

Gene expression profiling of meningiomas: current status after a decade of microarray-based transcriptomic studies

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Abstract

Purpose This article provides a review of the transcriptomic expression profiling studies that have been performed on meningiomas so far. We discuss some future prospects and challenges ahead in the field of gene expression profiling.

Methods We performed a systematic search in the PubMed and EMBASE databases in May 2010 using the following search terms alone or in combination: “meningioma”, “microarray analysis”, “oligonucleotide array sequence analysis”, or “gene expression profiling”. Only original research articles in English that had used RNA hybridized to high-resolution microarray chips to generate gene expression profiles were included.

Results We identified 13 articles matching the inclusion criteria. All studies had been performed during the last decade.

Conclusions The main results of the studies can be grouped in three categories: (1) several groups have identified meningioma-specific genes and genes associated with the three WHO grades, and the main histological subtypes of grade I meningiomas; (2) one publication has shown that

the general transcription profile of samples of all WHO grades differs in vivo and in vitro; (3) one report provides evidence that microarray technology can be used in an automated fashion to classify tumors. Due to lack of consensus on how microarray data are presented, possible general trends found across the studies are difficult to extract. This could obstruct the discovery of important genes and pathways universally involved in meningioma biology.

Keywords Meningioma · Microarray analysis · Oligonucleotide array sequence analysis · Gene expression profiling

Introduction

Medicine has been transformed by the genomic revolution, and classical population risk assessment and empirical treatment challenged by molecular classification and the concept of personalized therapy [1]. With high-throughput molecular genetic analyses, genes and pathways associated with, e.g., clinical progression, response to irradiation or drugs, and environmental exposure, can be discovered [2]. Thus, new biomarkers and therapeutic targets may be developed. During the last decade, microarray technology has been implemented in molecular biological laboratories world-wide, and numerous studies have been performed in a wide range of human tissues and conditions.

Microarray chips of the size of histology slides including all known human genes are currently manufactured with high precision. The main methods for the production of such chips are based on robotic spotting of cDNA probes or oligonucleotides to a surface [3] (Fig. 1). By labeling the RNA in the samples at study and hybridization to the

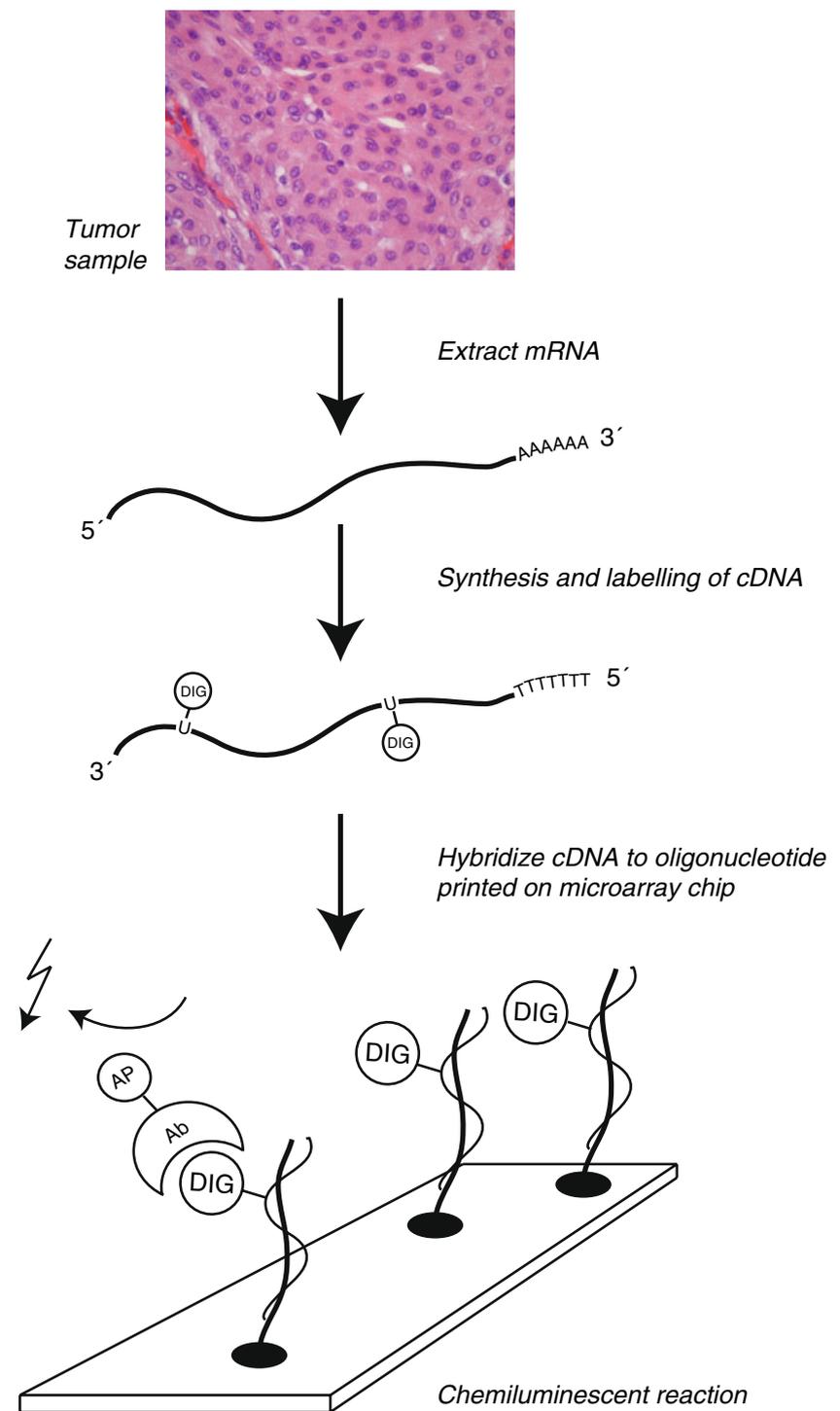
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Fig. 1 Principle behind microarray analysis (Human Genome Microarray, Applied Biosystems). mRNA extracted from a biological sample is labeled and converted into cDNA. On a microarray slide (“chip”), thousands of oligonucleotides representing individual genes are positioned in predefined positions. If the corresponding cDNA is present, it will hybridize to the oligonucleotide. By a chemiluminescent reaction, the presence of cDNA can be measured



