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Characterization of a High Copy Number Amplification at 6q24 in Pancreatic Cancer Identifies c-myb as a Candidate Oncogene

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Abstract

In a recent study designed to identify chromosomal aberrations in pancreatic cancer tissues using comparative genomic hybridization, a high copy number amplification on 6q was detected. To identify the most likely candidate oncogene, the extension of the amplification in pancreatic cancer tissues and cell lines was determined by Southern blot analysis. Exon trapping was performed with DNA from a yeast artificial chromosome clone containing the complete minimally amplified region. Only fragments from two genes, namely, the c-myb oncogene and a novel gene, were shown to be amplified. The c-myb proto-oncogene was amplified in 10% of the pancreatic carcinoma tissues and in the pancreatic cancer cell line PC2. Interestingly, the c-myb oncogene was overexpressed not only in the amplified samples but also in the majority of the examined pancreatic cancer tissues and cell lines, suggesting that amplification is only one of the mechanisms leading to overexpression. In contrast, the novel gene, which was called human eRF3b (eukaryotic release factor 3b), seems to be only coamplified with c-myb. Genetic alterations of c-myb were mainly found in advanced tumors, indicating a possible correlation to tumor progression and aggressive tumor phenotypes.

Introduction

Activation of cellular proto-oncogenes by amplification and subsequent enhanced expression has been identified as a frequent alteration during tumorigenesis (1). The resulting abnormally high levels of the protein encoded by the amplified oncogene contribute to cancer by positive modulation of growth. In this context, high copy number chromosomal amplifications have frequently been shown to contain oncogenes. The identification and characterization of high copy number amplifications and the affected genes is, therefore, an excellent tool for the identification of oncogenes involved in growth control and carcinogenesis of the examined tumor.

In comparison to what is known about other tumors, our knowledge of the molecular biology of pancreatic cancer is very limited. In Western countries, pancreatic cancer represents the fourth and fifth most common cause of cancer-related death in men and women, respectively, and the incidence appears to be increasing (2). Prognosis of the molecular biology of pancreatic cancer is very limited. In the development of new treatment modalities and diagnostic and preventive approaches requires the understanding of the molecular mechanisms underlying the complex multistep process of tumorigenesis in the pancreas. One contribution for elucidating the molecular biology of pancreatic cancer carcinogenesis is the identification of oncogenes that may confer growth advantage to tumor cells. In a recent study involving the identification of chromosomal imbalances occurring in vivo in pancreatic cancer tissues, 27 primary tumors were analyzed using comparative genomic hybridization (4). Among others, a distinct high-level amplification was found on the long arm of chromosome 6 in the proximity of 6q23—24, suggesting that this region may contain a potential oncogene.

Here, we present the detailed molecular characterization of this locus, with the goal of identifying the candidate proto-oncogene involved in pancreatic tumorigenesis.

Materials and Methods

Materials. Human tissues from patients with adenocarcinoma of the pancreas, human pancreatic tissue from organ donors, and chronic pancreatitis tissue were provided by the Institute of Experimental Medicine, University of Budapest (Hungary), the Department of Surgery, University of Bern (Switzerland), and the Department of Surgery, University of Ulm (Germany), with written consent from each patient and after approval by the local ethics committees. Tissue from advanced stages was obtained during palliative surgical procedures. The clinical stages of the tumors, according to UICC classification (5), are listed in Table 1.

The human pancreatic cancer cell lines were obtained from the following suppliers: Patu8902, Patu8988s, and Patu8988t from H. P. Elsässer (University of Marburg, Germany); MiaPac2 from European Collection of Animal Cell Cultures (Salisbury, United Kingdom); HPAF from R. S. Metzgar (Duke University Medical Center, Durham, NC); DanG, Capan 1, and Capan 2 from DFKZ, Tumorzell- und Datenbank (Heidelberg, Germany); IMIM-PC1 and IMIM-PC2 from F. Real (Instituto Municipal d’Investigacio Medica, Barcelona, Spain); and PC2 and PC3 from M. Bülow (Department of Surgery, University of Mainz, Germany). Cell lines were grown as adherent cells in DMEM with 10% FCS (Life Technologies, Inc., Eggenstein, Germany), as recommended by suppliers.

