Gene expression profiling in acute myeloid leukemia

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Since 1845, when the term leukemia was used for the first time by Virchow, advances in biochemistry, cytogenetics, cytochemistry, immunology, and subsequently molecular biology have led to the identification of different subtypes of acute myeloid leukemia (AML). Especially during the last couple of years, the almost exponentially growing understanding of the hematopoietic system has revealed that AML demonstrates extraordinary morphological, biological, and clinical heterogeneity. Therefore, clinically relevant classification systems that reflect the underlying tumor biology are needed. In an attempt to define a biologically and clinically useful working nomenclature, the current World Health Organization (WHO) classification of myeloid neoplasms incorporated those disease characteristics that have proven to possess clinical and biological relevance.[1] This effort resulted in a more sophisticated classification that divides AML into four large subclasses, which can be further subdivided into several distinct AML subtypes (Table 1). Nevertheless, for many myeloid leukemia subtypes no specific genetic or pathogenic event has been discovered yet, and within well-defined AML subgroups such as cases with t(8;21)(q22;q22) or inv(16)(p13q22) considerable clinical heterogeneity is observed.[2] Thus, additional subtypes may exist even within the same cytogenetic category, thereby highlighting the need to further refine the current classification of AML.

AML cytogenetics and molecular genetics

Cytogenetics currently represents the most powerful prognostic factor for assigning AML patients into risk-groups at diagnosis. However, novel molecular markers allow AML subclasses to be further dissected at the molecular level. For example in the large group of AML patients presenting with a normal karyotype internal tandem duplications (ITD) of the *FLT3* gene, partial tandem duplications (PTD) of the *MLL* gene, as well as mutations of *CEBPA* and *NPM1* have been shown to be of prognostic relevance, as have the expression levels of *EVI1* and *BAALC*.[3,4] Nevertheless, there is still no commonly accepted risk stratification for this group of leukemia patients, nor are the leukemogenic mechanisms fully understood yet.

Advances in molecular genetics have provided several lines of evidence that strongly suggest a multistep pathogenesis of AML. While the expression of a single fusion gene protein, e.g. RUNX1-CBFA2T1 resulting from a t(8;21), can block myeloid differentiation without causing leukemia, other events, such as constitutively activated FLT3 or RAS family members, can induce a myeloproliferative phenotype. Thus a combination of differentiation-blocking and proliferation-inducing mechanisms might be involved in leukemogenesis.[3]

Gene expression profiling in leukemias

Genomic studies now offer the possibility of capturing the molecular variation underlying the biological and clinical heterogeneity of AML, with DNA microarray based genome-wide gene expression profiling (GEP) representing one of the most powerful experimental approaches. Notably, the utility and promise of this novel technology was first demonstrated in leukemias. By analyzing AML and acute lymphoblastic leukemia (ALL) samples Golub *et al*. demonstrated the potential usefulness of GEP-based classification of leukemias.[5] Using an unsupervised class discovery procedure the authors were able to distinguish AML and ALL without previous knowledge of these classes, and by developing a supervised class predictor, new leukemia cases could be accurately assigned to one of these two leukemia classes. Unexpectedly, many of the genes characterizing the different leukemia subtypes were not markers of hematopoietic lineage, but genes related to cancer pathogenesis.[5] Thus, gene expression patterns that are useful for cancer classification can also provide further insight into cancer biology.

Gene expression patterns associated with genomic aberrations in AML

Trisomy 8 was one of the first recurrent cytogenetic aberrations in AML to be investigated by GEP. Compared to AML cases with normal cytogenetics, trisomy 8 cases are characterized by higher average expression of genes located on chromosome 8.[6] Similar gene dosage effects have been reported for other chromosomal gains and losses in AML.[7,8] Moreover, supervised analytical approaches also proved to be useful for discriminating characteristic gene expression patterns in AML cases with balanced chromosomal rearrangements, such as cases with inv(16), t(8;21), t(15;17) and t(11q23)/MLL.[9-14] Similarly, with the aid of supervised statistical algorithms characteristic gene expression patterns have been defined for *FLT3* ITD,[9,14-17] *CEBPA*,[14] and *NPM1* mutations.[18,19] However, in contrast to translocations involving the *MLL* gene, in larger studies no significant gene expression signature was detected for cases with *MLL* PTD[9,12] reflecting the molecular heterogeneity of *MLL* PTD cases and their clear distinction from AML with t(11q23). Likewise, AML cases with NRAS mutations did not display an apparent gene expression signature.[16] Thus, not all molecular genetic alterations necessarily have to affect gene expression levels in a characteristic way. A possi-

