths worldwide [8]. Per year, there are over 1 000 000 new cases of HCC worldwide [9]. When the tumour is small, the treatment that is more effective for HCC treatment is ablation therapy or surgical resection, thus early detection is critically important. However, the distinguishing between small HCC and benign conditions is difficult because the findings are frequently non-specific [10]. In such circumstances, a marker that could differentiate HCC from metastasis or other hepatic lesions would be useful.

Heparan Sulfate Proteoglycans (HSPG) are a family of ubiquitous proteins attached to the extra-cytoplasmic surface of the cell membrane and they have been implicated in promoting tumour growth [11]. Glypicans are members of this family and there are 6 glypican family members identified in mammals (glypican-1 to glypican-6). Most of the *in vivo* evidence suggests that their function is to regulate the signalling of Wnts and Bone Morphogenetic Proteins (BMPs), Hedgehogs (Hhs), Fibroblast Growth Factors (FGFs) [12].

Glypican-3 (GPC3) is an oncofetal protein that is extremely expressed during embryogenesis and organogenesis and is associated with the regulation of cell morphogenesis and proliferation [13-15]. Precisely, it is overexpressed in fetal hepatoblasts and is supressed in adult tissues including normal adult liver [16], except for normal breast, mesothelial and ovarian tissues [17].

Studies suggest that GPC3 is a cell proliferation inhibitor and a tumor suppressor in a tissue-specific manner [18]: down-regulation is observed in malignancies like mesothelioma, ovarian and breast [17,19] and up-regulation is observed in HCC at the messenger RNA and protein levels when compared with corresponding normal tissues and benign hepatic lesions [20,21]. The malignant tumors with high GPC3 expression are associated with high malignancy and poor prognosis because they exhibit a rapid development, lymph node metastasis and invasion.

GPC3 is more commonly expressed in HCC with poorly differentiation compared with well differentiated ones [22], with an immune reactivity ranging from 6% to 75% in high-grade dysplasia and from 0% to 25% in low-grade dysplasia [23]. Pancreatic carcinoma frequently metastasizes to the liver and may mimic HCC architecturally and cytologically [24]. Could then the GCP3 be a good differentiator between HCC and pancreatic metastization in the liver?

On the other hand, Glypican-1 (GPC1), a protein associated with the regulation of cell division and growth [25], is overexpressed in a diversity of tumours, including pancreatic and breast tumours [26,27]. Several signalling pathways, including the ERK MAPK and c-Myc signalling, are stimulated by GPC-1 [28], and it is required for efficient heparin binding growth factor signalling [29].

A review of the recent literature was performed to analyse if the conjunction of GPC1 and GCP3 could identify PDAC.

Abbreviations

PDAC : Pancreatic Ductal Carcinoma;

HCC : Hepatocellular Carcinoma

HSPG : Heparan Sulfate Proteoglycans

BMP : Bone Morphogenetic Proteins

Hhs : Hedgehogs

FGF : Fibroblast Growth Factors

GPC3 : Glypican-3

GPC1 : Glypican-1

crExox : Circulating Exossomes

VEGF : Vascular Endothelial Growth Factor

Methods

A PubMed search was conducted focusing on glypican in pancreatic cancer. The MeSH database was searched with the terms: "Pancreatic neoplasms"[MeSH Terms] AND ("Glypicans"[MeSH Terms] OR "Glypicans"[All Fields] OR "Glypican"[All Fields]). A total of 29 articles were initially collected. Six articles were subsequently excluded from this review because they were perspectives, highlights or letters to the editor, and did not manifest new knowledge. Ultimately, 23 studies were included in the analysis.

Results

The main results of the selected studies are listed in Table 1.

