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ANALÝZA KOMPLEXNÍCH ZMĚN KARYOTYPU V NÁDOROVÝCH BUŇKÁCH A JEJICH VÝZNAM PRO PATOGENEZI A PROGNÓZU MALIGNÍCH ONEMOCNĚNÍ

ANALYSIS OF COMPLEX CHROMOSOMAL REARRANGEMENTS IN TUMOR CELLS AND THEIR IMPACT ON PATHOGENESIS AND PROGNOSIS OF MALIGNANT DISEASES

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ANALYSIS OF COMPLEX CHROMOSOMAL REARRANGEMENTS IN TUMOR CELLS AND THEIR IMPACT ON PATHOGENESIS AND PROGNOSIS OF MALIGNANT DISEASES

PhD thesis summary

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Souhrn

Analýza genomu nádorových buněk cytogenetickými a molekulárně cytogenetickými metodami je nedílnou součástí vyšetření nemocných s nádorovým onemocněním. Cytogenetické nálezy napomáhají nejen ke stanovení nebo upřesnění diagnózy, prognózy a monitorování úspěšnosti terapie, ale hrají také nezastupitelnou roli při objasňování příčin maligní transformace buněk. Pro většinu nádorových onemocnění je v současné době známa celá řada specifických chromosomových aberací, které jsou charakteristické pro určitý subtyp nádorového onemocnění s odpovídající prognózou. V maligních buňkách však také dochází ke vzniku celé řady dalších genetických aberací, které se mohou vyskytovat u různých nádorů. Pro nádorové buňky jsou tyto náhodné numerické a strukturní změny typické a odrážejí jejich celkovou genomovou nestabilitu. Na chromosomové úrovni se velká míra nestability genomu nádorových buněk obvykle projevuje vznikem komplexních změn karyotypu.

Analyzovali jsme komplexní přestavby karyotypu moderními molekulárně cytogenetickými metodami (I-FISH, mFISH, mBAND, CGH, arrayCGH, SNP array) u vybraných hematologických malignit a difúzních gliomů. Detailně jsme popsali jednotlivé chromosomové aberace a vytipovali jsme chromosomy a chromosomové oblasti, které jsou u konkrétních onemocnění do těchto přestaveb zahrnuty nejčastěji. Určili jsme rekurentní zlomová místa na chromosomech a poukázali tak na oblasti s možnou důležitou rolí v počátečních i pokročilých stádiích kancerogeneze u daných onemocnění. Z klinického hlediska jsme prokázali, že komplexní změny karyotypu v době diagnózy u různých malignit jsou velmi špatným prognostickým ukazatelem. Nález komplexního karyotypu vedl u nemocných ke špatné odpovědi na léčbu, častým relapsům a krátké době přežití. Potvrdili jsme negativní vliv komplexních změn na prognózu i u těch pacientů, u kterých se v karyotypu vyskytovala prognosticky příznivá chromosomová aberace.

Prokázali jsme nesporný význam cytogenetického vyšetření nejen pro prognózu nemocných s nádorovým onemocněním, ale i pro studium maligní transformace buněk. Především stálý rozvoj molekulárně cytogenetických metod umožňuje detailnější analýzu genomu nádorových buněk a vymezení relativně malých oblastí s nesporným významem v patogenezi maligních onemocnění. Cytogenetická analýza nádorových buněk je tak základním krokem pro identifikaci genů a objasnění konkrétních patogenetických mechanismů, které mohou být dále využívány při vývoji nových léčebných intervencí.

Disertační práce je tvořena stručným úvodem shrnujícím současné poznatky o nestabilitě genomu nádorových buněk na chromosomové úrovni a souborem publikovaných prací opatřených komentářem k vlastním výsledkům.

Summary

Cytogenetic abnormalities are characteristic attribute of cancer cells. To date, clonal chromosomal aberrations have been found in majority of tumors and they represent important part of management of patients with malignant diseases. Specific chromosomal abnormalities are detected in almost all hematological malignancies and certain types of solid tumors and most of them are associated with known clinical significance in relation to diagnosis and prognosis. Many are also of special interest because of the insights they have provided into the molecular mechanisms of tumor pathogenesis. Beside specific chromosomal aberrations other random genetic abnormalities can be detected in various tumors. These abnormalities may be numerical or structural, with many karyotypes containing both types of change. Random numerical and structural aberrations are typical for tumor cells and they represent genome instability of these cells. At the chromosomal level, high genome instability of cancer cells usually lead to creation of complex chromosomal rearrangements (CCR).

Using modern molecular cytogenetic methods (I-FISH, mFISH, mBAND, CGH, aCGH, SNP array) we performed precise analysis of complex chromosomal rearrangements in patients with various hematological malignancies and difuse gliomas. We described particular aberrations in detail and found chromosomes and chromosomal parts which were involved in CCR most frequently. We determined recurrent chromosomal breakpoints and pointed out to regions with important role in initiation and progression of the disease. From the clinical point of view, we proved that complex chromosomal aberrations found at the time of diagnosis are poor prognostic factor. In our cohorts of patients, complex chromosomal rearrangements were associated with resistance to treatment, higher occurrence of relapses and shorter overall survival. In addition, we showed negative prognostic impact of CCR even in patients with primarily favorable prognostic chromosomal aberration in karyotype.

