

Correlation between gene expression profile and tumor behavior of pancreatic neuroendocrine tumors and carcinoids

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Abstract

Background. Clinical parameters are often inadequate to predict the behavior of common neuroendocrine tumors (NETs) such as non-functioning pancreatic NETs (NF-PNETs) and mid-gut carcinoid tumors (carcinoids). Molecular markers of tumor behavior are not clear but needed to assist clinical decision making.

Methods. Gene expression profile of 7 NF-PNETs and 6 carcinoids was obtained through Affymetrix Human Gene 1.0 ST Array. The tumors were clinically classified by aggressiveness (indolent v. aggressive). The microarray data were analyzed using Genespring 11. Microarray data files were preprocessed with RMA algorithm. Genes were ranked according to expression levels and only those presented in top 80% in at least one sample were included for unpaired t-test. Benjamin Hochberg false discovery rate control was used for multiple test correction.

Results. For NF-PNETs, 322 genes were differentially expressed >3-fold in indolent v. aggressive tumors, and 112 genes were differentially expressed with $p < 0.005$. ACMSD (Aminocarboxymuconate semialdehyde decarboxylase), FGB (fibrinogen beta chain), AGT (angiotensinogen), APOH (apolipoprotein H), HAO1 (hydroxyacid oxidase 1) were >8 fold upregulated in aggressive tumors. For carcinoids, 159 genes were differentially expressed >3-fold in indolent v. aggressive tumors, and 47 genes were differentially expressed with $p < 0.005$. SLC38A3 (solute carrier family 38, member 3) was 15-fold upregulated in aggressive tumors and MX2 (myxovirus resistance 2) was 5-fold upregulated in indolent tumors. When taken as a group, 68 genes were differentially expressed >3-fold in indolent v. aggressive tumors, and 38 genes were differentially expressed with $p < 0.005$. MEP1B (meprin A, beta) was ~10-fold upregulated in aggressive tumors. Pathway analysis suggested interleukin 4 and 9 pathways were differentially regulated between indolent and aggressive NF-PNETs. **Conclusion.** Indolent and aggressive NETs, especially pancreatic ones, exhibit distinct gene expression profile. Specific genes are differentially expressed in indolent v. aggressive NETs and may serve as markers for tumor behavior.

Aims

To discover molecular markers for behaviors of non-functioning pancreatic neuroendocrine tumors (NF-PNETs) and mid-gut carcinoids (carcinoids).

Background

Clinical parameters are often inadequate to predict the behavior of NF-PNETs and carcinoids. Molecular markers of tumor behavior are not clear.

Patient and methods

- 7 patients with NF-PNETs and 6 patients with carcinoids
- Total RNA extracted from tumors and subjected to Affymetrix Human Gene 1.0 ST Array
- Microarray data analyzed with Genespring 11 software
- Expression of significant genes validated by real-time PCR

Results

Table 1. Patients

RNA label	Age	Sex	Tumor path	Clinical Staging	Behavior
PNET 1	57	F	PNET	Local	Indolent
PNET 8	53	F	PNET	local	Indolent
PNET 15	64	M	PNET	Local	Indolent
PNET 7	42	F	PNET	Advanced	Aggressive
PNET 11	34	F	PNET	Advanced	Aggressive
PNET 14	62	F	PNET	Advanced	Indolent
PNET 12	39	F	PNET	Advanced	Aggressive
CND 10	54	M	Carcinoid	Local	Indolent
CND 16	48	F	Carcinoid	Local	Indolent
CND 5	68	M	Carcinoid	Advanced	Indolent
CND 6	69	F	Carcinoid	Advanced	Aggressive
CND 9	54	F	Carcinoid	Advanced	Aggressive
CND 3	49	F	Carcinoid	Advanced	Indolent

Table 2. Differentially expressed genes in indolent v. aggressive tumors

	Differentially expressed genes		
	PNETs	Carcinoids	Both
#genes >3 fold	322	159	68
#genes $p < 0.005$	112	47	38

Figure 1. Interleukin-4 pathway in PNETs

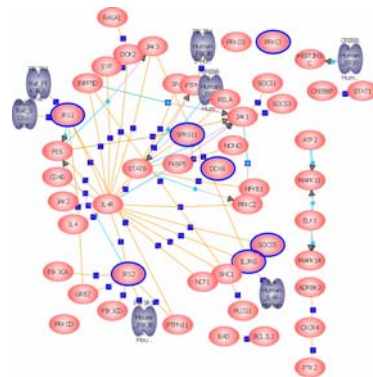


Figure 2. Validation of gene expression levels in PNETs

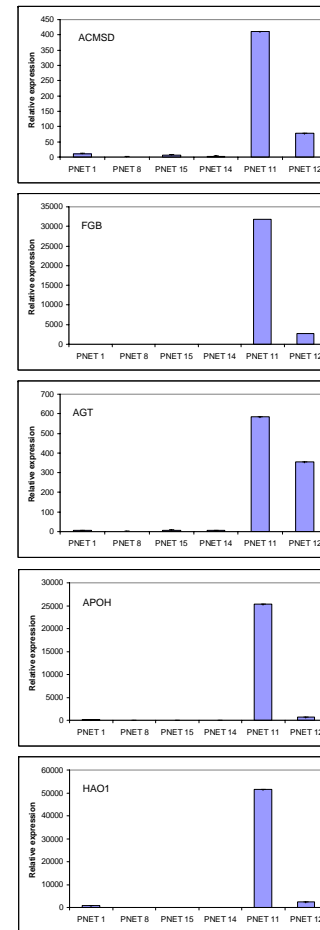


Figure 3. Validation of gene expression levels in carcinoids

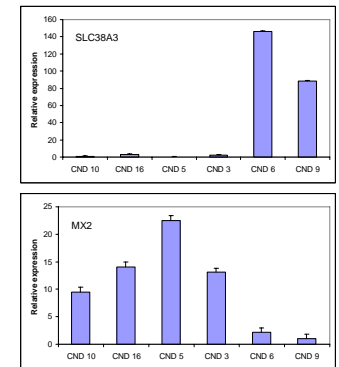
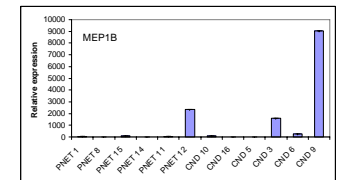


Figure 4. Validation of gene expression levels in PNETs and carcinoids as a group



Summary and Conclusions

- There appears to be different patterns of gene expression between indolent and aggressive non-functioning pancreatic neuroendocrine tumors and mid-gut carcinoids.
- Distinct genes are differentially expressed.
- Global gene expression pattern and specific gene markers may be used in predicting tumor behavior.
- Further and larger studies are needed to confirm the results and to examine potential clinical application.