Southern Blot Hybridization. High molecular weight genomic DNA from healthy pancreatic tissues, pancreatic carcinoma tissues, and pancreatic cancer cell lines was prepared from the supernatants of a cesium fluoride gradient centrifugation, according to standard protocols. Five μg of DNA were digested with EcoRI, size-fractionated in a 1% agarose gel, and transferred to a Biodyne A nylon membrane (Pall, Dreieich, Germany). Gene fragments from rhoI (3.6-kb NotI cDNA fragment, ATCC no. 65238), fyn (1.6-kb HindIII/EcoRI cDNA fragment, ATCC no. 57588), myb (genomic 2.6-kb EcoRI fragment, ATCC no. 57396), and estr (1.3-kb EcoRI cDNA fragment, ATCC no. 57680) were obtained from the American Type Culture Collection (Rockville, Maryland). A masl probe and a D6S270 STS marker probe were prepared by genomic PCR with specific primers (masl, 5'-CGCCGAGAAGCACTTG-TAA-3' and 5'-GGATGAGATGTTCTCTG-3'; D6S270, 5'-GTGAATCT-GATCTGAATGTGTCCTCC-3' and 5'-GATGAGGACCTGATGTCGG-3'). All probes were labeled by random hexamer priming using [α-32P]dCTP and the DNA Multiprime labeling kit (Amersham, Buckinghamshire, United Kingdom). To avoid cross-hybridization to human repetitive DNA some labeled probes were labeled by random hexamer priming using [α-32P]dCTP and the DNA Multiprime labeling kit (Amersham, Buckinghamshire, United Kingdom).

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3 The abbreviations used are: UICC, Union International Contre Cancer; STS, sequence-tagged site; YAC, yeast artificial chromosome; RT, reverse transcription; FISH, fluorescence in situ hybridization; LOH, loss of heterozygosity.

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probes (STS marker and subcloned YAC ends) were suppressed with 250 μg/ml Cot-1 DNA (Life Technologies, Inc., Eggenstein, Germany) in 5X SSC and 0.1% SDS for 2 h at 65°C. Hybridization was performed at 42°C for 16 h in 50% formamide, 6X SSC, 5X Denhardt's solution, 0.5% SDS, and 250 μg/ml sonicated salmon sperm DNA (Sigma, Deisenhofen, Germany) and blots were then washed twice for 10 min in 2X SSC/0.1% SDS at room temperature and twice for 30 min in 0.2X SSC/0.1% SDS at 65°C.

Screening of a YAC Library. A human YAC library filter from the Reference Library data base (MPI for Molecular Genetic, Berlin, Germany) was screened with a genomic c-myb probe using the conditions described above. The positive clone YAC1 (ICRFy900AO311Q) was ordered from the Reference Library data base (MPI for Molecular Genetic, Berlin, Germany).

Exon Trapping. Genomic DNA from the 620-kb YAC ICRFy900AO311Q, spanning the 6q23–24 region, was purified by pulsed-field electrophoresis, partially digested with Sau3AI, and cloned into the pSPL3 exon trap vector. Exon trapping was performed according to the detailed protocol of Church et al. (7).

RT-PCR. RNA from shock-frozen healthy pancreatic tissue, chronic pancreatitis tissue, pancreatic carcinoma tissue, and pancreatic cancer cell lines was extracted by use of a standard guanidinium thiocyanate extraction, followed by centrifugation in a cesium fluoride gradient. After DNaseI treatment, first-strand cDNA was prepared by the use of reverse transcriptase and oligo(dT) primers. PCR was performed with the myb-specific primers 5'-GTTGAAGAGCTTGCACGATAA-3' and 5'-GTCGAGCTAGCTTTG-3', using an annealing temperature of 60°C for 35 cycles or with primers specific for acidic ribosomal phosphoprotein (GenBank/NCBI data base accession no. M17885), 5'-CTGGCTAAGTTGTGCGTCTTT-3' and 5'-GCAGCTGATCAAGACTGA-3', using an annealing temperature of 58°C for 19 cycles. Acidic ribosomal phosphoprotein has been shown to be expressed at the same level in normal, inflamed, and malignant pancreatic tissue and cell lines (8). RT-PCRs were electrophoresed through a 1.5% agarose gel, Southern-blotted onto a nylon membrane, and probed with a 32P-labeled c-myb exon 5-specific probe.