Results of our study proved indisputable significance of molecular cytogenetic analysis not only for diagnosis and prognosis of patients with hematological diseases and solid tumors but also for understanding of malignant transformation of the cell. Technical possibilities to detect genomic rearrangements in neoplasms have increased tremendously in recent years. They enable to delineate small regions in cancer genome (far beyond the detection limit of banding techniques) with significant implication in tumor pathogenesis. Consequently, cytogenetic and molecular cytogenetic analysis is the fundamental step for identification of genes and novel pathogenetic mechanisms which can serve as targets for development of new therapeutic intervention.

The PhD thesis is composed of short introduction concerning the genome instability at chromosomal level and the set of publications accompanied by a brief comment.

Introduction

Genome instability of cancer cells at chromosomal level

The function of mitotic chromosomes is to faithfully transfer genetic material and information during the cell division (Ye et al. 2007). To ensure the genome stability during this complex process, many repair and checkpoint mechanisms have been developed during the course of evolution (Foijer and te Reile 2006). However, frequently occurring aberrations can incidentally survive, some of which could lead to malignant diseases.

Genome instability of cancer cells and related chromosomal abnormalities has been studied for almost 100 years. Acquired chromosome abnormalities were first suggested to be causal factors in the origin of cancer by Boveri (Boveri 1914). Consequently, it was proved that cancer cells may encompass several acquired genetic aberrations. These include substitutions of one base by another; insertions or deletions of small or large segments of DNA; rearrangements, in which DNA has been broken and then rejoined to a DNA segment from elsewhere in the genome; copy number increases from the two copies present in the normal diploid genome, sometimes to several hundred copies (known as gene amplification); and copy number reductions that may result in complete absence of a DNA sequence from the cancer genome (Stratton et al. 2009).

The cancer genome also have acquired epigenetic changes, such as DNA methylation or histone acetylation, which alter chromatin structure and gene expression, and which can be, in some cases, responsible for malignant transformation of the cell (Kanwal and Gupta 2010, Mitsiades and Anderson 2009, Tuna et al. 2009). In addition, the cancer cells may have acquired, from exogenous sources, completely new DNA sequences, notably those of viruses such as HPV E6, EBV, Hep B, HHV8, HTLV-1, each of which is known to contribute to the genesis of one or more type of cancer (Nicholas et al. 2008).

At the chromosomal level, the degree of genome instability is demonstrated by creation of numerical or structural chromosomal abnormalities which can be studied by several cytogenetic methods. Numerical aberrations originate as a result of defects in chromosomal segregation during the mitosis. Recent studies have shown that several factors can result in segregation defects, including abnormal kinetochore–spindle interactions, premature chromatid separation, centrosome amplification, multipolar spindles, and abnormal cytokinesis (Gollin 2005). Structural aberrations are usually generated by increased formation of DNA breaks due to failure of cell cycle checkpoints and DNA damage response or

telomere dysfunction. However, exact mechanisms that result in such chromosome rearrangement in cancer cells are still largely unknown (Zhang and Rowley 2006).

Chromosomal aberrations lead to dysregulation of many genes at molecular level. Nevertheless, there are two main classes of cancer-relevant genes, the oncogenes and the tumor suppressor genes, that have been recognized as main pathogenic targets for cancer-associated karyotypic abnormalities.

Balanced chromosomal rearrangements, intrachromosomal (translocations and insertions) either as intrachromosomal (inversions), lead to activation of oncogenes by two alternative mechanisms: overexpression of a gene in one of the breakpoints or the creation of a hybrid gene through the fusion of two genes, one in each breakpoint. It was shown that recurrent balanced aberrations, in particular translocations, are strongly associated with distinct tumor entities and there is substantial evidence that these alterations are early or even initiating events in tumorigenesis (Mitelman et al. 2007).

Oncogenes may be activated also by chromosomal gains including complete or partial duplication of certain chromosome. Generally, a simple dose effect could be the mechanism whereby the external DNA is influential by adding one or more active oncogene alleles (Heim and Mitelman 2009). Amplification of particular oncogenes (e.g. *EGFR, MYC, RAS, MLL*) is common finding in cancer cells. Cytogenetically, this amplification is manifested as homogeneously staining regions (HSR) and double-minute chromosomes (dmin), respectively.

Genomic losses are represented by deletions, unbalanced translocations, or loss of entire chromosome. Such changes lead to loss of heterozygosity which is usually accompanied by loss of one or several tumor suppressor genes (e.g. *RB1, TP53, p16, APC*). However, there are now some examples of fusion genes that have been produced by juxtaposition of parts of two genes delineating, most often, cryptic deletion (*STIL/TAL1, FIPL1/PDGFRA*) (Heim and Mitelman 2009). For many recurrent genomic losses the critical genes are still unknown. In these cases, hemizygous deletions could cause the disease by allelic insufficiency for one or more genes (Fodde and Smits 2002) as it was already shown in some myeloid (Joslin et al. 2007, Ebert et al. 2008) as well as lymphoid hematologic malignancies (Mullighan et al. 2007).

It is commonly accepted that malignancies are initiated, for the most part, by genetic and/or epigenetic alterations of protein-coding oncogenes and tumor suppressor genes (Croce 2008). Exact identification of these molecular mechanisms have led (in some tumors) to development of novel targeted therapies that are based on specific genetic aberrations which are involved in disease pathogenesis. For example, in chronic myeloid leukemia (CML) the

discovery of t(9;22)(q34;q11) and the understanding of its molecular basis (i.e. *BCR/ABL* fusion gene with dysregulated tyrosine kinase activity) has resulted in development of tyrosine kinase inhibitor called Imatinib (Glivec, Novartis), which revolutionized treatment in patients with CML. The fact that epigenetic changes are also prevalent in cancers and play a causative role in their biologies has led to the development of therapeutic approaches in which the goal is to reverse gene silencing (Jones and Bailin 2007), e.g. reactivation of genes scilenced by DNA methylation or histon deacetylase inhibitors (Bots and Johnstone 2007).