corresponding gene probes on the microarray chip it is subsequently possible to measure the abundance of every gene expressed at time of tissue sampling. The measured signals are then converted to numerical values and interpreted with bioinformatic tools to produce the *gene expression profile*.

Meningiomas (Fig. 2), being the second most common intracranial neoplasm (20–30% of all cases) [4], have been

extensively studied in the past. An important contribution to the understanding of the pathogenesis was the identification of the NF2 gene located on chromosome 22q12.2 [5–8]. Loss of one allele of this gene is causing the autosomal dominant syndrome neurofibromatosis type 2, in which bilateral vestibular schwannomas are pathognomonic, and multiple meningiomas often develop. From research on sporadic (non-NF2-related) meningiomas it has been

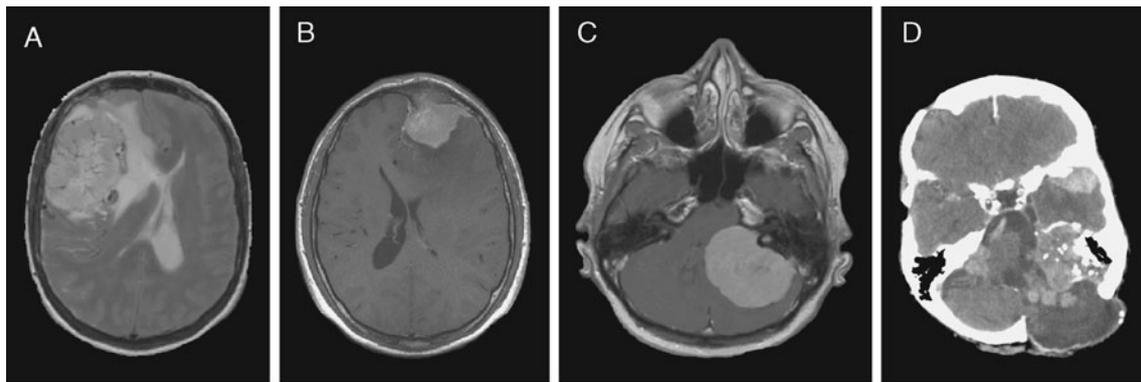


Fig. 2 Radiological appearances of meningiomas. **a** Magnetic resonance imaging (MRI) showing a large convexity meningioma with edema and displacement of the midline to the anatomical left. **b** MRI section illustrating a WHO grade I convexity meningioma

invading the frontal bone. **c** Large meningioma arising in the cerebello-pontine angle compressing the brain stem. **d** Computerized tomography showing multiple meningiomas and postoperative changes in a patient with neurofibromatosis type 2

found that loss of heterozygosity is found in 40–70% of cases and mutations in the remaining allele present in 60% [9–12]. Thus, a main mechanism of meningioma initiation follows the pattern of Knudsons two-hit hypothesis: first, a risk allele is deleted, and then a mutation in the remaining allele containing a tumor suppressor gene initiates neoplastic growth [13]. However, it follows that this mechanism is not uniformly causing meningiomas, and that other genes or pathways are contributing to the tumorigenesis. Hence, gene expression profiling studies have the potential to discover novel genes and signaling pathways with a role in meningioma biology.

