Comprehensive molecular analysis of several prognostic signatures using molecular indices related to hallmarks of breast cancer: proliferation index appears to be the most significant component of all signatures

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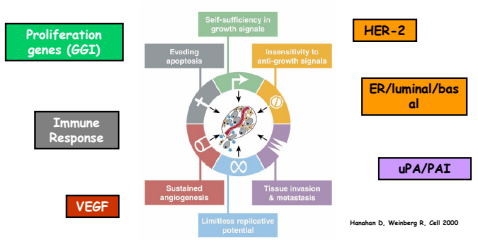
Introduction

Although the development of high-throughput gene expression technologies has led to the identification of several "molecular signatures" predicting clinical outcome, no attempt has yet been made to perform a comprehensive analysis integrating well characterized biological processes and gene expression data. Here we aim to elucidate the relationship of gene expression patterns defined by several biologically relevant indices with previously reported prognostic signatures and their interaction with prognosis

Materials & Methods

·**Selection of prototype genes** related to several biological processes in breast cancer **(hallmarks of cancer)** such as basal/luminal phenotype, ERBB2, proliferation, fully captured by the gene expression grade index, stroma/invasion, angiogenesis, apoptosis and immune response (Sotiriou et al ASCO 2006)

Hallmarks of breast cancer



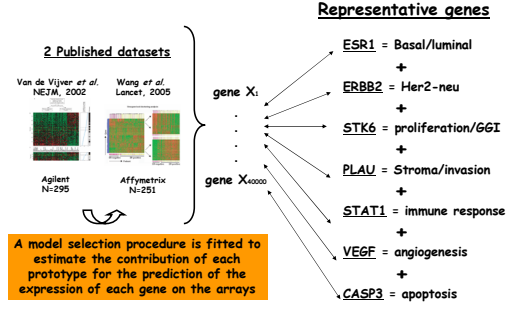
·**Use of a model selection procedure** based on cross-validation error estimation in order to select the genes that are able to predict significantly et specifically one of the prototypes **(molecular indices)**

·**Application to several previously reported prognostic signatures** (70-gene, 76-gene, wound healing, p53, genomic grade and recurrence score)

·**Characterization of dependency patterns** between these indices for each prognostic signature and their impact on survival using several microarray datasets

Defining Molecular Indices

(Sotiriou et al. ASCO 2006)

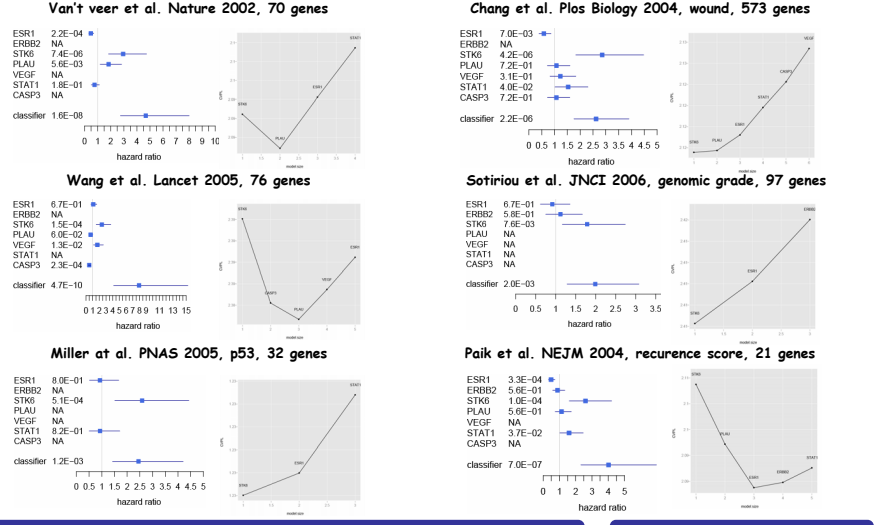


Dissecting Gene Expression Prognostic Signatures

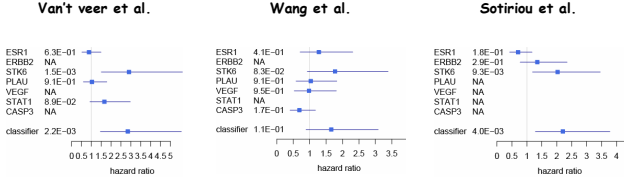
	70 genes Van't veer et al. Nature 2002	76 genes Wang et al. Lancet 2005	P53 (32 genes) Miller et al. PNAS 2005	Wound (573 genes) Chang et al. Plos Biology 2004	Genomic grade (97 genes) Sotiriou et al. JNCI 2006	Recurence Score (21 genes) Pail et al. NEJM 2004
ESR1 (lumina/basal)	73% (10%)	38% (3%)	88% (34%)	42% (4%)	73% (1%)	69% (19%)
ERBB2	60% (0%)	35% (0%)	53% (0%)	30% (0%)	37% (2%)	44% (6%)
STK6 (proliferation)	63% (14%)	55% (16%)	53% (16%)	52% (13%)	99% (54%)	69% (13%)
PLAU (stroma/invasion)	47% (3%)	42% (5%)	47% (0%)	39% (3%)	64% (0%)	38% (6%)
VEGF (angiogenesis)	43% (0%)	26% (1%)	28% (0%)	35% (1%)	43% (0%)	25% (0%)
STAT1 (immune response)	29% (1%)	30% (0%)	19% (3%)	30% (0%)	43% (0%)	25% (0%)
CASP3 (apoptosis)	60% (0%)	16% (1%)	38% (0%)	40% (3%)	30% (0%)	38% (0%)

% of genes related to each prototype; % of genes specific for each prototype

Survival Analysis DMFS (original data sets)



Survival Analysis DMFS, TRANSBIG VALIDATION N=198



Conclusions

Proliferation seems to be the common denominator of many existing prognostic gene signatures, recapitulating their prognostic power.

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