Precise analyses of, in particular, recurrent chromosomal abnormalities have resulted in identification of more than 400 protein-coding genes with a fundamental role in tumorigenesis (Stratton et al. 2009, Cancer Genome Project: www.sanger.ac.uk/genetics/CGP/Census/). However, recently it was shown that chromosomal aberrations may lead to inactivation of genes that do not encode proteins. For example, several genomic regions that are recurrently deleted in a variety of tumors contain microRNA (miRNA) genes. These genes encode small RNAs involved in posttranscriptional regulation of gene expression, and there is growing evidence that the loss of specific miRNA contribute to tumorigenesis (Fröhling and Döhner 2008). This mechanism was for instance shown in patients with chronic lymphocytic leukemia (CLL) and deletion of miR-15a and miR16-1 at 13q14 locus (Calin and Croce 2006). In addition, alterations of miRNA genes can be caused not only by deletions but also by other mechanisms such as amplifications or mutations involving miRNA loci, epigenetic scilencing or the dysregulation of transcription factors that target specific miRNAs (Croce 2009).

Each chromosome abnormality (including its molecular impact) can be found in cancer cells either solely or in combination with others. High level of genome instability of cancer cells is usually characterized by the presence of several random numerical as well as structural aberrations, i.e. complex chromosomal rearrangements (CCR). Traditionally, CCR are defined as those involving more than three chromosomes and/or more than three breakpoints (Schoch et al. 2001).

Complex chromosomal rearrangements can be analyzed by various cytogenetic methods including conventional cytogenetic analysis and molecular cytogenetic techniques based particularly on fluorescence in situ hybridization (FISH). Applications for whole-genome analysis such as multicolor FISH (mFISH), comparative genomic hybridization (CGH) or multicolor banding (mBAND) are mostly used for resolving complex rearrangements. Currently, arrays technologies (i.e. arrayCGH, SNP array) are available for efficient detection of gains and losses of genome sequences and allelic imbalances.

Complex karyotypes are found in hematological malignancies as well as solid tumors. They can originate either as secondary aberrations after previous treatment or can be detected at the time of diagnosis. In this case, they are obviously not treatment related and they arise during the malignant transformation of the cell. Although the exact mechanisms that are leading to CCR are still unknown, some authors proved direct correlation of complex karyotypes and poor prognosis, resistance to antileukemic treatment or shorter overall survival (Alvarez and Cigudosa 2005, Zemanova et al. 2006a, Babicka et al. 2007). Therefore, current World health organization (WHO) classification of tumors of haematopoietic and lymphoid tissues includes CCR as a part of prognostic criterion in some diseases (Swerdlow a et al. 2008). However, in most malignancies precise significance of complex chromosomal rearrangements has not been evaluated yet.

In addition, exact assessment of complex rearrangements (besides the prognostic impact) increases our knowledge about malignant transformation of the cell. Precise analysis of particularly recurrent chromosomal breakpoints included in CCR could lead to detection of novel pathogenetic mechanisms with important role in initiation and progression of the disease. Consequently, genes involved in these mechanisms can serve as targets for development of new therapeutic strategies.

We performed cytogenetic and molecular cytogenetic analysis of complex chromosomal rearrangements in selected hematological malignancies and difuse gliomas in purpose to determine chromosomes, chromosomal parts and breakpoints involved in complex rearrangements and to estimate the impact of CCR on prognosis.

Aims of the study

Hematological malignancies

1. **Analysis of complex chromosomal rearrangements**
   - **1.1. Chronic myeloid leukemia (CML)**
   - **1.2. Myelodysplastic syndromes (MDS)**
   - **1.3. Acute myeloid leukemia (AML)**

Cytogenetic and molecular cytogenetic analysis of complex chromosomal rearrangements in bone marrow cells of adult patients with selected hematological malignancies; detection of recurrent chromosomal aberrations; estimation of chromosomal parts and breakpoints frequently involved in complex rearrangements; evaluation of the significance of complex chromosomal rearrangements for the course of the disease and patients prognosis.

2. **Analysis of complex chromosomal rearrangements in patients with prognostically favorable chromosomal aberration in karyotype**
   - **2.1. Acute lymphoblastic leukemia (ALL)**

Cytogenetic and molecular cytogenetic analysis of complex chromosomal rearrangements in bone marrow cells of pediatric patients with ALL and prognostically favorable aberration t(12;21)(p13;q22); evaluation of the significance of complex chromosomal rearrangements for the course of the disease and patients outcome.

Difuse gliomas

3. **Analysis of additional chromosomal aberrations in patients with favourable chromosomal aberration**
   - **3.1. Difuse gliomas**

Implementation of molecular cytogenetic analysis for detection of recurrent chromosomal aberrations in patients with various subtypes of difuse gliomas; evaluation of the significance of additional chromosomal aberrations in patients with prognostically favorable combined deletion 1p/19q in patients with oligodendroglial tumors.

Summary of results from published papers

1. Analysis of complex chromosomal rearrangements

1.1 Chronic myeloid leukemia (CML)

Chronic myeloid leukemia is a clonal myeloproliferative disorder of the hematopoetic stem cell and is consistently associated with the *BCR/ABL* fusion gene. (Vardiman et al. 2008, Melo et al. 2007). CML represents 15-20% of leukemias in adults (Hochhaus et al. 2002) and usually occurs in the 5th and 6th decades of life. From the clinical point of view, the disease is characterized by an initial relatively benign chronic phase (CP), followed by an accelerated phase (AP) and finally aggressive blast crisis (BC).

