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Review

Complementary gene and protein expression studies and integrative approaches in toxicogenomics

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Abstract

Parallel transcript and protein profiling is a strategy to gain further insight into the mechanisms of toxicity and disease. The technologies used to measure expression at the transcript and protein levels each convey different information and have different technical capabilities that can complement each other when combined. In this review, over twenty studies are considered for the use of -Omics platform, the chemical or disease being profiled, tissues, the number of genes and proteins found by each platform and common expression products. A strategy is suggested for toxicant expression profiling that combines the transcriptomics and proteomics of both the target tissue and blood/serum that could provide a more complete characterization of toxicity as well as synergize expression technologies toward biomarker discovery.

Keywords: Proteomics; DNA microarray; Toxicogenomics; Integration; Biomarkers

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Introduction

Many researchers have performed parallel transcript and protein expression analysis to gain further insight into the gene expression of toxicity and disease (Betts, 2002). The technologies used to measure expression at the transcript and protein levels each convey different information and have different technical capabilities. Biologically, differences in a specific gene expression product can occur from RNA splicing, RNA and protein turnover, posttranslational and proteolytic processing, changes in protein–protein interactions, and subcellular shuttling and localization. Transcript expression technologies rely upon the hybridization of extracted mRNA while proteomic technologies are more diverse because the complex biophysical nature of proteins requires more involved separation and identification procedures. Transcript platforms usually encompass cDNA and oligonucleotide microarrays and cDNA macroarrays (Storck et al., 2002). Proteomic analyses are most frequently conducted by 2D gel electrophoresis for protein separation and mass spectrometry for identification. However, other recently developed proteomic technologies also include SELDI (surface enhanced laser desorption ionization), antibody microarrays and various types of liquid chromatography tandem mass spectrometry (LC MS/MS) and its

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specific platform variations, called ICAT (isotope coding affinity tags) and MuDPIT (multi-dimensional protein identification technology) techniques (Yates, 2000). Among these expression technologies, clearly, DNA microarray platforms provide the most comprehensive number of expressed genes while proteomic technologies are still developing to provide more comprehensive measurements of total protein expression. However, proteomics holds the promise for global analysis of posttranslational changes, biofluid proteomes, subcellular compartments and structural complexes that are usually inaccessible research areas to gene profiling analysis.

A few reviews have discussed parallel transcriptomic and proteomic studies (Betts, 2002; Celis et al., 2000; Hegde et al., 2003; Sinchaikul et al., 2002). Parallel expression technologies have been used in studies of human disease for drug discovery and diagnostics (Celis et al., 2000) and in functional genomic characterization of unicellular organisms like *Bacillus* sp. (Sinchaikul et al., 2002) and *Mycobacterium tuberculosis* (Betts, 2002). The dichotomous and complementary aspects of parallel expression studies were recently reviewed (Hegde et al., 2003). The differences in relative abundance between transcripts and corresponding proteins (Table 1, lower section) have sometimes been interpreted as a "poor correlation" between transcriptomics and proteomics (Futcher et al., 1999; Gygi et al., 1999; Griffin et al., 2002; Lee et al., 2003). In an early study, differences in relative abundance were first reported for 19 rat liver proteins and transcripts (Anderson and Seilhamer, 1997) for which they calculated a correlation coefficient of 0.48. Subsequent studies in yeast also performed abundance comparisons with many more proteins and transcripts and generally found a discordance in yeast (Table 1). Alternatively, the complementary aspect of gene expression can be also be viewed as a "glass half full" (Hegde et al., 2003) when considering that combinations of RNA profiling and protein biochemistries have eventually led to the identification of serum biomarkers in cancer (Tanwar et al., 2002; Welsh et al., 2003; Zhou et al.,