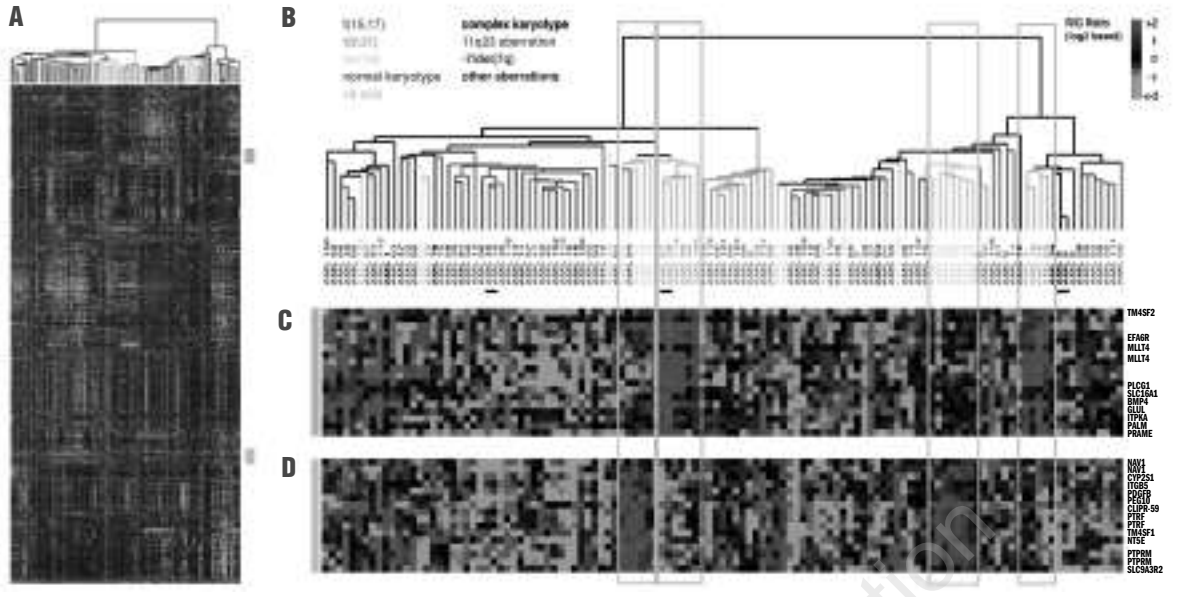

Figure 1. **Hierarchical cluster analysis of diagnostic AML samples. A. Thumbnail overview of two-way hierarchical cluster of 119 AML samples (columns) and 6,283 variably-expressed genes (rows). Mean-centered gene expression ratios are depicted by a $\log_2$ pseudocolor scale (indicated). Gray denotes poorly-measured data. B. Enlarged view of the sample dendrogram. Samples are color-coded according to prognostically-relevant cytogenetic groups, based on conventional chromosome banding and fluorescent *in situ* hybridization analysis (color key indicated). Three paired samples of peripheral blood and bone marrow are indicated by horizontal black bars. C and D. Gene expression *features* extracted from clusters correlating with t(8;21) and inv(16), respectively (locations indicated by vertical colored bars). Due to space limitations, only named genes (and not EST) are indicated (*modified with permission from Büllinger et al.,*[9] *Copyright 2004, Massachusetts Medical Society*).**

ble explanation might be that additional events in *MLL* PTD or *NRAS* mutated cases result in various different pathomechanisms.

GEP-based prediction of AML subtypes - a powerful tool for AML classification

Importantly, the distinct gene signatures associated with cytogenetic and molecular genetic aberrations can also be used to accurately predict the respective leukemia subgroups.[12,19,20] Furthermore, classifiers generated from pediatric AML samples accurately stratified adult leukemia cases exhibiting the same genetic aberrations,[12] thereby indicating age-independent aberration-specific pathomechanisms. Moreover, these diagnostic signatures seem to be quite robust with regard to technical aspects of specimen sampling and target preparation.[21]

Therefore, in the future gene expression profiling might offer a global, highly accurate approach for the diagnosis of known leukemia subgroups, especially for those associated with recurrent genetic aberrations (*see also Table 1*), and indeed first efforts towards this goal are very promising.[20,22] In addition, this approach will most likely significantly contribute to a refined classification of AML, as problems in predicting certain leukemia subgroups might be indicative that the current classification system does not fully reflect the underlying biology and that novel tumor classes remain to be discovered.