Genetically, CML is characterized by the presence of the Ph chromosome, resulting from the t(9;22)(q34;q11), seen in 90-95% of patients. In remaining cases either masked or variant Ph translocation is detected (ZhaoY 2009). Masked Ph chromosome can be found in cases with a normal karyotype, as a result of cryptic rearrangement, or in patients with complex changes where the typical t(9;22)(q34;q11) is not detectable by G-banding (La Starza et al. 2002). Variant Ph translocations are those involving chromosomes 9, 22 and one or more other chromosomes (Naumann and Decker 2003). The common molecular event underlying classical, masked and variant Ph translocations, is production of the *BCR/ABL* fusion gene. This chimeric gene is located on the Ph chromosome or, less frequently, on one of the other chromosomes participating in the translocation (Morel et al. 2003).

In most instances, t(9;22)(q34;q11) is the single chromosomal abnormality during chronic phase of the disease, whereas additional genetic changes are demonstrable in 60-80% of cases during progression to AP/BC. These secondary chromosomal aberrations are clearly non-random, with the most common abnormalities being +8 (34%), +Ph (30%), i(17)(q) (20%), +19 (13%), -Y (8% of males), +21 (7%), +17 (5%) and –7 (5%) (Johansson et al. 2002). Complex chromosomal rearrangements are rather rare in CML and their role in pathogenesis of CML is still poorly understood. It seems they represent random aberrations as a result of the genome instability.

The aim of this study was a comprehensive analysis of complex chromosomal rearrangements found in bone marrow cells of at first 18 (**Babicka** et al. 2006a) and finally in 22 patients (**Babicka** et al. 2006b) with CML by molecular cytogenetic methods,

determination of chromosomes and chromosomal parts which are involved in CCR during progression of the disease and estimation of frequency of non-random changes if they exist.

During the years 2000-2006 we examined bone marrow samples of more than 250 patients with chronic myeloid leukemia. Using G-banding we found complex chromosomal rearrangements in 22 of them (11 males and 11 females). In all of them *BCR/ABL* fusion gene was confirmed by interphase FISH and/or RT-PCR. Variant Ph translocation (involving chromosomes 9, 22 and one or more other chromosomes) was found in ten patients, the rest of the cohort had a classical Ph translocation associated with additional structural aberrations. Most of the patients were in the CP at diagnosis. At the time of data evaluation, 11 patients progressed from CP to AP or BC and 12 patients died.

We detected a common genesis of variant translocation, i.e. translocation of part of chromosome 9q34→9qter on chromosome 22 at 22q11 region, translocation 22q11→22qter on the third chromosome and translocation of part of the third chromosome to 9q34 region in most of the patients. We determined more complex type of variant translocation in other three patients. In one patient we proved *BCR/ABL* fusion on chromosome 9.

In patients with classical Ph translocation we found various numerical and structural rearrangements. No one of complex translocation was seen more than once. We expected the presence of isochromosome i(17q) in two patients according the results of conventional cytogenetic analyses. However, mFISH method proved that derivative chromosome 17 consisted of the part of chromosome 3 and 19, respectively, which were translocated on chromosome 17. This finding confirms the imperfections of conventional cytogenetic analyses due to sometimes poor quality of analyzed mitoses and strongly suggests to do in every case the verification of i(17)(q) by FISH.

We did not detect any rearrangement occurring repeatedly in our cohort of 22 patients. Although a small group of patients, we determined chromosomes, chromosomal regions and breakpoints that were involved in structural rearrangements more often than others. The most frequent chromosomes involved into complex chromosomal rearrangements were found to be Nos. 2 (6x), 7 and 17 (5x), 1, 3, 4 and 5 (4x). Chromosomal regions 1p, 2p, 5q, 7p and 17p were often involved in complex aberrations and the breakpoints repeatedly affected were 17p11.2 (3x) and 7p15 (2x).

The results of this study demonstrate the very high instability of the genome of malignant cells at the chromosomal level than was expected on the basis of classical cytogenetic analyses. We determined chromosomal parts and breakpoints with possible involvement in tumorigenesis and disease progression. We also proved that CCR are associated with rather poor prognosis and resistance to antileukemic treatment.

1.2 Myelodysplastic syndromes (MDS)

The myelodysplastic syndromes are a heterogeneous group of clonal bone marrow disorders characterized by the presence of dysplastic maturation of hematopoetic cells coupled with one or more peripheral cytopenias and a propensity to progress to an acute myeloid leukemia (Vardiman 2003, Cazzola and Malcovati 2005). The incidence of MDS increases with age and men more than women are affected (Ma et al. 2007). Most cases of MDS occur without any apparent cause (Strom et al. 2008), approximately 10-15% follow treatment (therapy-related MDS; t-MDS) with chemotherapy and radiation for both neoplastic as well as benign disorders (Godley and Larson 2002).

The cytogenetic evaluation of bone marrow cells from patients with MDS has become an integral part of clinical care. Not only does this analysis confirm the diagnosis, it is invaluable in assessing the prognosis, the risk for progression to an acute myeloid leukemia and survival. On a more fundamental level, cytogenetic analysis has been instrumental in establishing the clonality of these syndromes as well as providing hints about their pathobiology (Olney and Le Beau 2009).