FISH. The YAC probe, containing genomic DNA of the myb locus, was biotin-labeled and hybridized to metaphase chromosomes of the PC2 cell line, as described in Lichter et al. (9). Briefly, 150 ng of labeled YAC DNA were combined with 10 μg of unlabeled Cot-1 DNA in a 12-μl hybridization cocktail. Posthybridization washes were to a stringency of 0.1X SSC at 60°C, followed by detection of the DNA probe with avidin-FITC. Chromosomes were counterstained with propidium iodide and embedded in antifade solution (Vectorshield). Images were acquired with a cooled charged coupled device camera (Photometrics, Tucson, AZ).

### Results

**Determination of the Extension of the High Copy Number Amplification at 6q24 by Southern Blot Analysis.** DNA was prepared from 22 pancreatic cancer tissues, 13 different pancreatic cancer cell lines, and 5 healthy pancreatic tissues, digested with EcoRI, and used for Southern blot hybridizations with five potential oncogenes, which are known to be localized near the 6q24 region, namely, rosl, fyn, myb, mas1, and esr. Only the c-myb probe detected a clear high copy number amplification in two cancer tissues (nos. 1 and 7) and the cancer cell line PC2 (Fig. 1). The genomic 2.6-kb EcoRI c-myb probe identifies a two-allele EcoRI restriction fragment polymorphism with two bands at 1.5 kb and 1.1 kb (allele 1) and one band at 2.6 kb (allele 2; Ref. 10). A rough estimation of the copy number, based on the comparison of the hybridization signals of serially diluted amplified DNA versus normal DNA, revealed a more than 32-fold DNA amplification for the pancreatic cancer cell line PC2 and more than 16- and 3-fold amplifications in the two pancreatic cancer tissues, nos. 7 and 1, respectively. Due to the fact that pancreatic tissue is characterized by a strong desmoplastic reaction and usually contains varying amounts of tumor cells, the degree of amplification in tumor tissues may be much higher.

![Representative Southern blot hybridization showing amplification of c-myb in pancreatic cancer tissues and cell lines. Five μg of DNA from pancreatic cancer cell lines (Lanes 1, PC3; Lanes 2, PC2; Lanes 3, Patu9882; Lane 4, PaTu8; Lane 5, MiaPac1; Lane 6, Capan1; Lane 7, Capan2; Lane 8, Patu8988b) and pancreatic carcinoma tissue (see Table 1) were digested with EcoRI, size-fractionated on a 1% agarose gel, transferred to a nylon membrane, and probed with a genomic c-myb fragment that detects an EcoRI restriction fragment polymorphism. Note that the strength of the hybridization signal for the one of the myb alleles is much weaker in pancreatic cancer cell line no. 8 (Patu8988b) and in pancreatic cancer tissue nos. 13 and 15. Solid arrows, amplifications; open arrows, LOH.](image-url)
In this context, it should also be mentioned that there were alterations indicative of LOH of the c-myb gene in 3 of 22 pancreatic carcinoma tissues (case nos. 13, 15, and 25) and in the pancreatic cancer cell lines Patu8988t (no. 8) and DanG (no. 10; see Fig. 1). These findings are based on a disproportionally strong decrease of signal intensity of only one of the two myb alleles in the respective patients, whereas similar alterations on the same Southern blot were not obtained with other molecular probes.

To determine the precise extension of the amplification, a YAC contig was constructed around the myb locus, by screening a YAC library with the c-myb probe and using subcloned ends of the positive YAC1 (ICRFy900AO311Q) for the identification of neighboring YACs. Each YAC end and the STS marker D6S270 were tested for amplification on Southern blots.