Table 1. **WHO classification of acute myeloid leukemia.**

Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22), (*AML1/ETO*)
AML with inv(16)(p13q22) or t(16;16)(p13;q22), (*CBFβ/MYH11*)
AML with t(15;17)(q22;q12), (*PML/RARα*) and variants
AML with 11q23 (*MLL*) abnormalities

Acute myeloid leukemia with multilineage dysplasia
With prior myelodysplastic syndrome
Without prior myelodysplastic syndrome

Acute myeloid leukemia and myelodysplastic syndromes, therapy related
Alkylating agent/radiation-related
Topoisomerase II inhibitor-related type
Others

Acute myeloid leukemia, not otherwise categorized
AML, minimally differentiated
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic and monocytic leukemia
Acute erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma

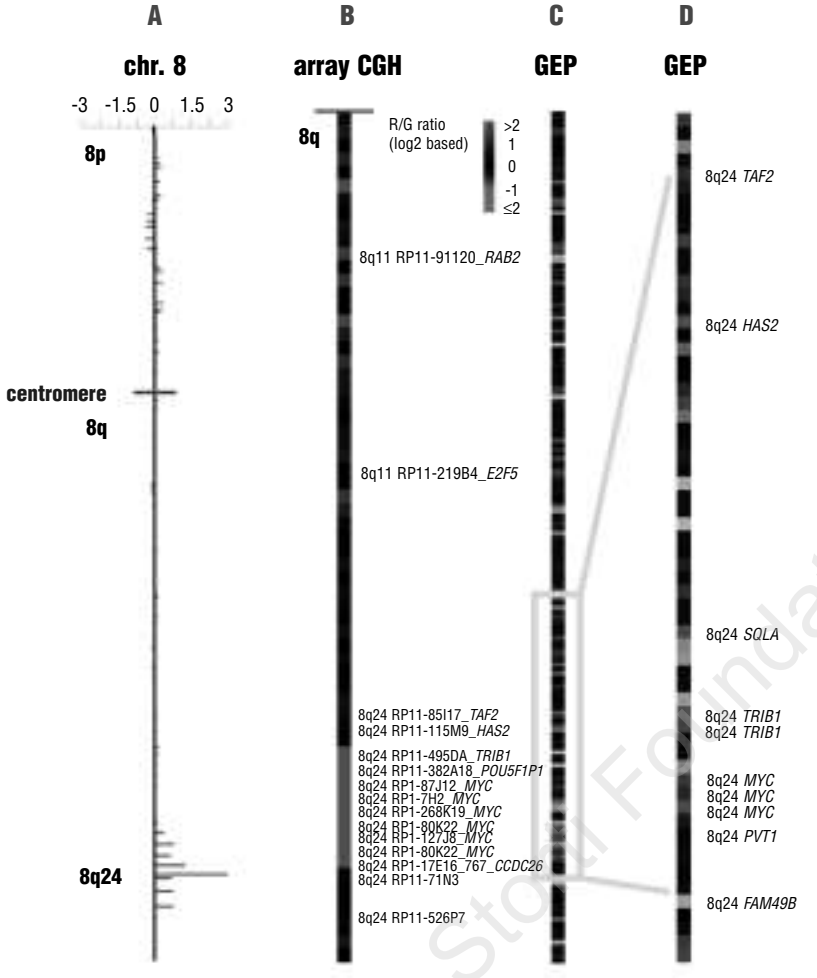

Figure 2. 8q24 amplification in HL-60.[40] A. Enlarged view of the HL-60 cell line array comparative genome hybridization (CGH) profile of chromosome 8 encompassing a high-level DNA amplification in band 8q24. The amplified clones are colored in red. B-D. Correlation of array CGH (b) and GEP (C and D) findings identifies overexpressed candidate genes located in the amplified region. Genomic gains and gene expression levels are color-coded according to the indicated pseudocolor scale.