Recurrent chromosomal abnormalities are found in approximately 40-70% of patients with primary MDS and in 95% of patients with t-MDS (Haase 2008). More prevalent are unbalanced chromosomal aberrations reflecting a gain or loss of genetic material, whereas balanced rearrangements are rather rare. The most recurrent structural karyotypic abnormality is an interstitial deletion of the long arm of chromosome 5 [del(5q)] occurring in 30% of primary MDS and in 50% of t-MDS cases. Other common cytogenetic abnormalities, which have been incorporated into prognostic scoring system of MDS, are deletion of long arm of chromosome 7 [del(7q)] or monosomy 7 (-7), trisomy 8 (+8), deletion of long arm of chromosome 20 [del(20q)], etc. There are three major risk categories of cytogenetic findings in MDS: (i) good risk - isolated del(5q), isolated del(20q), -Y and normal karyotype (ii) poor risk – complex aberrations, del(7q)/-7 and (iii) intermediate risk – all other abnormalities (Greenberg et al. 1997).

During the years 2007-2009 we prospectively and retrospectively analyzed bone marrow cells from patients with MDS and complex chromosomal aberrations. The aim of the study was to evaluate significance of specific chromosomes and/or chromosomal regions involved in CCA, to establish the exact localization and frequency of chromosomal breakpoints and to assess prognostic relevance of CCR.

Partial results were presented at international meetings (**Zemanova** et al. 2009a, **Zemanova** et al. 2009b, **Zemanova** et al. 2009c), final study included 88 patients with MDS

and complex chromosomal aberrations - 46 men and 42 women. Median age 64,5 years (range 22-83 years), primary MDS was diagnosed in 74 (86.0%) patients and in 12 cases therapy related MDS was ascertained. Only 6 patients are living, all after bone marrow transplantation.

Various modifications of molecular cytogenetic techniques were used for detailed analysis of CCR: FISH, mFISH/mBAND, CGH and/or array CGH. Deletion of 5q31 region was proved in 79 patients as the most common structural aberration. Except the chromosome 5, most often involved chromosomes in CCR were found to be: 7 (59x), 3 (46x), 17 (46x), 12 (44x), 11 (29x) and 21 (26x). The most recurrent breakpoints were at regions: 5q33 (31x), 5q31 (25x), 12p11 (7x), 7p11 (6x) a 7q11 (7x).

In patients with 5q deletion mFISH analyses showed that parts of deleted chromosome 5 were translocated to other chromosomes. Fragmentation of 5q was also frequently found. The most recurrent partners of del(5q) in unbalanced translocations were chromosomes 17 (11x), 3 (7x), 7 (7x) and 12 (6x). Interestingly, no patient with monosomy 5 was identified in this study. Even in patients with suspect monosomy 5 detected by conventional cytogenetics, further detailed molecular cytogenetic analyses revealed parts of chromosome 5 material were retained in means of insertions within CCR.

Presence of CCR at diagnosis was connected with poor response to the therapy and short overall survival (OS). Median of OS in our cohort was 4 months. For detailed survival analysis patients were classified into three groups according to the molecular cytogenetic findings: (1) deleted chromosome 5 involved in CCR- 40 patients (2) deletion of 5q and additional CCR – 39 cases and (3) CCR without deletion 5q – 9 cases. The shortest overall survival was found in group 1 (median 3 months), followed by group 2 (median 4 months) and 3 (median 6 months).

Using combination of molecular cytogenetic techniques we found a wide variety of cryptic aberrations not detectable by conventional cytogenetics. The most frequently affected was chromosome 5, which was very unstable and was often involved in different types of cryptic unbalanced rearrangements (translocation, insertions). We suggest monosomy of chromosome 5, quoted in the literature, does not actually exist in MDS as no patient with this aberration was identified in our cohort. Finding of CCR in our patients with MDS was associated with very poor prognosis in general (median of OS - 4 months). However, patients with del(5q) involved in CCR should be considered as a unique entity as they have extremely poor outcome.

1.3 Acute myeloid leukemia (AML)

Acute myeloid leukemia represents a heterogeneous group of malignant diseases which is characterized by the excessive accumulation of immature myeloid blasts in bone marrow. AML is diagnosed in all age groups, however the incidence rises steeply after the age of 55-60 years (Johanson and Harrison 2009). In some cases, AML resulted from MDS or originated as a secondary disease after previous treatment for other neoplastic disorders (Weinblatt et al. 2004).

Cytogenetic findings in bone marrow cells of patients with acute myeloid leukemia are essential for precise diagnosis and classification of the disease. Karyotype of leukemic cells is one of the important prognostic factors and it was proved by multivariate analyses that it is an independent predictor of therapy response, remission duration and survival (Mrózek et al. 2001).

Acquired cytogenetic aberrations are detected in 55-70% of newly diagnosed patients with AML (Lindvall et al. 2004). Most of karyotypic abnormalities are associated with specific disease subtypes, characteristic morphologic and immunologic profiles and distinct therapeutic and/or prognostic implications. However, approximately 10-15% of AML with abnormal karyotype have no specific aberrations, but do have complex chromosomal rearrangements (Alvarez and Cigudosa 2005). Three major specific aberrations t(8;21)(q22;q22), t(15;17)(q22;q21) and inv(16)(p13q22) found in AML are indicators of good prognosis. Group of patients with normal karyotype, trisomy 8, del(9q), loss of Y in men, trisomy 21 and trisomy 22 and other structural or numerical defects have an intermediate prognosis. Patients with abnormalities of 11q23, inv(3)(q21q26), del(5q), -7/del(7q), t(9;22)(q34;q11) and complex chromosomal rearrangements have very poor prognosis.

