

A Web-Based Data Warehouse on Gene Expression in Human Malignant Melanoma

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The identification of melanoma-specific dysregulated genes could identify new molecular markers. By applying bioinformatic tools for screening of biomedical databases, a melanoma-specific gene expression profile “data warehouse” was constructed. Utilizable data sets of global gene expression analyses were available from nine studies that applied different technology platforms. A single study used cell lines, five investigations analyzed cell lines and tissues obtained from patients, two studies used exclusively specimens obtained from patients, and one study analyzed blood cells prepared from patients. The total number of investigated patients was 116. From 815 differential-regulated genes, 772 (95%) were identified merely in a single study, 37 in at least two studies, five (*RAB33A*, *ERBB3*, *ADRB2*, *MERTK*, *SNF1LK*, and *ITPKB*) in at least three studies, and a single gene, *RAB33A*, in four studies. These data show that the accuracy, reproducibility, and comparability among different gene expression profile studies are low in melanoma. In conclusion, the study demonstrates the high diversity of gene expression profiles associated with melanoma, the necessity to include a sufficient number of samples regarding clinical standards, for the design of standardized sample collecting and preparation, for the development of common standards for microarray data processing, and for developing standardized bioinformatic tools.

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INTRODUCTION

Malignant melanoma (MM) is one of the most aggressive human neoplasms. MM develops from the malignant transformation of melanocytes, the pigment-producing cells that reside in the basal epidermal layer in human skin. Recognized as the most common fatal skin cancer, melanoma incidence and mortality has rapidly increased during recent decades. There are about 133,000 new cases of MM worldwide each year, of which almost 80% occur in North America, Europe, Australia, and New Zealand (Stewart and Kleihues, 2003). MM is characterized by a high risk for metastasis. At present, no effective treatment exists for metastatic melanoma and the advanced disease is incurable, associated with a mean survival of only 6–9 months after detection of the first metastases (Whittaker, 2000) and 5-year-survival rates of less than 5% (McGovern *et al.*, 1985). A curative treatment of MM is possible only by early, adequate surgical resection. Unfortunately, chemotherapeutic protocols are extremely ineffective and unsatisfactory. Chemotherapeutic regimes based on dacarbazine are still the most

commonly applied strategies for treatment of disseminated MM, but only a minority of patients obtain long-lasting response rates (Middleton *et al.*, 2000).

Both genetic predisposition and exposure to environmental agents are risk factors for development of MM (Chudnovsky *et al.*, 2005). As many tumors, this type of skin cancer arises owing to accumulation of mutations in genes critical for cell proliferation, differentiation, and cell death (Hanahan and Weinberg, 2000). Moreover, the neoplastic cells acquire the ability to initiate and sustain angiogenesis, invade across tissue planes, and metastasize. The clinical and histologic progression observed in the growth phases of MM is hypothesized to correspond to the accumulation of these genetic changes, and therewith, with alterations in gene expression profiles (Clark *et al.*, 1984). In order to develop treatments for advanced disease and to increase survival from metastatic MM, it is critical to understand the genetic changes leading to each progressive step of the tumor. Furthermore, an understanding of the alterations that permit invasion through the epidermal basement membrane and thus allow for subsequent metastasis will permit the rational design of treatments for early stages of MM and potentially the design of chemopreventive treatments for patients with premalignant lesions or who are at high risk for MM development. In addition, an understanding of tumor biology and immunology will aid in the rational design of new chemotherapeutic or immunotherapeutic agents for more advanced stages of disease.

Changes in gene expression due to mutations observed in human MM patients as well as in various *in vitro* and *in vivo* models provide starting points for a detailed analysis of the

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Abbreviation: MM, malignant melanoma

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Table 1. Data sets used in our analysis