Study/Author	Year	Subjects	Conclusion
Yao H, et al. [30]	2016	106 Pancreatic Ductal Adenocarcinoma (PDAC) tissues + 35 peritumoral tissues + 55 benign pancreatic tissues + 13 normal pancreatic tissues	· The positive rate of GPC 3 expression was significantly higher in PDAC tumors than normal pancreatic tissues, benign lesions and peritumoral tissues (p<0,01).
			· The percentage of positive GPC3 expression was significantly higher in larger tumor size (p<0,01), poorly differentiated tumors (p<0,05), lymph node metastasis (p<0,01), invasion (p<0,01) and TNM stage II/IV stage disease (p<0,05).
			· PDAC patients with positive GPC3 survived significantly shorter.
			· Positive GCP3 expression negatively correlated with survival and was a negative prognostic factor.
Askan G, et al. [31]	2016	27 primary pancreatic tumors (11 pure pancreatic acinar cell carcinomas, 11 mixed acinar neuroendocrine carcinomas, 4 mixed acinar ductal carcinomas, 2 mixed acinar, neuroendocrine and ductal carcinomas) + 1 metastatic pancreatic acinar cell carcinomas to the liver.	· Seven (25%) of the tumors were immunoreactive for GPC3.
			· Fifteen (53%) tumors were positive for at least one marker (albumin mRNA ISH, a-fetoprotein, hepatocyte paraffin antigen 1 and glypican 3).
			· None expressed arginase 1.

Mitsuma K, et al. [32]	2016	Adenocarcinoma of ampulla of vater with enteroblastic differentiation, neuroendocrine carcinoma and focal hepatoid and squamoid features.	· All components expressed GCP3.
Melo S, et al. [33]	2015	Pancreatic discovery cohort: 190 patients with PDAC, 18 patients with pancreatitis, 8 patients with a benign serous cystadenoma and 5 patients with an intraductal papillary mucinous neoplasm.	· The relative percentage of circulating exossomes (crExos) with GPC1+ increased proportionally with tumor growth and correlated with tumor burden (r=0.98, P=0.004).
		Pancreatic cohort: 56 patients with PDAC, 6 patients with chronic pancreatitis, and 20 healthy donors.	· Exosomes derived from cancer cell lines and circulating cancer cell-derived exosomes from tumor-bearing mice were almost exclusively positive for GPC1.
		Breast cancer cohort: 32 women with breast cancer.	· All PDAC crExos revealed levels of GPC1+ crExos higher than levels noted in serum of healthy individuals (P<0.0001).
		Blood samples: 29 patients with PDAC, 4 patients with chronic pancreatitis and 4 patients with an intraductal papillary mucinous neoplasm.	· Mutant Kras transcript was only detected in the GPC1+ crExos.
		Mices for breast pad injections and cerulean injections.	· GPC1+ crExos showed a sensitivity and specificity of 100% in each stage of pancreas cancer.
		11 human cell lines + 5 murine cell lines	· GPC1+ crExos revealed to be an independent prognostic and predictive marker for disease-specific survival (P=0.005).
			· The GPC1 ELISA was similar to circulating CA 19-9 assay (sensitivity of 82.14%, specificity of 75%).
Vanoli A, et al. [34]	2015	Hepatoid carcinoma of the pancreas with lymphoid stroma	· The tumor was diffusely and strongly positive for glypican-3.
Ortmann C, et al. [35]	2015	6 *drosophila* RNAi strains + 4 cell lines + 1 chick embryo	· Glypican heparan sulfate proteoglycans regulate the release of bioactive sonic hedgehog from pancreatic cancer cells.
Hirabayashi K, et al. [36]	2015	22 resected tumors from pancreatic solid pseudopapillary neoplasm patients	· 21 of 22 cases were positive for glypican 3, but the expression was focal and weak, and there was no significant sex difference (p=0,074).
Ibrahim T, et al. [37]	2015	48 cell blocks from liver: 30 Hepatocellular Carcinoma (HCC) + 18 metastatic carcinoma in liver	· GPC3 positive in 97% of cases of HCC.
			· GPC3 negative in 100% of metastatic carcinoma.
			· Sensitivity of GPC3 in the diagnosis of HCC was 96,7% and the sensitivity was 100%.
			· As the nuclear grade of HCC increases, the expression of GPC3 decreases, suggesting that GPC3 is a useful marker for early diagnosis (p=0,03).