Discovery of novel molecularly defined AML subclasses

Besides providing novel biological insights, unsupervised cluster analysis also represents a powerful tool for the discovery of novel AML subgroups of clinical relevance. In a large study based on unsupervised analysis samples from 285 patients with AML were grouped into sixteen clusters.[14] Some clusters were characterized by high frequencies of certain molecular lesions or mutations, for example two clusters (#1 and #16) which both harbored cases with t(11q23)/MLL abnormalities, but also included patients without these molecular lesions. Furthermore, this study identified a distinctive gene expression pattern associated with increased *EVI1* expression and poor treatment outcome. Another cluster associated with shorter survival included cases with high risk cytogenetic markers, such as monosomies 7 and 5, and the translocation t(9;22). Interestingly, this cluster displayed a signature comparable to that of $CD34^+$ cells, thereby suggesting a possible common mechanism for resistance to therapy.[14] While favorable cytogenetic subgroups were characterized by homogenous clustering, Valk *et al.* also observed a molecular variation within these *homogenously grouped* cases.[14] For example in cases with inv(16) or t(8;21) clustering was less stringent when more than 2,856 probe sets were included into the unsupervised analysis. In agreement with Valk *et al.*, based on unsupervised clustering using 6,283 genes we also detected some molecular heterogeneity within the cytogenetically well-characterized core binding factor leukemias, with each class, t(8;21) and inv(16), being separated into mainly two groups (Figure 1).[9] Distinct patterns of gene expression within each of these t(8;21) and inv(16) subgroups might reflect alternative co-operating mutations/deregulated pathways leading to transformation, since the primary translocation/inversion events themselves are not sufficient for leukemogenesis.[23]

In our study, cases with normal karyotype also segregated mainly into two distinct groups, each of which included a small number of cases from other classes.[9] *FLT3* aberrations were more prevalent in one subgroup, while M4/M5 morphologic subtypes defined according to French-American-British (FAB) criteria, were significantly more represented in the other subgroup. In agreement with these results, Valk *et al.* also identified normal karyotype-predominated clusters associated with *FLT3* ITD, as well as a cluster including mainly specimens from patients with AML of FAB M4 or M5 subtype.[14] Notably, in our study Kaplan-Meier analysis identified a statistically significant difference in overall survival between the two subclasses.[9]

Monitoring drug effects - drug discovery in AML

Analyzing the effects of all-trans retinoic acid (ATRA) in acute promyelocytic leukemia (APL)-derived cell lines, such as NB4 cells, showed that ATRA-regulated genes included members of the tumor necrosis factor (TNF) pathway suggesting that this pathway might intersect with ATRA signaling.[24,25] Indeed, the ATRA and TNF interaction involved increased NF-κB activity followed by a synergistic induction of NF-κB target genes.[25] This supports the idea that ATRA primes cells to be more susceptible to differentiation effects of other pathways. In addition, many promoters of ATRA target genes contain NF-kB binding sites, providing further evidence that this pathway might play a role in regulating cell survival in response to ATRA.[26]

Besides monitoring drug effects, GEP has also proven to be a powerful means for discovering both novel drug targets as well as novel drugs. For example gene expression-based high-throughput screening approaches can be used to screen for chemical compounds with differentiation-inducing activity in AML.[27] A microarray-based five-gene differentiation signature formed the cornerstone for a high throughput screening method using multiplexed reverse transcriptase polymerase chain reaction, single base extension reaction and MALDI-TOF (matrix-assisted laser desorption/ionization time-of flight) mass spectrometry. In HL-60 cells treatment with 1,739 different compounds revealed eight chemicals that reliably induced this differentiation signature. These drugs included DAPH1 (4,5-dianilinophthalimide), a compound with epidermal growth factor receptor (EGFR) kinase inhibiting activity. Therefore, the authors hypothesized in a subsequent study that the Food and Drug Administration (FDA)-approved EGFR inhibitor gefitinib might also promote differentiation in AML.[28] In accordance with this hypothesis, treatment of AML cell lines and primary patient-derived AML blasts *in vitro* with gefitinib promoted cellular differentiation even in the absence of EGFR expression suggesting an EGFR-independent mechanism of gefitinib-induced differentiation.[28]