References (year)	Technology	Number of identified genes	Validation used (no. of genes)	Samples used	Compared to
Talantov <i>et al.</i> (2005)	Affymetrix HGU133A	33	Quantitative RT-PCR (2)	45 primary melanoma	18 benign skin nevi and 7 normal skin
Schaefer <i>et al.</i> (2002)	Affymetrix human cancer G110	30	Quantitative real-time PCR (3)	GG-62 cell line	11 non-melanoma cell lines
Hoek <i>et al.</i> (2004)	Affymetrix HGU133A	590	RT-PCR and Western blot (19)	9 melanoma cell lines	Normal human melanocytes
Segal <i>et al.</i> (2003)	Affymetrix HGU95A	30	—	20 MM cell lines and 9 tissue samples	47 STS patient and 1 CCS/MSP cell line
Schaefer <i>et al.</i> (2004)	Affymetrix HGU95Av2	92	Quantitative real-time PCR and Northern blot (1)	6 cell lines	21 other cell lines
Nambiar <i>et al.</i> (2005)	Atlas human apoptosis and cancer array	33	Quantitative real-time PCR (3)	10 melanoma metastases	Normal human melanocytes
de Wit <i>et al.</i> (2005)	Custom oligos	25	Quantitative real-time PCR (9)	IF6 and Mel57 cell lines	Nevus nevocellularis
Xu <i>et al.</i> (2004)	Agilent human 1 cDNA	9	Quantitative real-time PCR (10)	15 MM patient T cells	15 healthy control T cells
Weeraratna <i>et al.</i> (2004)	SAGE	61	Immunohisto-chemistry (2)	3 melanoma tissues	7 different tissues

MM, malignant melanoma; RT, reverse transcriptase; SAGE, serial analysis of gene expression; STS, soft tissue sarcoma.

molecular and cellular biological characteristics of MM. In the last years, powerful new techniques for transcriptomic investigations have been developed to detect modifications in genome-wide gene expression profiles. These new tools have been broadly applied in studying the biology of MM. The hope is that the newly obtained data will now allow a classification of disease on molecular basis, deep insights into the pathophysiology of MM, prognostic statements, and finally a systematic search for new diagnostic and therapeutic targets. Owing to the complexity of the biological systems under investigation, the most significant contribution of translational research in MM is expected to derive not from the analysis of single experiments but from libraries of experiments. In other words, the results obtained so far by transcriptomic research tools in different clinical and experimental settings need to be compared, contrasted, and if possible synthesized. Thus, based on the biomedical literature databases, we tried a first step for constructing such “data warehouse” specific to human MM.

The specific aims of this study were to screen transcriptomic MM studies and to elaborate a kind of “meta-analysis of gene expression” in MM. Our hypothesis was that we would be able to determine a common set of genes and gene products that are differentially regulated in human MM by overlapping results obtained from different transcriptomic studies.

RESULTS

Source data collection

All together nine studies were found, in which gene lists associated with MM are published. In these studies, various methods were used for large-scale gene expression analysis of

MM. These studies used various technologies, namely, micro-serial analysis of gene expression (one study), customized arrays (two studies), as well as “genomic” standard arrays (six studies). A single study merely used MM cell lines, in five investigations MM cell lines and tissues obtained from MM patients were used, two studies analyzed exclusively MM tissues, and one study used blood cells prepared from MM patients. An overview of these studies is summarized in Table 1.

At first, all genes associated with MM pathogenesis ($n = 815$) were extracted. Then, the genes that were identified in more than one paper were filtered ($n = 43$, Table 2, Supplemental Material). Of these, five were identified in three (*ERBB3*, *ADRB2*, *MERTK*, *SNF1LK*, and *ITPKB*) and one (*RAB33A*) in four papers.

Gene ontology

The top five overrepresented gene ontology categories are shown in Table 3.

DISCUSSION

Global transcript analysis techniques are highly efficient for developing an understanding of the overall gene expression profile in a given cell or tissue including MM. In the last years, these powerful techniques identified previously unrecognized subtypes of cutaneous MM and predicted phenotypic characteristics that may be of importance to disease progression (Bittner *et al.*, 2000). Furthermore, candidate genes for the prediction of response to drug treatment of MM were identified (Györfy *et al.*, 2006). However, these studies were not useful for this analysis, as they have compared MM specimens to other MM samples.

Table 2. Genes associated with melanoma in at least two different microarray studies