In retrospective study we analyzed complex chromosomal rearrangements in 37 patients with AML or MDS RAEBt (MDS RAEBt is classified as AML according to WHO classification) examined in our laboratory during the years 1998-2004 (**Babicka** et al. 2007a). In consequence, we extended our cohort of patients in next two years. Final analysis included 58 patients with AML and MDS RAEBt and complex karyotypes investigated during the years 1998-2006. This group included 32 females and 26 males with an average age 61,2 years, median of overall survival was just 3 months. Only three patients were living at the time of data evaluation, one after bone marrow transplantation, one in partial and one in complete remission, respectively. The majority of structural abnormalities were unbalanced. In 50 patients (86%) loss or rearrangements of chromosome 5, 7 and/or 11 was proved. Deletion of critical region 5q31 was determined in 35 (60,3%) and deletion of 7q31 in 16

(27,5%) patients, respectively. Aberration of MLL gene (11q23) was found in 11 cases (19%). Trisomy of chromosome 8 was the most frequent numerical change (11 patients). Chromosomal parts repeatedly included in CCR were found to be 5q, 7q, 11q, 10p, 12p a 17p, with the most frequent breakpoints 5q33 (20x), 5q13 (12x), 5q12 (8x), 7q11.2 (5x), 10p12 (5x), 11q23 (11x), 12p13 (9x) and 17p11.2 (7x) (**Babicka** et al. 2007b).

As the chromosome 7 is very often rearranged in myeloid malignancies, we analyzed bone marrow cells of 33 patients with AML and MDS and structural aberrations of chromosome 7. Using conventional cytogenetic analysis, we proved deletion of long arm of chromosome 7 (7q) in 8 and translocation of chromosome 7 in 25 patients, respectively. Complex karyotypes were confirmed by mFISH in 29 out of 33 cases. For detection of chromosomal breakpoints and deleted regions commercially available locus specific probes for regions 7q22, 7q31 and 7q35 and mBAND technique were used. Chromosomal breakpoints on chromosome 7 were heterogeneous. Chromosomal regions 7q31 and 7q35 on long arm and segment 7p13.2~ 7p15.2 on short arm were deleted in most cases. Aberrations of chromosome 7 were associated with poor outcome, median of survival time 7 months (**Brezinova** et al. 2007).

Using conventional and molecular cytogenetic methods we also analyzed different types of chromosome 11 duplication/amplification in 10 patients (out of 119) with newly diagnosed AML. The amplification was presented as: amplification including only 5´ segment of the MLL gene - 11q23 (1 patient), trisomy 11 (3 patients), partial trisomy 11q (2 patients), isochromosome 11q (1 patient) and multiple amplification of specific regions (3 patients). In two cases, amplification involved parts of not only long arm but also of short arm of chromosome 11: 11p15 and 11p11-11p13. Duplications/amplifications of 11q were found as a part of complex karyotype in 8 patients and they were nonrandomly associated with aberrations of chromosome 5, 7 and 17. Clinically, patients with 11q amplifications were characterized by older age and a rapid disease progression (**Šárová** et al. 2010).

Our study demonstrates the clinical importance of cytogenetics in adult patients with AML. We proved that complex chromosomal rearrangements are one of the most important prognostic factors, are associated with very poor prognosis and poor response to antileukemic treatment. Precise identifications of these aberrations and delineation of breakpoints in bone marrow cells of patients with AML at the time of diagnosis could lead to a better understanding of genetic events during leukemogenesis as well as quiding further molecular studies of genes involved in evolution of leukemia. We believe that these findings could provide clinically relevant information that can assist in the development of risk-adapted therapeutic strategies.

2. Analysis of complex chromosomal rearrangements in patients with prognostically favorable chromosomal aberration in karyotype

2.1 Acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia is the most common type of hematological malignancy in children, representing 80% of childhood leukemias. The incidence of the disease in Czech Republic is 2,3-3,5 per 100 000 cases and boys are more affected than girls. ALL is characterized by the accumulation of malignant, immature lymphoid cells in the bone marrow and, in most cases, also in peripheral blood. The disease is classified as B- and T-lineage ALL and is derived from immature B-cell precursors (BCP-ALL) in majority of patients (Harrison and Johanson 2009). The primary cause of ALL is unknown, however there is evidence that some childhood acute leukemias originate in utero (Gale et al. 1997, Wiemels et al. 1999, Maia et al. 2003, Zuna et al. 2003, Broadfield et al. 2004).

Clonal chromosomal abnormalities are detected up to almost 90% of children with ALL (Harrison et al. 2005) and most of them are nonrandom with known clinical significance in relation to diagnosis and prognosis. Many are also of special interest because of the insights they have provided into the molecular mechanisms of ALL pathogenesis. The abnormalities may be numerical or structural, with many karyotypes containing both types of change. (Harrison and Johanson 2009). Clinically, the most important are either t(9;22)(q34;q11), structural abnormalities of MLL gene (11q23) and hypodiploidy (23-29 chromosomes) which are considered as poor prognostic factor or translocation t(12;21)(p13;q22) and high hyperdiploidy (>50 chromosomes) which are associated with favorable outcome.

In cooperation with Department of Paediatric Haematology and Oncology of University Hospital Motol, we are involved in examining children with ALL. Bone marrow cells of all patients are analyzed by conventional and molecular cytogenetic methods focusing on prognostically most important aberrations, i.e. hyperdiploidy, hypodiploidy, t(12;21)(p13;q22), t(9;22)(q34;q11) and MLL rearrangements (**Babicka** et al. 2006c).