Prognostic signatures in AML

As already mentioned, GEP allows the identification and prediction of specific signatures correlated with *low-risk* and *high-risk* cytogenetics, as well as with prognostically relevant molecular genetic aberrations.[9,14,20] However, supervised approaches have also been used to identify novel gene signatures predictive, for example, of response to chemotherapy. Although not statistically significant, an early attempt to explore candidate genes with potential biological significance overexpressed in AML patients in whom treatment failed included *HOXA9*.[5] *HOXA9*, a gene known to be frequently activated in AML,[29] has recently been associated with *NPM1* mutations,[18] which have been shown to be of prognostic relevance.[19,30] Recently, Heuser and colleagues also made an attempt to identify a characteristic gene expression profile distinguishing AML samples from patients with good or poor response to induction chemotherapy.[31] Based on supervised data analysis, the authors successfully characterized a gene expression pattern associated with induction chemotherapy resistance. Importantly, this signature provided significant prognostic information in a previously published independent set of AML patients,[9] and in multivariate analysis this treatment-response signature proved to be an independent prognostic factor.[31]

However, other supervised approaches looking for signatures correlated with AML outcome have been less successful as in acute leukemia survival or survival time represent noisy surrogates for the underlying prognostically relevant tumor subclasses. For example, a *prognostic signature* generated in childhood AML by comparing patients with *good* and *poor* outcome,[32] did not allow a significant risk stratification when the respective gene expression pattern was applied to an independent data set.[12]

Semi-supervised outcome prediction approaches

To discover novel prognostically relevant and biologically meaningful subclasses in AML, a strategy combining the strengths of both supervised and unsupervised approaches has been shown to provide a better means for outcome prediction.[33] Using such a *semi-supervised method* called supervised clustering, we were able to devise an outcome class predictor in AML that was an independent prognostic factor in multivariate proportional hazards analysis.[9] Importantly, this predictive gene expression signature also defined good and poor outcome classes when applied to AML samples with normal karyotype only, and this result has recently been validated by an independent study group analyzing 68 AML cases with normal karyotype.[34] On the other hand, as in the study by Heuser *et al,*.[31] our AML data also served as an independent test set for a prognostic signature defined in prostate cancer that displays a stem cell-like expression profile.[35] This signature possessed prognostic power in independent samples obtained from 1,153 cancer patients diagnosed with 11 different types of cancer including AML. Thus, several prognostic signatures might be found in gene expression data sets, thereby clearly demonstrating the importance of making data sets publicly available, as ongoing data mining of existing data sets will significantly contribute to our better understanding of leukemogenesis.

Future challenges in AML: integration of GEP and whole genome approaches

Hematologic malignancies have been an attractive field for genomic approaches such as DNA microarray technology,[36,37] and GEP has contributed an important new facet to the exploration of AML.[38] Nevertheless, while the above-mentioned findings are definitely encouraging, further validation of these observations in larger cohorts and in independent studies is clearly required before clinical implementation becomes feasible in AML. However, this requires that large sets of expression profiles are collected and that cross-platform classification and validation are introduced. First

analyses have already demonstrated the feasibility of such approaches, but in order to make cross-platform classification a powerful, diagnostically accurate tool, standardized statistical methods are needed. By testing several data normalization algorithms Nilsson and colleagues clearly demonstrated that cautious data processing represents an effective way to overcome microarray platform differences.[39] Using a normalization method based on *relative ranks with unit variance*, the authors were able to show that cross-platform classification is feasible with high consistency and reproducibility in both childhood ALL and adult AML data sets. As increasing numbers of well-annotated gene expression data sets have recently become publicly available, this powerful approach will contribute significantly to a successful exploration and comparison of existing data sets, thereby providing the prerequisite for the future contribution of GEP towards a comprehensive molecular leukemia classification and improved risk-adapted AML management.

An additional challenge for the future will be the integration of DNA microarray technology and other whole genome approaches to validate the numerous biological hypotheses generated by GEP in AML. Integrative analyses evaluating the AML transcriptome in the context of other data sources derived, for example from comparative genome hybridization arrays (Figure 2), single nucleotide polymorphism arrays, tiling arrays, promoter arrays, and proteomics, will provide new insights into leukemogenesis. However, for a successful integration, a common language for communicating genomic profiles across diverse experimental systems will have to be defined, and integrative bioinformatics solutions for sharing and analyzing the data will have to be developed.

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