Li C, et al. [38]	2014	38 pairs of the pancreatic ductal adenocarcinoma and corresponding non-tumor adjacent tissue samples	· GPC1 was overexpressed in 65,8% of the pancreatic cancer tissues and an inverted correlation was observed between the expression of miR-96-5p and GPC1 protein (r=-0,38; p=0,018)
			· MiR-96-5p could directly inhibit GPC1 to suppress proliferation of pancreatic cancer cells.
Duan L, et al. [39]	2013	62 specimens of pancreatic cancer adenocarcinoma + 16 normal pancreatic specimens	· The expression of GPC1 in PDAC was found upregulated (p<0,01).
			· It was positively related with perineural invasion (p=0,01) and a worse prognosis post-surgery (p=0,003).
			· GPC1 was found to be the most significant factor that was related to the degree of perineural invasion and a worse prognosis.
Mounajjed T, et al. [40]	2013	98 neoplasms of the gastrointestinal tract (GI) + 60 neoplasms of the pancreas + 2 control groups: 32 hepatocarcinomas and 16 cholangiocarcinomas	· GPC3 positive: 58,5% acinar cell carcinomas, 27,5% squamous carcinomas, 2,5% neuroendocrine carcinomas of the GI tract, 75% hepatocellular carcinoma.
			· GPC3 negative: pancreatic adenocarcinoma, neuroendocrine neoplasms of pancreas and cholangiocarcinoma.
			· GPC3 immunoreactivity in HCC correlates with poor differentiation (p<0,05).
Kai K, et al. [41]	2012	Hepatoid carcinoma of the pancreas.	· Tumor cells showed the expression of GPC3.
Fujiwara M, et al. [42]	2012	98 fine-needle aspiration biopsies: 37 hepatocellular carcinomas and 61 adenocarcinomas involving the liver.	· Glypican 3 was negative in non-neoplasic hepatocytes and it had immunoreactivity in 81% of the hepatocellular carcinomas. It lacked immunoreactivity in pancreatic adenocarcinoma.
			· Glypican 3 was positive in 8% of adenocarcinomas (2 colorectal and 3 breast adenocarcinoma); 43% strongly positive in poorly differentiated hepatocellular carcinoma; sensitivity of 54% and specificity of 92%.
Whipple C, et al. [43]	2012	Wild-type mouse for GPC1 ($GPC1^{+/+}$ mice) + GCP1 null mouse that combines pancreas-specific Cre-mediated activation of oncogenic Kras with deletion of a conditional INK4A/Arf allele ($GPC1^{-/-}$ mice)	· $GPC1^{-/-}$ mice exhibited attenuated pancreatic tumor growth and invasiveness, decreased cancer cell proliferation, Mitogen Activated Protein Kinase (MAPK) activation, suppressed angiogenesis and decreased expression of mRNAs encoding several pro- angiogenic factors.
			· $GPC1^{-/-}$ mice formed smaller tumors that exhibited an attenuated metastatic potential.
Hav M, et al. [44]	2011	8 resected cases of pancreatic solid pseudopapillary neoplasm + 8 resected cases of pancreatic endocrine neoplasm	· All 8 pancreatic solid pseudopapillary neoplasms expressed GPC3 and all 8 pancreatic endocrine neoplasms had no expression of GPC3.
Yan B, et al. [45]	2011	Surgically resected samples from 941 primary liver tumors + 50 metastatic adenocarcinomas + 30 normal livers + 17 primary adenocarcinomas of the pancreas + 30 gallbladders + 20 extrahepatic bile duct	· From the liver neoplastic tissue samples, 52% demonstrated positive staining for GPC3.
			· An expression of GPC3 of 65% was observed in HCC.
			· Intrahepatic cholangiocarcinomas, adenocarcinomas, and benign liver lesions displayed rare positive cases.
			· There were significant correlations between GPC3 and histologic grade (p=0.001), intrahepatic metastasis (p=0.007), and positive serum hepatitis B surface antigen (p=0.042), in patients with HCC.