Cryptic translocation t(12;21)(p13;q22) which give origin to the *TEL/AML1* (also known as *ETV6/RUNX1*) hybrid gene can be found by FISH in approximately 20–25% of children with BCP ALL as the most frequent specific rearrangement (Alvarez et al. 2004). This aberration is not usually seen in infants, and decreases in frequency in older children (Borowitz MJ and Chan 2008). It has been demonstrated that the formation of *TEL/AML1* fusion is a prenatal event. Evidence for this came from the finding of the same *AML1*

oncogenic breakpoint in monozygotic twins who both developed *TEL/AML1* positive ALL at different times, and the finding of the fusion in neonatal blood spots of children who later developed *TEL/AML1* positive ALL (Gale et al. 1997, McHale et al. 2003, Zuna et al. 2004).

Although translocation t(12;21)(p13;q22) is generally associated with good outcome, late relapses may occur within this group of patients (Forestier et al. 2008). One of the reasons could be the high instability of the genome of *TEL/AML1* positive leukemic cells, which is manifested at the chromosomal level by additional aberrations and/or complex chromosomal rearrangements. The presence of these abnormalities was proved in 50-70% of *TEL/AML1* positive patients with the most frequent ones: deletion of non-translocated *TEL* allele, trisomy or tetrasomy 21 and duplication of the derivative chromosome 21 with *TEL/AML1* fusion (Attarbaschi 2004).

In retrospective and prospective study and in cooperation with other cytogenetic and hematologic departments in Czech Republic and CLIP (Childhood leukemia investigation Prague) laboratory, we have evaluated frequency and significance of additional and/or complex chromosomal aberrations for prognosis of children with *TEL/AML1* positive ALL. At first we analyzed complex chromosomal rearrangements in 87 **(Babicka** et al. 2005) and then in 107 patients (**Zemanova** et al. 2006a). Final analysis involved 127 children with *TEL/AML1* positive ALL diagnosed during the years 1992-2006. The cohort included 53 girls and 74 boys with median of age 4,3 years. In all of them *TEL/AML1* fusion gene was assessed by RT-PCR and/or I-FISH. Most of the patients are living in first and second complete remission respectively. Relapse appeared in 22 children (17,3%), five of them died. Median of follow up of our cohort is 7 years.

In 85 (67%) children only one or two chromosomal aberrations were detected. The most frequent ones were found to be deletion of non-translocated *TEL* allele (29 cases), trisomy/tetrasomy of chromosome 21 (23 cases), deletion of long arm of chromosome 6 (8 cases) and/or rearrangements of the long arm of chromosome X (6 cases). In remaining 42 children (33%) complex karyotypes were identified. In 14 of them variant translocations of chromosomes 12 and 21 with other partners were observed. In rest of the patients classical translocation t(12;21)(p13;q22) with complex aberrations were found.

Children with complex karyotypes had higher occurrence of relapses compared to patients with one or two chromosomal aberrations (35,7% vs. 10,6%). In addition, statistical analysis proved significantly shorter Event-free survival (EFS) in group of children with complex chromosomal aberrations (p=0,001) (**Zemanova** et al. 2008).

Using conventional and molecular cytogenetic methods we carried out precise analysis of chromosomal aberrations in bone marrow cells of 107 children with *TEL/AML1* positive

ALL. From the clinical point of view, in our cohort of patients complex karyotypes indicated poor prognosis. They were associated with higher risk of relapse and shorter EFS in comparison with children with one or two chromosomal aberrations. Thus, we proved that finding of complex chromosomal aberrations in leukemic cells is accompanied by higher risk of relapse and shorter EFS even in those cases where the prognostically positive aberration is primarily present.

3. Analysis of additional chromosomal aberrations in patients with prognostically favorable chromosomal aberration

3.1. Difuse gliomas

Difuse gliomas are the most common primary neuroepithelial brain tumors affecting adults. It is a heterogenous group of tumors with various histological subtypes that differ in response to treatment and the prognosis of the disease (Smith et al. 2000). According to WHO classification of tumors of the central nervous system, difuse gliomas include astrocytomas that are further divided into low-grade astrocytoma (WHO grade II), anaplastic astrocytoma (WHO grade III), and glioblastoma multiforme (WHO grade IV) and comprise also low-grade and anaplastic oligodendroglioma and oligoastrocytoma (WHO grade II-IV).

The treatment of diffuse gliomas is problematic due to their diffuse nature, surgical intervention not always succeeds in removing the tumour tissue completely. This is why the disease often relapses and progresses even in case of lower-grade tumours (Godard et al. 2003). Also precise diagnostics of difuse gliomas can be questionable. Differentiation of glial subtypes based solely on nuclear and cellular morfology is subjective and various subtypes sometimes cannot be distinguished even when using specific immunohistochemical markers. Therefore, new diagnostic and prognostic indicators concerning the genome of tumor cells are sought to enable stratification of the treatment and to help reduce morbidity and mortality of patients.

Over the last few years, certain molecular cytogenetic and molecular genetic techniques have been developed and applied to the workup of gliomas. Genome-wide analyses of glial tumors performed during the last decade identified several recurrent genetic abnormalities (such as specific gene mutations, loss of heterozygosity, deletions and/or amplifications of

entire chromosomal regions) associated with different subtypes of gliomas and known prognosis.