The aim behind this article is to provide a review of the mRNA microarray studies that have been performed on meningiomas, and to reflect the advances in the biological understanding of the tumors gained by this technology. We also address some future prospects and challenges ahead in the field of gene expression profiling.

Material and methods

We performed a systematic search in the PubMed and EMBASE databases in May 2010 with the following medical subject headings (MeSH) terms: “meningioma”, “microarray analysis”, “oligonucleotide array sequence analysis”, “gene expression profiling” (Table 1). Upon literature review only original research articles in English that had used RNA

hybridized to high-resolution microarray chips to generate gene expression profiles were included.

Results

Based on our search criteria we detected a total of 70 studies. There were no additional studies found in EMBASE to those located in PubMed. All microarray studies found by search term 1 were also found with search term 3. With search term 2, one additional study was identified; however, it was excluded since it was a review article. With search term 3, we found one additional RNA-based microarray study that was included. However, many of the studies were based on quantitative reverse transcriptase real time polymerase chain reaction (qRT-PCR) for selected genes with an a priori hypothesis. Other excluded studies were proteomic profiling projects, tissue arrays, review articles, and non-human material. We identified 13 original research articles that analyzed meningioma RNA with microarray chip technology (Table 2). All studies have been performed during the last decade.

Microarray platforms

Six different microarray platforms had been used in the studies, with technology from Affymetrix being most frequently used (eight of 13 studies). Three of the studies used chips that were spotted with cDNA clones; the remaining used

Table 1 Search terms used to identify RNA microarray studies performed on human meningioma samples in the PubMed (<http://www.ncbi.nlm.nih.gov/>) and EMBASE (<http://www.embase.com/>) databases

Search term no.	Search term	PubMed hits	EMBASE hits
1	“Meningioma and microarray analysis”	44	14
2	“Meningioma and oligonucleotide array sequence analysis”	37	0
3	“Meningioma and gene expression profiling”	70	27

Table 2 mRNA microarray studies on human meningiomas identified with our search strategy

Year	Author	Microarray platform	No. of transcripts	No. of meningiomas	Distribution WHO grades	Source of control	No. of controls	Main results	Selected interesting molecules or pathways
2002	Watson et al. [14]	Affymetrix HCG110	2,059	15	6 grade I 6 grade II 3 grade III	Meninges	3	Gene expression profiles associated with WHO grade subtypes	Growth hormone receptors, endothelin receptor A, IGF2, IGFBP-7
2003	Sasaki et al. [15]	Affymetrix U95A	12,000	3	1 grade I 1 grade II 1 grade III	Primary cultures of the samples	3	Differing transcriptomic profiles between original frozen meningioma samples and primary cultures	Wnt, Notch, PI3K, MAP kinase
2003	Fathallah-Shaykh et al. [16]	19 K gene microarrays (Ontario Cancer Institute)	19,200	10	Not declared	Human brain	4	Differential gene expression between meningiomas and control human brain	PRKDC, PSIP2, NCOR2, TAF13
2005	Wrobel et al. [17]	Custom made cDNA microarray	4,211	30	3 grade I 12 grade II 5 grade III	Human RNA pool	Pool of 8 different tissues	Meningioma signature genes and differences in gene expression according to WHO grade	PTGDS, CLU, BAD, MGP, LIG1, ANXA2, MMP12, VIM, TIMP1, CCND1
2005	Lusis et al. [18]	Affymetrix U133A and U133B	39,000	10	Not declared	–	–	Loss of transcripts in grade III meningiomas	NDRG2
2006	Sayagues et al. [19]	Affymetrix U133A	18,400	7 spinal and 11 intracranial	Only WHO grade I	–	–	Differential gene expression between intracranial and spinal meningiomas	NR4A3, DUSP5, HOXA5
2007	Carvalho et al. [20]	Affymetrix U133 Plus 2.0	47,400	23	8 grade I 7 grade II 8 grade III	–	–	Differential gene expression between grade I and III meningiomas	TGF- β signaling pathway
2008	Aarhus et al. [21]	Applied Biosystems 1700	30,000	27	22 grade I 5 grade II	Arachnoid cyst membranes	4	Differential gene expression between arachnoid cells and meningiomas, and between meningeal and fibrous meningiomas.	WWOX, TYMS, BMPR1B, RAMP1, DMD
2008	Lillehei et al. [22]	Affymetrix U133 Plus 2.0	47,400	5 radiation induced and 6 sporadic	Not declared	Pediatric nervous system tumors	62	Differential gene expression between sporadic and radiation-induced meningiomas	RGS3, ZNF564, GYPA, CRHR1, MSTIR, INPP5B
2008	Hankins et al. [23]	Affymetrix U95A	12,000	6	6 grade I	Dura	4	Differential gene expression between meningiomas and dura	DLC1
2008	Claus et al. [24]	Affymetrix U133 plus 2.0	47,400	31	31 grade I	–	–	Differential gene expression between progesterone receptor positive and negative meningiomas	SLC24A3, SERPINB1, PDGFRB, MAP4K4, FAT4
2009	Fevre-Montange et al. [25]	CodeLink Uniset Human	55,000	17	10 grade I 6 grade II	Human brain	1	Differential gene expression between fibrous and	CD44, LOX, CKS2, BIRC5, Notch1, MMP2, TIMP3, FAT3