Aikawa T, et al. [46]	2008	Athymic nude mice + GPC1-knockout mice + PANC-1 human pancreatic cancer cells + T3M4 cells + COS-7 cells + murine B16-F10 melanoma cells.	· Decreased GPC1 expression in PANC-1 cells was associated with attenuated anchorage-independent growth, it exhibited decreased subcutaneous and intra pancreatic tumor growth and attenuated angiogenesis and metastasis by comparison with sham-transfected PANC-1 cells.
			· GPC1 protein levels were decreased by 48% ($P < 0.005$) and 34% ($P = 0.06$) in the tumors derived from GAS6 and GAS7 clones, respectively, by comparison with tumors arising from sham-transfected cells.
			· The tumors in the $GPC1^{-/-}$ group exhibited attenuated angiogenesis (52% decrease in microvessel density; $P < 0.0005$), and none of these tumors formed metastases.
			· Angiogenesis was decreased by 52% ($P < 0.04$) in the T3M4-derived tumors in $GPC1^{-/-}$ mice by comparison with tumors in the WT mice.
			· By comparison with WT mice, the melanoma cells formed 62% fewer pulmonary metastases in the GPC1-null mice ($P < 0.006$).
Korc M. [47]	2007	Literature	· The stroma cells stores and synthesizes GPC1 and all this microenvironment involving pancreatic cancer cells contribute to their invasive and metastatic potential.
Kayed H, et al. [48]	2006	23 PDAC tissue samples + normal pancreatic tissues + pancreatic cancer cell lines (Aspc-1, BxPc-3, Capan-1, Colo-357, SU8686, T3M4, MiaPaCa-2 and Panc-1).	· There was a statistically significant increase in GPC1 in the cancer samples by comparison with normal pancreatic tissue samples ($p<0.05$).
			· There was a significant correlation between GPC1 mRNA levels and TßRII, act-R1a, act-R1b, act-R2a, BMP-R1a, and BMP-R2 mRNA expression in normal pancreatic tissues.
			· GPC1 mRNA expression correlated directly with act-R1a and BMP-R1a in N0 PDAC cases and with act-R2a and BMP-R1a in lymph node positive cases.
			· Down-regulation of GPC1 resulted in increased doubling time in Panc-1 ($p<0.05$) but not in T3M4 cells, and decreased colony formation in both cell lines ($p<0.05$).
Li J, et al. [49]	2004	Colo-357 pancreatic cancer cell line transfected with full-length GPC1 antisense construct (4 positive clones and 4 negative controls)	· The four positive clones showed a decreased ($p<0,05$) colony forming ability compared with Colo-357 cells.
			· TGF ß 1-mediated growth inhibition was observed in all four control clones, and this effect was dose-dependent.
			· The TGF- ß 1-mediated growth inhibition was abrogated in glypican-1 antisense transfected cells.
			· The TGF- ß 1 induced Smad2 phosphorylation pattern was attenuated in glypican-1 antisense transfected cells compared to controls.
Terris B, et al. [50]	2002	13 intraductal papillary-mucinous tumors (9 noninvasive + 4 invasive cases)	· Glypican-1 was highly expressed exclusively in invasive IPMT

Kleeff J, et al. [51]	1999	10 PANC-1 human pancreatic cancer cells transfected with full-length GPC1 antisense construct	· Transfected PANC- 1 pancreatic cancer cells expressing a glypican- 1 antisense construct exhibit a marked attenuation of the mitogenic response specifically to hepatin-binding growth factors and displayed a markedly attenuated capacity to grow in vivo.
Kleeff J, et al. [52]	1998	12 normal human pancreatic tissue samples + 14 chronic pancreatitis tissues + 16 pancreatic cancer tissues + human pancreatic cell lines (PANC-1, MIA-PaCa-2, ASPC-1, CAPAN-1, COLO-357, T3M4).	· GPC1 was expressed at high level in both cancer cells ($p<0.01$) and the adjacent fibroblasts, whereas expression of glypican-1 is low in the normal pancreas, in chronic pancreatitis and in distant fibroblasts.
			· Treatment with the enzyme phosphoinositide-specific Phospholipase-C (PI-PLC) abrogated the mitogenic responses of cancer cell lines Fibroblast Growth Factor 2 (FGF2) and heparinbinding EGF-like growth factor (HB-EGF).
			· The expression levels of glypicans -2, -3, -4, or -5 are exceedingly low in pancreatic cancer cell lines
			· Reduction of glypican-1 protein levels in PANC-1 after expression of a glypican-1 antisense construct was associated with a marked attenuation of the mitogenic effects of FGF2 and HB-EGF in these cells, without altering EGF– and IGF-1– induced mitogenesis

Table 1: Main results of selected studies.