In cooperation with Department of Neurosurgery of the 1st Medical Faculty of Medicine and Central Military Hospital in Prague we introduced a detailed molecular cytogenetic analysis of difuse gliomas. For the detection of chromosomal aberrations in glial cells FISH with locus-specific (LSI) and centromeric (CEP) probes is used with focus on detection of the most frequent and prognostically most important chromosomal aberrations described in difuse gliomas, i.e. deletion of genes *TP53*, *CDKN2A* (*p16)*, *RB1* and *PTEN*, deletion of chromosomal regions 1p36 and 19q13, amplification of *EGFR* gene, trisomy of chromosome 7 and monosomy of chromosome 10. All examinations are carried out on whole cell nuclei acquired from fresh non-fixed tumor tissue taken during a routinely performed neurosurgical procedure. When a sufficient amount of a sample is available, part of the tumor tissue is used for isolation of DNA, which is further processed by CGH and SNP array.

Pathogenesis of cerebral tumors has been still unknown to a large extent. We summarized present knowledge about the rise and development of glial tumors from the view of genetics in two review articles (**Kramar** et al. 2006a, **Kramar** et al. 2006b).

Consequently, we evaluated frequency and significance of specific chromosomal aberrations in glial cells in 81 patients with histologically confirmed difuse gliomas admitted to the Department of Neurosurgery of the 1st Medical Faculty and Central Military Hospital in Prague between March 2004 and December 2005. Patients were divided into three groups: Group I-low grade tumors (20 patients), Group II-high astrocytic tumors (45 patinets) and Group III-oligodendroglial tumors (16 patients). In this study molecular cytogenetic analyses were successful in 74 patients (91,3%) and were uninformative due to inadequate tissue specimen in 7 cases only. In all patients I-FISH analyses were consistent with morphological and clinical data. Furthermore, in most of them cytogenetic analyses specified diagnosis and/or prognosis. The most important finding was deletion of 1p36 and 19q13 which predicts longer overall survival for patients with oligodendroglial tumors (**Kramar** et al. 2007).

Oligodendroglial tumors are relatively uncommon category of difuse gliomas and in 50-80% of patients combined loss of short arm of chromosome 1 (1p) and long arm of chromosome 19 (19q) is present. Alellic loss of 1p/19q has been shown to predict longer overall survival regardless of treatment modality (Kanamori et al. 2008). Because of its strong correlation with favourable outcome it is already in widespread clinical use in neurooncology and is becoming part of a standard care for patients with oligodendroglioma. We proved the importance of molecular cytogenetic analysis for detection of 1p/19q deletions in 16 patients with histological confirmed oligodendroglioma. Using I-FISH we detected combined deletion

1p/19q in 13 patients, in six of them we found other chromosomal aberrations typical for high-grade astrocytoma (**Zemanova** et al. 2006b).

The significance of additional chromosomal aberrations typical for high-grade gliomas in oligodendroglial tumors is still poorly understood. Using I-FISH, CGH and SNP array we analyzed 43 patients with oligodendroglial tumors. Deletion of 1p and 19q was detected in 32 cases (74,5%). In 16 of them combined deletion was found as a sole cytogenetic abnormality. Median of progression free survival (PFS) in this group was 45 months and only one patient died. In other 16 cases additional chromosomal rearrangements typical for high-grade gliomas were proved by methods mentioned above. In these patients significantly worse PFS was conferred (23,5 months, 6 patients died) (**Lizcova** et al. 2010).

Although, deletion of 1p and 19q was shown as a powerful favorable prognostic marker, our study demonstrates that prognosis is influenced by additional chromosomal aberrations. However, further comprehensive whole-genome analyses of large series with sufficient follow-up are needed to prove real prognostic significance and recurrence of these aberrations.

Conclusion

Using modern molecular cytogenetic methods we performed analysis of complex chromosomal rearrangements in patients with various hematological malignancies and difuse gliomas. We described particular aberrations in detail and found chromosomes and chromosomal parts which were involved in CCR most frequently. We determined recurrent chromosomal breakpoints and pointed out to regions with important role in initiation and progression of the disease.

From the clinical point of view, we proved that complex chromosomal aberrations found at the time of diagnosis are poor prognostic factors in general. In our cohorts of patients, complex chromosomal rearrangements were associated with resistance to treatment, higher occurrence of relapses and shorter overall survival. In addition, we showed negative prognostic impact of CCR even in patients with primarily favorable prognostic chromosomal aberration in karyotype. Therefore, we suppose that patients with complex chromosomal rearrangements represent unique entity with extremely poor outcome regardless of tumor subtype or presence of prognostically favorable chromosomal aberration in karyotype.

Results of our study proved the significance of molecular cytogenetic analyses not only for diagnosis and prognosis of patients with hematological diseases and solid tumors but also for clarification of mechanisms leading to malignant transformation of the cell. Modern array-based molecular cytogenetic methods which were in last few years introduced into laboratory practice enable efficient detection of unbalanced aberrations with high resolution as well as genomic imbalances such as uniparental disomy. Thanks to detailed analyses of chromosomal parts and breakpoints involved in genomic rearrangements, several genes with important role in tumorogenesis were identified in various malignancies.

Although development in molecular genetic methods is increasing tremendously, cytogenetic analysis is still one of the most important parts of management of patients with malignant diseases. It is the only low-cost whole genome screening technique allowing the identification of numerical as well as structural genomic rearrangements in a single cell. Moreover, cytogenetic and molecular cytogenetic analysis of tumor cells has a fundamental role in identification of genes and novel pathogenetic mechanisms which can serve as targets for development of new therapeutic interventions (e.g. as it was adopted in chronic myeloid leukemia). In CML, the discovery of t(9;22)(q34;q11) and the understanding of its molecular basis resulted in development of tyrosine kinase inhibitors which are now successfully widely used for targeted treatment of patients with chronic myeloid leukemia.

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