2009	Castells et al. [26]	The human CNIO oncochip 12 K cDNA microarray	11,500	18	7 grade III	meningothelial meningiomas, and between WHO grades	Automated prediction of brain tumor biopsies	GFAP, DSP

GBM glioblastoma multiforme

oligonucleotide microarrays. A high number of transcripts were represented on the chips; however, some of the early works included relatively few gene probes due to technical limitations at the time of study.

Meningioma subtypes

Altogether, 227 meningiomas were included in the studies; according to the WHO classification these were 151 grade I, 42 grade II, and 34 grade III. Some papers did not describe the histological subtypes present in their material; however, from the studies with histology data available we found the following subtypes present among the grade I tumors: fibrous ($n=31$), meningothelial (48), transitional ($n=27$), secretory ($n=1$), and psammomatous ($n=1$). Apart from two cases of clear cell meningiomas (WHO grade II), there was no further information on histological subtype for the grades II and III cases.

Source of control tissue

The aims of the various studies are different, and thus the source of control tissue is variable. For those studies aiming at detecting gene expression profiles separating meningiomas from tissue of origin the authors have extracted RNA from meninges, dura, arachnoid cyst membranes, normal brain, pooled normal tissue from various sources, and other brain tumors. Other studies have aimed at detecting gene expression changes due to irradiation, anatomical location (spinal vs. intracranial), and WHO grade; hence, samples from each of the categories have been compared with no external controls applied.

Statistics

Of the 13 microarray studies, ten provided a clear description of statistical procedure for the detection of differentially expressed genes between cases. Most frequently the Student's *t* test was applied (seven studies), two studies used the Mann–Whitney test, one study used significance analysis of microarrays (SAM), and finally one study used receiver operating characteristic curve.

Summary of main results (Table 2)

In the pioneering oligonucleotide microarray study on meningiomas by Watson and colleagues [14], 15 meningiomas (WHO grade I, $n=6$; WHO grade II, $n=6$; WHO grade III, $n=3$) and three post mortem leptomeninges were studied. The main result was the detection of gene expression profiles associated with WHO grade subtypes (growth hormone receptors, endothelin receptor A, IGF2, IGFBP-7). Selected genes were confirmed using qRT-PCR.

Sasaki and colleagues [15] aimed at comparing the transcriptomic profiles of original meningiomas ($n=3$; one of each WHO grade) and primary cultures of the same samples. They found that 51 genes were up-regulated > fivefold, and 19 genes were down-regulated by twofold or more in the primary cultures. The results were validated with qRT-PCR.

Fathallah-Shaykh and colleagues [16] studied ten meningiomas and compared them with pooled post mortem brain RNA from the occipital lobes of four individuals. With their approach 364 genes were differentially expressed, and they found evidence of activation of different signaling pathways like Wnt, MAP kinase, PI3K, and notch. No validation of the findings with alternative approaches was performed.

In a study of 30 meningiomas (WHO grade I, $n=13$; WHO grade II, $n=12$; WHO grade III, $n=5$) Wrobel and colleagues [17] investigated 2,600 genes using cDNA microarrays. The gene expression profiles of each category were compared with each other. The main finding was that 37 genes were decreased and 27 increases in grades II and III meningiomas compared with grade I. Compared with a pool of RNA from various human tissues (heart, spleen, placenta, kidney, skeletal muscle, liver, brain, and lung) a gene signature of the meningiomas was identified: PTGDS, CLU, BAD, MGP, LIG1, ANXA2, MMP12, VIM, TIMP1, and CCND1 were highly expressed in the meningiomas. Selected genes were validated with qRT-PCR, and for several candidates the results corroborated with those found by microarray. The authors concluded that the study showed that genes related to cell cycle regulation, cellular proliferation, as well as the IGF and WNT signaling pathways were up-regulated in grades II and III meningiomas. However, a main limitation of the study was the low number of cDNA probes, covering <10% of all human genes.