The distinction between pancreatic cancer, primary hepatocellular carcinoma and metastatic carcinoma is crucial, as the treatment goal for these tumors is different. The biopsy is the only way to clarify the origin of a mass nowadays, but it is an aggressive procedure.

Alpha-fetoprotein has a low sensitivity (it ranges between 30% to 50%) and staining is often only focal, so its utility in small biopsy samples is very limited [53].

The authors believe that GPC 1 and 3 could be good markers to differentiate the carcinomas.

Discussion

Yao H, et al. concluded that GPC3 had a similar diagnostic value compared with CA 19-9. The authors named several aspects that correlate negatively with overall survival and are positively correlated with mortality: patients with a tumour mass greater than 5cm, high TNM stage (III or IV), poorly differentiated tumours, lymph node metastasis, and invasion. The authors proposed the histological staining of GPC3 expression as a feasible tool for the early diagnosis of PDAC [30].

Exosomes are very small vesicles that are released from a variety of cell types. They arise from the intracellular compartment, so they enclose proteins and nucleic acids that can be transmitted to other cells upon fusion of their extracellular membrane. Cancer cells secrete exosomes at higher rates than healthy cells and they have an important role in cancer dissemination and progression [4,54,55].

Melo S, et al. found that the levels of circulating exossomes (crExos) with GPC1 positive could differentiate patients with precursor lesions of pancreatic cancer from healthy individuals and patients with benign pancreatic disease and to inform about pancreatic cancer burden. $GPC1^{+}$ crExos of PDAC patients are variable according to the extension of the disease: metastatic disease showed considerably higher levels of $GPC1^{+}$ crExos (average 58.5%) when compared to lymph nodes restricted disease (average 50.5%) or no metastases (average 39.9%). After surgical resection, a substantial decrease in $GPC1^{+}$ crExos levels was observed ($P<0.0001$). Moreover, it is a predictive marker disease-specific survival and its sensitivity and specificity were higher when compared with GPC1 levels [33].

Ortmann C, et al. showed that glypican heparan sulfate proteoglycans act as a scaffold or activator for sonic hedgehog ligands and mediate the release of bioactive sonic hedgehog from pancreatic cancer cells. The hedgehog family includes a group of signaling proteins that control development and contribute to cancer formation and progression in the adult [35].

Ibrahim T et al, demonstrated that the GPC3 expression among the different grades of primary HCC ($p=0.03$) was significantly different and there was a difference between GPC3 expression in HCC (97%) compared to metastatic carcinoma (0%) ($p<0.001$) [37].

It has been verified that microRNAs (miRNA), miR-96-5p and -182-5p, could regulate expression of GPC3 [56]. Emerging evidence has been showing that, in human carcinoma tissue, the regulation induced by miRNA contributes to maintain a biological process of the proliferation, differentiation, and apoptosis [57]. Li C, et al. found that the expression of miR-182-5p was higher in tissues of pancreatic cancer patients and these patients tended to suffer poorer differentiation and poorer survival. However, no correlation was found between expression of miR-182-5p and GPC1 protein, nor effects of miR-182-5p treatment on GPC1 protein expression. On the other hand, miR-96-5p was significantly down regulated in pancreatic cancer and it could significantly suppress pancreatic cancer cell proliferation in vitro what suggests a close relationship between miR-96-5p and GPC1 in pancreatic cancer [38].

Perineural invasion constitutes one of the principal modes of dissemination in pancreatic cancer, which can occur even in the initial stages [58]. It limits radical resection and promotes local recurrence, which negatively impacts survival time and life quality of the patients with pancreatic cancer [59]. Duan L, et al. concluded that the expression of GPC-1 was significantly linked to perineural invasion and it was the most hazardous factor to predict perineural invasion [39].

Mounajjed T, et al. reported that GPC3 can be expressed in 14% of the gastrointestinal tract carcinomas and pancreatic tumours. It is particularly overexpressed in pancreatic acinar cell carcinoma. In all tumour types, GPC3 expression showed no meaningful correlation with tumour dimensions [40].

Fujiwara M, et al. demonstrated positivity of GPC3 in hepatocellular carcinoma and it has a role in differentiating well-differentiated hepatocellular carcinoma from benign hepatic lesions [42].