Affymetrix HGU133A ID	UniGene ID	Symbol	Gene title	Selected gene ontology
206039_at	Hs.56294	RAB33A	RAB33A, member RAS oncogene family	Small GTPase-mediated signal transduction
202454_s_at	Hs.306251	ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	Transmembrane receptor protein tyrosine kinase signaling pathway
206170_at	Hs.2551	ADRB2	adrenergic, beta-2-, receptor, surface	G-protein-coupled receptor protein signaling pathway
206028_s_at	Hs.306178	MERTK	c-mer proto-oncogene tyrosine kinase	Cell growth and/or maintenance
208078_s_at	Hs.380991	SNF1LK	SNF1-like kinase	Protein amino-acid phosphorylation
203723_at	Hs.78877	ITPKB	inositol 1,4,5-trisphosphate 3-kinase B	Signal transduction
201580_s_at	Hs.169358	DJ971N18.2	hypothetical protein DJ971N18.2	Electron transport
208891_at	Hs.298654	DUSP6	dual specificity phosphatase 6	Inactivation of MAPK
209569_x_at	Hs.79404	D4S234E	DNA segment on chromosome 4 (unique) 234 expressed sequence	Dopamine receptor signaling pathway
212091_s_at	Hs.415997	COL6A1	collagen, type VI, alpha 1	Cell adhesion
202718_at	Hs.433326	IGFBP2	insulin-like growth factor binding protein 2, 36 kDa	Cell growth and/or maintenance
203510_at	Hs.419124	MET	met proto-oncogene (hepatocyte growth factor receptor)	Cell proliferation
203851_at	Hs.274313	IGFBP6	insulin-like growth factor binding protein 6	Cell growth and/or maintenance
200605_s_at	Hs.280342	PRKAR1A	protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)	Intracellular signaling cascade
201564_s_at	Hs.118400	FSCN1	fascin homolog 1, actin-bundling protein (<i>Strongylocentrotus purpuratus</i>)	Actin cytoskeleton organization and biogenesis
201860_s_at	Hs.274404	PLAT	plasminogen activator, tissue	Blood coagulation
202644_s_at	Hs.211600	TNFAIP3	tumor necrosis factor, alpha-induced protein 3	Antiapoptosis
203010_at	Hs.437058	STAT5A	signal transducer and activator of transcription 5A	JAK-STAT cascade
203186_s_at	Hs.81256	S100A4	S100 calcium binding protein A4 (calcium protein, calvasculin, metastasin, murine placental homolog)	—
204086_at	Hs.30743	PRAME	preferentially expressed antigen in melanoma	—
204252_at	Hs.19192	CDK2	cyclin-dependent kinase 2	G2/M transition of mitotic cell cycle
205483_s_at	Hs.458485	G1P2	interferon, alpha-inducible protein (clone IFI-15K)	Cell-cell signaling
205824_at	Hs.78846	HSPB2	heat shock 27 kDa protein 2	Protein folding
206498_at	Hs.510807	OCA2	oculocutaneous albinism II (pink-eye dilution homolog, mouse)	Eye pigment biosynthesis
210663_s_at	Hs.444471	KYNU	kynureninase (L-kynurenine hydrolase)	Tryptophan catabolism
212543_at	Hs.422550	AIM1	Absent in melanoma 1	—
213094_at	Hs.419170	GPR126	G protein-coupled receptor 126	Neuropeptide signaling pathway
201508_at	Hs.1516	IGFBP4	insulin-like growth factor binding protein 4	DNA metabolism
203574_at	Hs.79334	NFIL3	nuclear factor, interleukin 3 regulated	Immune response
204979_s_at	Hs.47438	SH3BGR	SH3 domain binding glutamic acid-rich protein	Protein complex assembly

Table 2 continued on following page

Table 2. continued

Affymetrix HGU133A ID	UniGene ID	Symbol	Gene title	Selected gene ontology
205591_at	Hs.74376	OLFM1	olfactomedin 1	Development
209283_at	Hs.408767	CRYAB	crystallin, alpha B	Muscle contraction
209621_s_at	Hs.71719	PDLIM3	PDZ and LIM domain 3	—
209967_s_at	Hs.231975	CREM	cAMP responsive element modulator	Regulation of transcription, DNA-dependent
211535_s_at	Hs.748	FGFR1	fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome)	MAPKKK cascade
211959_at	Hs.369982	IGFBP5	insulin-like growth factor binding protein 5	Cell growth and/or maintenance
212805_at	Hs.23311	KIAA0367	KIAA0367	—
221577_x_at	Hs.296638	GDF15	growth differentiation factor 15	Cell-cell signaling
201842_s_at	Hs.76224	EFEMP1	EGF-containing fibulin-like extracellular matrix protein 1	Visual perception
204929_s_at	Hs.534425	VAMP5	vesicle-associated membrane protein 5 (myobrevin)	Myogenesis
205174_s_at	Hs.79033	QPCT	glutaminyl-peptide cyclotransferase (glutaminyl cyclase)	Protein modification
209848_s_at	Hs.95972	SILV	silver homolog (mouse)	Melanin biosynthesis from tyrosine
208622_s_at	Hs.403997	VIL2	villin 2 (ezrin)	Cellular morphogenesis

GTP, guanosine triphosphate; MAPK, mitogen-activated protein kinase; MAPKKK, MAPK kinase kinases.

