hPG80 (Progastrin)
A Novel Blood-Based Biomarker for Detection of Neuroendocrine Neoplasms

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BACKGROUND

Current blood-based biomarkers for neuroendocrine neoplasms (NENs) lack both sensitivity and specificity. This is especially true for high-grade NENs (small and large cell neuroendocrine carcinomas). hPG80, progastrin, is a novel bio-marker which is easily measured in plasma using an ELISA test. Recently discovered to be elevated in colorectal **(Fig.1)**[1], gastro-esophageal, hepatic and pancreatic adenocarcinoma, this study is the first to explore hPG80 in NENs. In a normal physiological state, hPG80 is a precursor protein to hormone gastrin and comprises of 80 amino acid. Overexpression of GAST gene in neoplastic tissue has been implicated in elevated hPG80. Since GAST is a target of Wnt/ß-catenin/Tcf4 pathway, it is not surprising that hPG80 is elevated in various solid tumors.

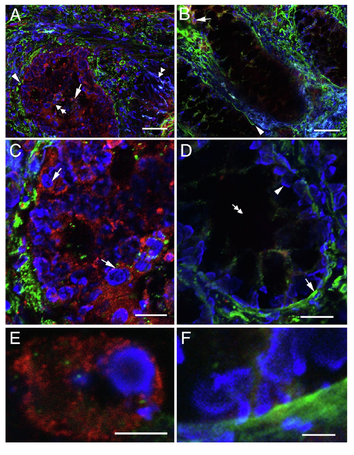

Figure. 1. High expression of hPG80 by tumor cells from colorectal cancer. **(A)** Confocal image of a tumoral mass showing high expression of hPG80 in colon cancer (patient 6607). The tumor cells expressing hPG80 were visualized with IHC for hPG80 (red). The hPG80-immunoreactive cells were often clustered into masses (arrow) into low-differentiated glands surrounded by disrupted basement membranes (arrowhead, HSPG-immunoreactivity, green). The double arrowhead indicates autofluorescence in the connective tissue (blue), which contrasts with cell nuclear counterstaining with bisbenzimide (blue, double arrow). **(B)** The tissue peripheral to the tumor mass showed scarce hPG80-immunoreactive cells in the connective tissue (arrow) and linear basement membranes (arrowhead). **(C)** Magnified field of the area indicated by an arrowhead in (A) showing the perinuclear location of hPG80-immunoreactivity (arrows). **(D)** Magnified field of the peripheral tissue showing the linear basement membrane (arrow), nuclei of epithelial cells (arrowhead) and the lumen of the gland (double arrow). **(E)** Highly-magnified field showing one cell and the cytoplasmic localization of hPG80. **(F)** Absence of hPG80-immunoreactive cells in the peripheral tissue. Scale bars: A and B: 50 mm; C and D: 20 mm; E and F: 5 mm.[1]

Reference:
*1. B. You, **Alexandre Prieur**, et al. / EBioMedicine 51 (2020) 102574*

METHODS

hPG_{80} concentrations were quantified in plasma from 95 patients with mainly stage IV NEN using DxPG80 technology (ECS Progastrin, Switzerland) and compared with hPG_{80} concentrations in 50-80 year old (n=252) and 18-25 year old (n=137) healthy donors.

RESULTS

The median hPG_{80} in NENs patients was 5.54 pM (IQR 2.07-17.11 pM) as compared to 1.5 pM (IQR 0.60-3.09 pM) for patients in the 50-80 year old control group and 0.29 pM (IQR 0.00-1.27 pM) for patients in the 18-25 year old cohort ($p<0.0001$, two-tailed Mann-Whitney *U*-test). A subgroup analysis of NENs revealed a median hPG_{80} of 3.54 pM (IQR 2.02-19.91 pM) in neuroendocrine carcinoma (NEC n=25) and 5.8 pM (IQR 1.91-16.74 pM) in neuroendocrine tumor (NET n=70). Interestingly, small cell lung cancer sub cohort (n=13) also showed significant elevation of hPG_{80} with a median at 9.09 pM (IQR 2.66-25.33 pM). All the above-mentioned differences were statistically significant as compared to healthy controls. Diagnosis accuracy estimated by the ROC AUCs is 0.89 for all NENs, 0.97 for NETs and 0.92 for NECs when compared to the young 18-25 yo control group and 0.75 for all NENs, 0.74 for NETs and 0.75 for NECs when compared to the old 50-80 yo control group.