The aim of the study of Lusic et al. [18] was to identify genetic events responsible for malignant progression of meningiomas. Using the Affymetrix U133A/B GeneChip Microarrays the authors searched for transcripts that were lost in grade III meningiomas compared with grade I. They found that approximately 40% of down-regulated genes in grade III meningiomas were located at chromosomes 1p and 14q. One of the candidates, the NDRG2 genes, was consistently down-regulated in all grade III meningiomas both at the mRNA and protein level, and that this was correlated with hypermethylation of the corresponding promoter.

As a part of a larger study of the genomics of spinal meningiomas Sayagues et al. [19] performed gene expression profiling to compare spinal and intracranial meningiomas. They included seven spinal and 11 intracranial meningiomas in the study. The main result was differential expression of 1,555 genes, of which 35 genes showed the highest correlation ($r^2 > 0.7$ or $r^2 < -0.7$). Thirty of these had lower expression in the intracranial tumors, whereas the remaining

five genes were up-regulated. Three genes were selected for qRT-PCR validation, and a significant correlation ($p < 0.001$) with microarray expression was found for all genes (NR4A3, DUSP5, and HOXA5).

In the study of Carvalho et al. [20] the purpose was to identify molecular signatures that characterize the different grades of meningiomas and molecular mechanisms driving meningioma tumorigenesis. They included 23 meningiomas (WHO grade I, $n=8$; WHO grade II, $n=7$; WHO grade III, $n=8$). Using SAM, the authors found 28 genes differentially expressed between grades I and II meningiomas, and no differential expression between grades II and III. A total of 1,212 genes were differentially expressed between grades I and III meningiomas. In an unbiased unsupervised cluster analysis the 23 meningiomas grouped in two branches. All grades I and grade III meningiomas were located in separate branches, and the authors thus designated each branch as “low proliferative” and “high proliferative”, respectively. The grade II meningiomas were located in both branches, three of seven in the low-proliferative group, and the remaining four in the high-proliferative group. A selection of genes were validated using qRT-PCR.

In 2008, our group [21] published a microarray study on meningiomas of grades I ($n=22$) and II ($n=5$), where the aim was to study the gene expression profiles of meningiomas in comparison to progenitor meningioma tissue (arachnoid cells). Unsupervised cluster analysis of a filtered data set of 16,430 genes showed that five of seven fibrous meningiomas clustered together, while the remaining samples (meningotheial, transitional, and atypical) made no clear branching. As control tissue we used samples from the membranes of four arachnoid cysts (AC), and all these samples formed a separate cluster indicating a very homogeneous transcription profile. Using the *t* test, we detected 20 genes that differentiated between meningiomas and ACs ($p < 4.3 \times 10^{-7}$), in which the tumor suppressor gene WWOX was down-regulated and the oncogene TYMS was up-regulated. We also found 20 genes separating fibrous from meningotheial meningiomas ($p < 1.1 \times 10^{-5}$), where DMD and BMP1B were up-regulated in the fibrous, and RAMP1 was down-regulated in the meningotheial meningiomas. qRT-PCR was performed on a selection of genes and showed similar expression profiles as those generated using microarray analysis.

Since a recognized mechanism of meningioma initiation is irradiation, Lillehei et al. [22] performed a microarray study of five radiation-induced meningiomas (RIM) and six spontaneous meningiomas to find unique genes behind this phenomenon. Interestingly, based on a microarray of 54,675 genes unsupervised hierarchical cluster analysis did not show separate clustering of RIMs and spontaneous meningiomas. Using a *t* test to compare the gene expression profiles of RIMs and spontaneous meningiomas the authors found a small subset of 20 genes separating the two groups ($p < 0.001$).

Hankins et al. [23] studied the expression profiles of 12,000 genes in six meningiomas (WHO grade I) and four dural samples. By this approach, the authors found five up-regulated and 35 down-regulated genes in the meningiomas. The down-regulation of the *DLC1* gene was confirmed with qRT-PCR and immunohistochemical staining. No evidence of CpG methylation of the corresponding promoter was found. The authors concluded that *DLC1* may function as a tumor suppressor gene in meningiomas.