Bold: genes identified in three studies.

The RAB33A was identified in four studies.

Table 3. Top five gene ontology categories of all genes identified in at least one publication

GO description	Number of genes (in selected category)	χ^2	P-value
Transmembrane receptor protein tyrosine kinase pathway	29 (241)	37.8	8.4E-10
Organ development	107 (1536)	33.1	9.4E-9
Morphogenesis	124 (1870)	31.9	1.7E-8
Eye pigmentation biosynthesis	3 (6)	31.5	2.2E-8
Response to virus	14 (91)	28.7	8.8E-8

GO, gene ontology.

Thus, those studies identified signatures that are specific for subclassification of MM or drug resistance of MM.

This investigation was aimed at screening different published studies performing global gene expression analyses of MM, and to elaborate a kind of meta-analysis of gene expression in MM in order to generate a data warehouse useful for identification of repeatedly validated MM-specific markers with potential clinical impact. A significant number of transcriptome analysis studies dealing with MM are available, starting in 2002. This has created a

significant amount of different data that were compiled in this study.

The starting hypothesis of the study was that it would be possible to determine a common set of expressed genes, a warehouse of gene expression, that are differentially regulated in human MM by comparing results obtained by different authors. However, merely one gene, *RAB33A*, could be found to be associated with MM in four studies, five genes, *ERBB3*, *ADRB2*, *MERTK*, *SNF1LK*, and *ITPKB*, were identified to be differentially regulated in at least three studies, and 37 genes were altered expressed in only two studies.

The most promising gene, the Ras-associated gene *RAB33A* encodes a 237-amino-acid protein belonging to the RAB subfamily of small GTPases with 61 members (Zerial and McBride, 2001). These proteins are involved in many cellular functions, including signal transduction, vesicular transport, and control of cytoskeleton and chromatin structure (Olkonen and Stenmark, 1997). They all contain conserved regions, termed G1 through G5, that are involved in GTP/GDP binding and GTPase activity. Although data are available, showing that RAB small GTPases and their associated regulatory proteins and effectors are involved in multiple human diseases including cancer (Cheng *et al.*, 2005), no direct link between *RAB33A* and MM or an alternative neoplasm has been described so far. Thus, the putative impact of *RAB33A* for diagnostics or prognostics of MM has to be elucidated in further studies.

The *ERBB3* gene product is member of the ErbB family of tyrosine kinases that play important roles in carcinogenesis, in regulating cell proliferation, and differentiation during development. *ERBB3* encodes a receptor for neu differentiation factor (NDF)/heregulin that can engage in heterodimerization with other type I receptor tyrosine kinases. Despite very limited kinase activity, it can stimulate responses in heterodimers not evoked by other ErbB family members. It is overexpressed frequently in several common solid tumors and is assumed to represent a target for new therapies (Gullick, 1996). Hence, *ERBB3* may be considered as an interesting factor for diagnostics or therapy design of MM, but it seems not to be a MM-specific marker.

ADRB2 encodes the β -2-adrenergic receptor, a member of the large superfamily of G-protein-coupled receptors. β -2-Adrenergic receptor agonists are the most widely used bronchodilators for the management of people with asthma and other chronic conditions affecting the airways (Johnson, 2006). β -Adrenergic receptor antagonists, commonly designated as β -blockers, play an important role in the management of cardiovascular disease, including hypertension and chronic heart failure (Weber, 2005). Although the *ADRB2* gene product represents a clinically extremely important target molecule, no data are available that it may be involved in any aspect of cancer including MM.

The *MERTK* gene encodes the 175 kDa Mer receptor tyrosine kinase, the human orthologue of a rat retinal dystrophy gene, that causes retinitis pigmentosa (Gal *et al.*, 2000). It could be demonstrated that Mer plays a role in phagocytosis and clearance of apoptotic cells (Scott *et al.*, 2001). However, so far no data are available that this receptor tyrosine kinase may play a role in malignant diseases or MM.

The human *SNF1LK* gene is member of the SNF1/AMPK family of kinases. The gene product, the Snf1-like kinase, possibly plays a role in regulation of the G₂/M checkpoint in the cell cycle (Stephenson *et al.*, 2004), but there are no further data available that could demonstrate a role in human diseases including cancer.