Table 1
Parallel transcript and protein profile studies in cells and tissues

Author	Platform	Chemical or disease	Tissue	Genes	Protein	Common
Heijne et al. (2003)	2D-MS, cDNA array	Bromobenzene	Rat liver	98	24	2
Iida et al. (2003)	2D-MS, cDNA array	Oxazepam and Wyeth 14,643	Mouse liver	256	82	11
Prabakaran et al. (2004)	2D-DIGE-MS/MS, Affy array, NMR	Schizophrenia	Human brain	3406; 59**	50; 26**	Pathway analysis
Fessler et al. (2002)	2D-MS, Affy array	LPS	Human PMNs	156	25	6
Ruepp et al. (2002)	2D-DIGE-MS, GDA filters and RTQ-PCR	APAP	Mouse liver	26	14	0
Grolleau et al. (2002)	2D-MS, oligo arrays	Rapamycin	Jurkat T cells	187	22	15
Lister et al. (2004)	LC/MS/MS, Affy array	Rotenone	*Arabidopsis thaliana*	43	17	7
Dhodda et al. (2004)	2D-MS, Affy array	Preconditioned ischemia	Rat brain	40	8	5
Ahn et al. (2003)	2D-MS, cDNA array	Uterine leiomyoma	Uterine tissue	71	33	0
Mostertz et al. (2004)	2D-MS, cDNA array	H_2O_2 and paraquat	*Bacillus subtilis*	138	160	19
White et al. (2004)	2D-DIGE, cDNA array	ErbB2 overexpression	HMELC cell lines	667	30	5
Verhoeckx et al. (2004)	2D-MS, Affy array	PMA-induced differentiation	U937 cell line	104	41	23
Juan et al. (2002)	2D-MS, cDNA array	TPA-induced differentiation	HL-60 cell line	96	32	4
Ahram et al. (2002)	2D-MS, cDNA array	Prostate cancer	Human prostate tissue	52	33	0
Le Naour et al. (2001)	2D-MS, oligo array	Differentiation	Human CD14+ blood monocytes	255	18	2
mRNA/protein expression—abundance comparison						
Gygi et al. (1999)	2D-MS/MS, SAGE	*mRNA/protein abundance	Yeast		156	
Washburn et al. (2002)	MuDPIT; oligo array	*mRNA/protein abundance	Yeast		77	
Chen et al. (2002)	2D-MS, oligo array	*mRNA/protein abundance	Non-neoplastic lung tissue		165	
Griffin et al. (2002)	ICAT; cDNA array	*mRNA/protein abundance	Yeast		245	
Kleffmann et al. (2004)	MS/MS, oligo array	*mRNA/protein abundance	Chloroplasts		690	
Lee et al. (2003)	2D-MS, oligo array	*mRNA/protein abundance	*Escherichia coli*		129	
Futcher et al. (1999)	2D-PAGE, SAGE	*mRNA/protein abundance	Yeast		148	
Anderson and Seilhamer (1997)	2D-PAGE, cDNA library; Incyte DB	*mRNA/protein abundance	Rat liver		23	

Representative literature studies reporting parallel transcript and protein profiles in target tissues. Citations are categorized by author, transcript and proteomic expression platform, the chemical or disease being profiled, tissue undergoing expression profiling, number of differentially genes, number of differentially expression proteins, number of transcripts and proteins found in common between profiles. Abbreviations: 2D-MS, two-dimensional gel electrophoresis mass spectrometry; DIGE, differential gel electrophoresis; Affy, Affymetrix oligonucleotide microarray; NMR, nuclear magnetic resonance for metabolomic analysis; oligo, oligonucleotide microarray; SAGE, Serial Analysis of Gene Expression platform; MuDPIT, multi-dimensional protein identification technology; ICAT, Isotope Coded Affinity Tag platform; MS/MS, tandem mass spectrometry; LPS, lipopolysaccharide; APAP, acetaminophen; TPA, 12-*O*-Tetradecanoyl-phorbol-13-acetate; H_2O_2, hydrogen peroxide; PMNs, polymorphonucleocytes. *Representative unconventional profiling studies which quantified proteins (see protein column) and compared the relative proportions of corresponding transcripts and protein amounts. **Study using pathway analysis to select 59 transcripts and 26 proteins for comparison.