Claus and colleagues [24] studied 31 samples from sporadic meningiomas (WHO grade I, $n=25$; WHO grade II, $n=6$) with the aim of examining the gene expression profiles in relation to hormone receptor status. Estrogen receptor positivity was present in 33% and progesterone receptor positivity in 84%. In a comparison of PR+ and PR- meningiomas, the study showed up-regulation of ten genes, and down-regulation of 14 genes. No genes separated ER+ from ER- meningiomas. As the number of candidate genes was small, no single pathways or groups of genes were clearly identified.

In 2009, Fèvre-Montange and colleagues [25] published a transcriptomic study of 17 meningiomas (WHO grade I, $n=10$; WHO grade II, $n=5$; WHO grade III, $n=2$). As control tissue RNA from a human whole brain (72 years of age) was used. The aim was to distinguish between the different WHO grades and histopathological subtypes, and to identify factors predicating recurrence. Unsupervised cluster analysis showed three groups of samples: group A consisted of seven of ten grade I cases, group B of the remaining three grade I samples and all five grade II meningiomas, and finally group C consisted of the two grade III tumors. Statistical analysis revealed that 346 and 2,995 genes showed more than twofold over-expression in groups B and C, respectively. Similarly, 184 and 1,380 genes were down-regulated, respectively. Furthermore, the study showed differential gene expression between fibrous and meningothelial meningiomas, with 12 up-regulated and 20 down-regulated genes in the fibrous subset. Selected genes were validated with qRT-PCR.

The last published microarray study on meningiomas so far was published in 2009 and performed by Castells et al. [26]. The aim was to assess whether automated categorization of brain tumors can be made by the use of microarray. Biopsies from 35 patients (17 glioblastomas and 18 meningothelial meningiomas) were subjected to cDNA-based microarray analysis. The study showed up to 100% prediction accuracy by using microarrays, thus providing evidence of possible clinical diagnostic use of this technology.

Discussion

During the last decade, a total of 13 microarray-based studies have been performed on RNA from altogether 227 meningiomas. The aims, sources of control tissue, microarray platforms,

and statistical approaches vary between the studies. The main results of the studies can be grouped in three categories: (1) several groups have identified meningioma-specific genes, and genes associated with the three WHO grades and the main histological subtypes of grade I meningiomas. (2) One publication has shown that the general transcription profile of samples of all WHO grades differs *in vivo* and *in vitro*. (3) One report provides evidence that microarray technology can be used in an automated fashion to classify tumors.

We found no clear overlap between the studies regarding individual candidate genes. Other than the gross signature differences identified in the studies, we were not able to detect any shared deregulated genes. This illustrates a big challenge in gene expression profiling studies: the vast number of transcripts present on the chips makes it very difficult to compare the studies and isolate key candidate genes with a possible role in the biology. Critiques may regard this as a weakness of the technology; however, the lack of external validity may in fact be explained by the variation in microarray platforms, study populations, chip manufacturer, statistical approach, and quality of RNA in the tissue at study. In fact, the Microarray Quality Control (MAQC) project (<http://www.fda.gov/ScienceResearch/BioinformaticsTools/MicroarrayQualityControlProject/default.htm>) has shown that the microarray quality at present may be higher than that of, e.g., immunohistochemical analysis [27, 28]. So the question is how should we perform microarray studies? Would it be appropriate to standardize some factors, like the source of control tissue and statistical procedure? And should it be mandatory to post microarray data in publicly available databases so that independent researchers could perform meta-analyses with the aim of identifying biological markers that could be used clinically? If so, would it be reasonable to demand posting of certain data, e.g., the overall best candidate genes for comparison purposes? Some journals have implemented this policy, however it is our opinion that it should be adopted globally.