IP3 3-kinase B, encoded by the *ITPKB* gene, catalyzes the phosphorylation of IP3 to inositol-1,3,4,5-tetrakisphosphate, both of which are modulators of calcium homeostasis. It was demonstrated that *ITPKB* is essential for T-cell development (Pouillon *et al.*, 2003). However, likewise to *ADRB2*, *MERTK* and *SNF1LK*, no data were published that could provide evidence for an involvement of *ITPKB* in cancer or MM.

The objective, the determination of a common set of expressed genes that are up- or downregulated in human MM, was missed. The analysis of various transcriptomic studies demonstrated a low overlapping between published gene expression data in human MM. In fact, about 95% of the results could not be reproduced. Some explanations may help to explain this observation.

First of all, the studies were performed using heterogeneous material in particular MM cell lines, tissue samples prepared from primary tumors or metastases, as well as blood cells. Results obtained in cell lines do not allow accurate comparison between normal and MM cells, and the presence or absence of a transcript of interest has to be confirmed in

clinical samples. When clinical specimens were used, results of phenotypic comparisons depend on the type of samples examined (e.g., heterogeneous whole-tissue samples with surrounding cells, necrosis, blood, etc.), so that standardized sample preparation procedures are critical for obtaining reproducible results. Furthermore, the clinical samples did not exhibit the identical clinico-pathological parameters.

Secondly, the number of patients and cell lines included in the transcriptomic analyses of MM is low (all together 116 MM cases). As the interindividual genetic variability is very high in human MM, this may be an important problem for the comparison of expression profiles. Thus, some data associated with alterations in gene expression might be the result of the genetic diversity rather than the result of MM-related features.

Thirdly, differences in gene expression profiles may be caused by the array technology platform. In transcriptomics studies various factors influence the outcome of an expression analysis experiment, in particular technical, instrumental, computational, and interpretative factors. In fact, lack of reproducibility and accuracy is a major concern in microarray studies (Shi *et al.*, 2004). When cross-platform comparison was performed, reproducibility was insufficient: only four genes from a set of 185 common genes selected behaved consistently on three array platforms, and agreement of about 30% was found between two brands (Tan *et al.*, 2003).

Finally, the bioinformatic processing procedures applied for generating, formatting, storing, retrieving, and querying of the data are of major importance to assess methodological and biological variation in gene expression analysis. Owing to the limited number of samples, many variables, and absence of independent reproducing experiments, the statistical analysis is often not valid.

In conclusion, a gene expression profile data warehouse of human MM that is useful to help researchers active in the field to get an overview of the data available was established. Unfortunately, the comparability and reproducibility of gene expression data from different studies was not satisfactory. The study emphasizes the necessity for including a sufficient number of patients, regarding clinical standards, that is, histopathology, clinical management etc., design of standardized sample preparation, development of common standards for microarray data processing and exchange, paying attention to the variability of the applied technology platforms, and finally for developing software implementing these standards and promoting the sharing of these high quality, well-annotated data.

MATERIALS AND METHODS

Source data collection

For data collection, a literature survey of gene expression data published in human MM was performed. A search of the PubMed database (<http://www.pubmed.com>) of studies published in English up to 2005 using the keywords "melanoma", "array", "microarray", "gene chip", and "gene expression" with the limit "human" was performed and yielded 149 articles. All abstracts were reviewed and a related article search was performed on appropriate abstracts.

Articles were selected that satisfied the predetermined criteria: sample origin (human and/or cell lines) and preparation detailed, technology for gene expression studies defined, and detailed results of the gene expression changes available. Studies concerning single genes or arbitrarily selected genes were discarded. Results obtained in animal models were not considered. As gene expression data were not always obtained with quantitative, but in most cases with semiquantitative gene expression analysis technologies, no expression values or ratios were entered into the database. No threshold was defined so that some genes defined as differentially expressed might have shown only marginal differences. Unigene numbers and Affymetrix probe set IDs were used to identify single genes. Only descriptive statistics are provided, which were obtained with the in-built tools of the Microsoft Access and Excel softwares.

Gene ontology

Gene Ontology (Ashburner *et al.*, 2000) is widely accepted as the standard for vocabulary describing the biological process, molecular function, and cellular component for genes. We have used the Affymetrix Netaffx analysis centre (<http://www.affymetrix.com/analysis/index.affx>) for identification of overrepresented Gene Ontology categories.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Table S1. Complete list of all genes associated with melanoma.

Table S2. Genes associated with melanoma in at least two studies.

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