Whipple C, et al. used mouse models of PDAC with KRAS-driven oncogenic mutation to demonstrate that GPC1 increases the tumour invasion, angiogenesis and growth, so, a potential therapeutic strategic would be the suppression of GPC1 in PDAC. All these findings indicate that endogenous GPC1 plays a major role in pancreatic cancer progression [43]. Additionally, they demonstrated that GPC1 promotes tumour angiogenesis: $GPC1^{-/-}$ tumours exhibited decreased expression of Vascular Endothelial Growth Factor (VEGF)-A; endothelial cells from $GPC1^{-/-}$ mice did not migrate in response to VEGF-A; there was a noticeable decrease in Sox17 mRNA levels in tumours from $GPC^{1-/-}$ mice; there was concomitant down-regulation of six additional genes involved in angiogenesis; and GPC1 may also act to promote growth factor sequestration within the tumor microenvironment [43].

Yan B, et al. showed a lack of GP3 staining in normal liver tissues, 65% staining in hepatocarcinoma samples, 10% in extrahepatic bile duct, 7% in gallbladder and 6% in primary adenocarcinomas from the pancreas. GPC3 expression was notably correlated with histologic grade and intrahepatic metastasis, implying a role in tumour progression [45].

The TGF-ß superfamily comprises TGF-ßs, BMPs, activins, and related proteins. All these molecules have an essential role in differentiation, proliferation and migration. Additionally, TGF-ß has a growth-inhibitory influence on most epithelial cells, that indicates a role in tumour suppression in some cancer types. While the role of GPC1 as a co-receptor for heparin-binding growth factors is well established, its role in signaling of members of the TGF-ß family is less clear. Kayed H, et al. showed that an increased GPC1 expression is associated with BMP and activin receptors in pancreatic tumours. GPC1 down-regulation suppresses pancreatic cancer cell growth and slightly modifies signaling of TGF-ß family members. It seems, therefore, that GPC1 is not a major modulator of these signaling pathways [48]. Li J, et al. confirmed that, after glypican-1 antisense transfection, there was no change in the expression level of the two receptors and that glypican-1 is required for efficient TGF-ß1 signalling in pancreatic cancer cells [49].

Kleef J, et al. believe that a gene therapeutic approach by using GPC1 antisense constructs in pancreatic cancer may have the dual benefit of blocking the mitogenic effects of heparin-binding growth factors, and attenuating the angiogenic effects of these growth factors [51].

Conclusion

This review concludes that GCP3 is expressed by liver and pancreatic cancer, while GPC1 is only expressed in pancreatic cancer. Thus, GPC1 could be used when pancreatic cancer is suspected, and GPC3 could be used to distinguish malignant from benign liver mass.

However, one study proved that serum GPC1 was no better than the classical pancreatic cancer biomarker CA19-9 [33]. Additional studies, using larger human population samples, are required to better define sensitivity and specificity of these markers in a population-screening context.

Future Perspectives

The knowledge and utility of glypican in cancer is only in the beginning. It is very specific so it will become a good therapeutic target. The next step will be the immunotherapy in order to expand the population of tumor reactive T cells. There are ongoing experiments with GPC3 peptide vaccines. New drugs will arise targeting glypican, inducing antibody-dependent cell-mediated cytotoxicity against glypican-positive cancer cells.

Summary

- Pancreatic Ductal Adenocarcinoma (PDAC) is commonly diagnosed at an advanced stage so, it is the fourth leading cause of cancer death;
- Hepatocellullar Carcinoma (HCC) is third most common cause of cancer–related deaths worldwide and it is crucial the distinction between an HCC and a liver metastasis;
- Glypican-3 (GPC3) is an oncofetal protein overexpressed in fetal hepatoblasts and is suppressed in adult tissues including normal adult liver; glypican-1 (GPC1), a protein associated with the regulation of cell division and growth, is overexpressed pancreatic tumours;
- GPC3 as a similar diagnostic value compared with CA 19-9 and it is a feasible tool for the early diagnosis of PDAC. It is expressed in HCC but not in metastatic lesions or benign lesions;
- GPC1 could differentiate patients with precursor lesions of pancreatic cancer from healthy individuals, gives information about the tumoral burden and extension of the disease.

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