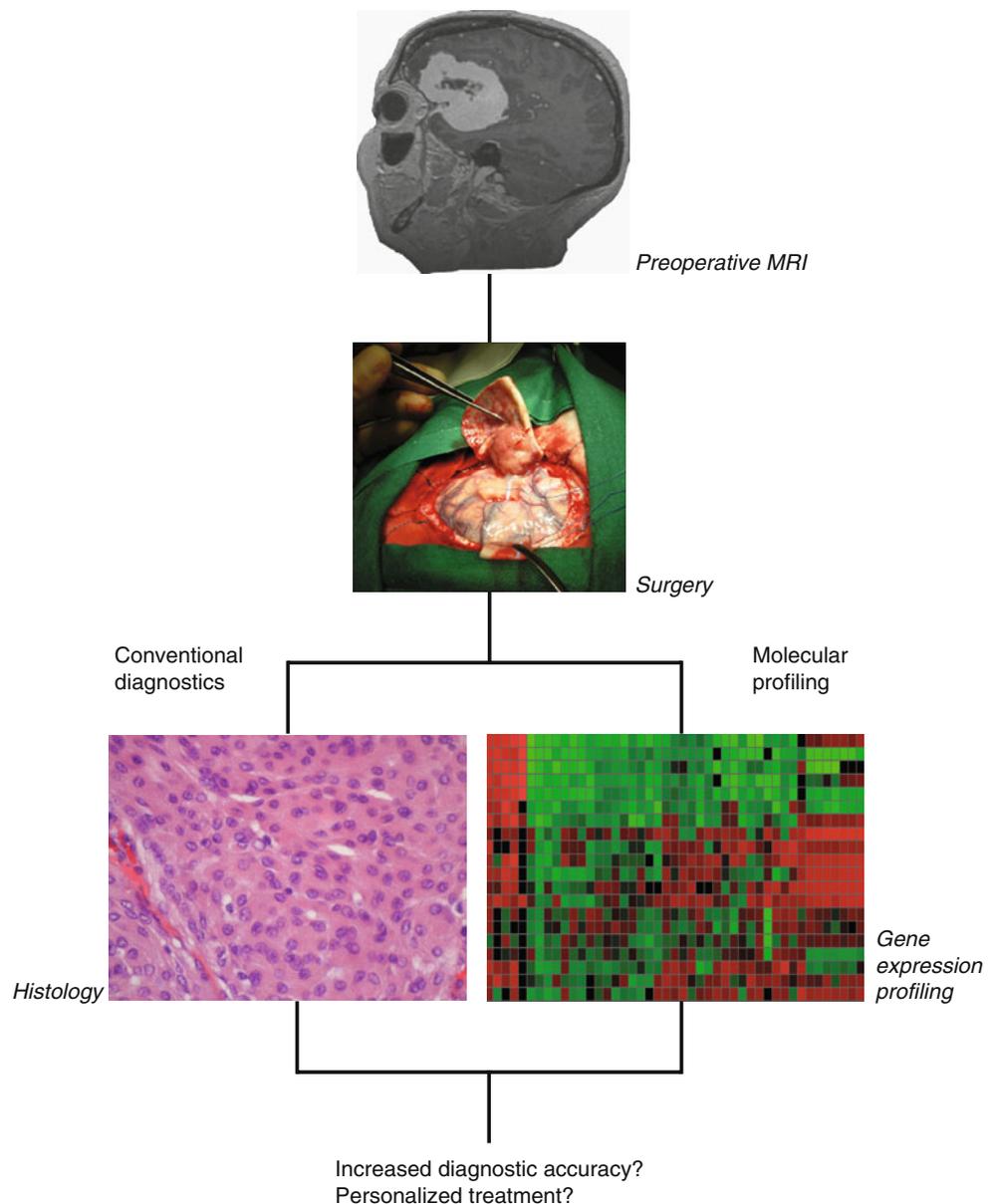
To draw firmer conclusions of the studies, consensus on source of control tissue and statistical approach, as well as replication of the most biological relevant findings so far is required. The time is therefore now due for a large replication study that includes the most significant and biologically relevant candidate genes generated from the various transcription studies that have been performed. This means that a custom-made microarray chip that includes these consensus genes should be designed, and quality controlled samples from several laboratories included. The data should also be compared with clinical outcome in order to identify clinically relevant genes. Recently, The Cancer Genome Atlas Research Network successfully applied this method to a large panel of glioblastomas [29]. Here, 206 glioblastomas were subjected to gene expression profiling, DNA copy number variation analysis, and CpG methylation status assessment of 601

selected genes. It follows that such a project demands considerable dedication, coordination, and financial support.

An interesting result was the difference in transcriptional profiles between original frozen specimens and primary culture of all three WHO grades. The study provides evidence that as tumors are removed from their native environment, the gene expression changes accordingly. Thus, results gained from cell culture experiments have to be interpreted with caution. Validation *in vivo* seems to be mandatory before firm conclusion can be made. It is however no surprise that the gene expression profile is altered when a tumor is removed from its site of origin. The dynamic transcriptome will rapidly adjust to changes in local environment to provide the substrates necessary to maintain the tumor.