FIGURE 1

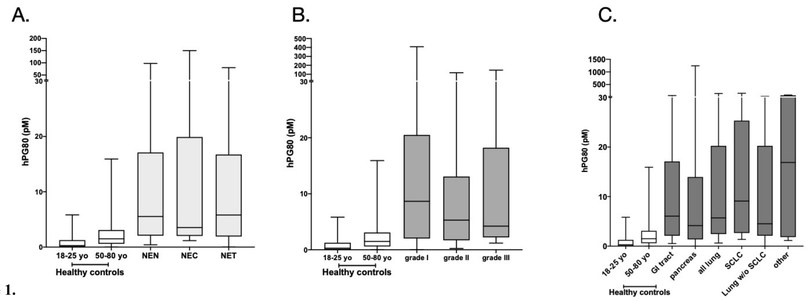

Figure 1.

Diagnostic performance of hPG_{80} in NENs, NEC and NET patient cohort compared to the 18-25 yo and 50-80 yo healthy individuals

FIGURE 2

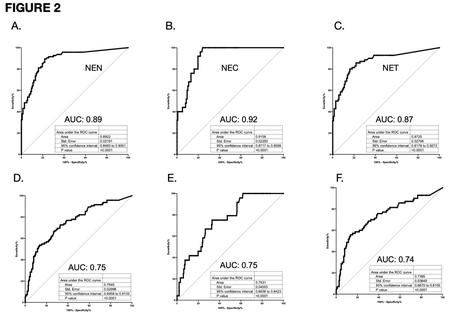

Figure 2.

Sensitivity of hPG_{80} in all patient cohort with a specificity set at 90%

		NEN	NEC	NET	Control cohorts	
					18-25 years old	50-80 years old
		N (%)	N (%)	N (%)	N (%)	N (%)
		n = 95	n = 25	n = 70	n = 137	n =252
Age, years	Median (range)	61 (37-86)	61 (37-78)	62 (37-86)	21 (18-25)	55 (50-80)
Gender	Male	38 (40%)	10 (40%)	28 (40%)	79 (57.7%)	99 (39.3%)
	Female	57 (60%)	15 (60%)	41 (60%)	58 (42.3%)	153 (60.7%)
hPG80	Median (IQR), pM	5.54 (2.07-17.11)	3.54 (2.02-19.91)	5.8 (1.91-16.74)		
	Mean (SD), pM	28.24 (128.8)	20.7 (39.96)	30.55 (148.5)	< LoD	1.50 (0.00-3.09)
grade	1	33 (34.7%)	0 (0%)	33 (47.2%)	< LoD	3.82 (0.55)
	2	28 (29.5%)	0 (0%)	28 (40%)		
	3	30 (31.6%)	25 (100%)	5 (7.1%)		
	unknown	4 (4.2%)	0 (0%)	4 (5.7%)		
primary site	GI tract	46 (48.4%)	4 (16%)	42 (60%)		NA
	pancreas	15 (15.8%)	2 (8%)	13 (18.6%)		
	SCLC	13 (13.7%)	13 (52%)	0 (0%)		
	Lung w/o SCLC	17 (17.9%)	4 (16%)	13 (18.6%)		
	other	4 (4.2%)	2 (8%)	2 (2.8%)		

Table 1.
Clinical and pathological characteristics for NEN, NEC, NET patients and control cohorts

CONCLUSION

Plasma hPG_{80} in NENs suggests hPG_{80} may be a diagnostic blood biomarker for both low- and high-grade NENs and further study is warranted. A prospective multicenter clinical trial is ongoing in Neuroendocrine Tumors to evaluate its role in monitoring of disease (NCT04750954)

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