Medicine has been transformed by the genomic revolution, and classical population risk assessment and empirical treatment has been challenged by molecular classification and prospects of individualized therapy [1]. With the help of microarray technology novel candidate genes, pathways, and networks may be linked with clinical scenarios, such as treatment response or environmental exposure. Thus, microarrays may be helpful in identifying biomarkers, developing new treatment strategies, and in tumor classification [2] (Fig. 3). Hence, a reasonable application of global gene expression profiling in oncology is to subclassify brain tumors of WHO grade II. Such tumors are generally infiltrative, have low-proliferative activity, tend to recur, and can undergo malignant transformation. Often there is marked clinical and

Fig. 3 Outline of possible application of microarray technology in the diagnostic armamentarium



morphological heterogeneity within tumors of this grade. Thus, the categorization of grade II tumors may be more challenging than that of purely benign or malignant entities. With microarray analysis, high- or low-proliferative gene expression signatures, or hyper- or hypo-mutator phenotypes may be revealed. Consequently, signatures indicating high or low risk of recurrence or transformation may be found. Such information may be useful when the addition of adjuvant therapy or follow-up schedule is discussed.

However, some technical issues make the use of this powerful technology difficult: (1) Since only minute amounts of RNA are required and probes corresponding to all known genes are analyzed, one must ensure that only representative tissue is subjected to hybridization to the microarray chips. Contamination with leucocytes, neighboring blood vessels or other normal tissue will contribute to the overall transcriptomic profile. (2) If the goal of the analysis is to measure therapeutic response to e.g. irradiation or cytotoxic drugs one must sample tissue at first-time surgery as well as after completed adjuvant therapy. Thus, the patient must undergo repeated surgery with the inherent risk factors. (3) RNA is very susceptible to time dependent degradation due to abundant RNase in the environment. Low quality RNA cannot be subjected to microarray analysis. Hence, the personnel involved in the sampling and handling of tissue must be dedicated and have a proper logistic procedure in order to preserve RNA. This means that tissue must be snap-frozen in liquid nitrogen in the operating theater and then transferred to permanent storage at ultra cold temperatures or in media containing RNase inhibitors. (4) Since transcriptome analysis can reveal genes that differ between tissue types, appropriate controls and groups of e.g. tumors have to be selected long before time of study. As meningiomas develop from arachnoid cells [4], it follows that such cells should be selected if the purpose was to find meningioma-specific genes. If dura or whole brain were used as controls the transcriptional profile would presumably be different due to the comparison of different tissue types. It would thus be impossible to call these genes different because of tumorigenesis per se. Only one of the 13 studies states that arachnoid tissue has been used as controls [21]. However, if the purpose is to identify genes associated with the different WHO grades it follows that no additional controls would be needed.

The main limitations of the studies were small sample size and unequal group sizes when performing statistical comparison. This illustrates how difficult it is to recruit patients and controls to such studies. It may also be due to the relatively high cost of performing microarray analysis. Furthermore, the results of the studies have to be functionally tested in order to safely identify biological markers and key players in meningioma pathogenesis.

As in most microarray studies of the transcriptome, new genes and pathways have been revealed in all the meningioma

studies. The challenge is to make use of the results clinically. At present, microarray chip technology is mature and with low technical error rate. Thus, the main issues that have to be handled in transcriptomic projects are study design, representative tissue source, logistics, and data interpretation. Since transcriptome analysis only provides snapshots of the gene expression state in cells constituting the tissue at study, clear improvements in diagnostic accuracy or clinical endpoints (e.g., improved recurrence free survival) must be objectively shown before the results of such studies can be safely implemented in the clinical armamentarium. This notion is by no means reserved for microarray studies, as all new methods have to be quality checked accordingly before clinical approval. Microarray studies have been taken into account for a trend towards personalized medicine, e.g. the genetic profile of a patient's tumor could tell which pathways that could be pharmacologically inhibited. However, as long as there are no individually designed drugs, such treatment is reserved for the future. How eager the pharmacological industry is to make such designed drugs, which presumably are more expensive than mass production, remains to be seen. Nevertheless, the molecular technology is continuously developing new and faster methods for the analysis of the nucleic acids. Next-generation sequencing is already "this generation"; the first people and cancers have been deciphered at base-pair resolution by the so-called deep sequencing technology. The complete sequencing of the human genome that took 10 years in the last decade of the twentieth century can now be performed in a few days. Therefore, awaiting individualized therapy, the era of the *personalized genome* is inevitably about to begin.

Conflicts of interest None.

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Comment

As a frequent reviewer for Acta, I have done my best to shoot down reports of immunostaining of this or that protein in this or that tumor as useless philately from by-gone decades.

At last—transcriptomic data on meningioma reviewed by the Norwegian colleagues in the era of genomics/transcriptomics/signalomics/metabolomics/glycomics/et al. mics (1–4). RNA sequencing of transcriptome of target tissue—analysis of differential signaling pathways—probing of synthetic molecules from drug libraries into key receptors—new ideas for phase I–II clinical drug trials. Furthermore, with the techniques cheaper, honed and widespread, each tumor in each carrier could be individually profiled for optimal therapies and outcome—we hope.

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