Search for Coamplified Genes to Identify the Candidate Oncogenes Involved in the 6q24 Amplification. The minimal commonly amplified region was found in the pancreatic cancer tissue no. 7 and is completely covered by the 620-kb YAC1 ICRFy900AO311Q (Fig. 2a). Therefore, we decided to use this YAC clone in a search for coamplified genes. In an exon trap approach, six gene fragments with open reading frames that are assumed to be exons from different genes were isolated (GenBank/NCBI data base accession nos. U93813–U93818) and hybridized to Southern blots. However, only one gene fragment was found to be coamplified with c-myb. Screening of a cDNA library with this exon trap fragment led to the identification of a full-length cDNA, which contains a 2508-bp open reading frame (GenBank/NCBI data base accession no. U87791). The hypothetical 684-amino acid protein of this novel gene showed a significant homology to the Saccharomyces cerevisiae SUP35 omnipotent suppressor gene, which is involved in translation termination fidelity.4

This novel gene shares a number structural features with all members of the eRF3 family, including GTP-binding and -hydrolysis consensus sequences, and was called human eRF3b (eukaryotic release factor 3b). Hybridization of the complete cDNA of eRF3b on Southern blots detects several restriction fragments. All of these fragments are amplified in PC2 and tissue no. 1, but only some of them are amplified in tissue no. 7, which contains the minimal commonly amplified region. This finding suggests that eRF3b is localized in the proximity of the breakpoint of the amplification in this tissue.

The position of c-myb, eRF3b, and et12, an exon trap fragment, coding for a novel Src homology 2 domain-containing protein, is shown on the restriction map of YAC1 (Fig. 2b). The extension of the amplified region ranges from approximately 300 kb in the pancreatic cancer tissue no. 7 to several megabases in cell line PC2, including the amplification of the STS marker D6S270.

Study of the Structural Arrangement of the 6q24 Amplification in a Pancreatic Cancer Cell Line by FISH. To study the structural arrangement of the amplified locus, FISH was performed on metaphase spreads of the PC2 cell line with a YAC probe spanning the myb locus. The experiments revealed, in addition to the expected signals on both homologous chromosomes 6, strong signals on two marker chromosomes containing the amplified DNA from the 6q24 region. As shown in Fig. 3, these large signals visualize clusters of amplified myb sequences, as is typically found in homogeneously staining regions.

Expression Analysis. To determine the transcript levels of the amplified genes, RT-PCR expression studies were done (Fig. 4). The studies revealed a clear overexpression of the c-myb oncogene, not only in tissues and cell lines showing 6q24 amplification but also in 70% of the examined pancreatic cancer tissues (14 of 20) and 54% of the examined pancreatic cancer cell lines (7 of 13). In contrast to the expression level of c-myb, that of eRF3b was nearly the same in all examined tissues, except amplified tissue no. 1 and the cell line PC2.
(data not shown). In tissue no. 7, containing the minimal commonly amplified region, eRF3b appeared to be amplified on Southern blots, but there was no evidence for overexpression.

**Discussion**

In a recent search for chromosomal aberrations in pancreatic cancer tissue using comparative genomic hybridization, a high copy number amplification was found on the long arm of chromosome 6 (4). The aim of the present study was to provide a molecular characterization of the amplified locus and to identify the candidate proto-oncogene.

An initial Southern blot analysis with probes from genes located in the proximity of 6q24 revealed a clear high copy number amplification, including the locus of the c-myb oncogene. This amplification occurs not only in pancreatic cell lines, which often harbor artificial amplifications developed during long-term culture conditions, but also in primary pancreatic tumors, emphasizing that this genetic alteration is of biological relevance in vivo for the development of pancreatic cancers. FISH analysis of metaphase spreads of a pancreatic cancer cell line, with a YAC probe covering the amplified region, later revealed that the amplified DNA was contained in a homogeneously staining region.

To identify the candidate oncogene involved in this high copy number amplification, a contig covering the amplified 6q23–24 region was constructed. For this purpose, a first YAC clone was isolated with a c-myb gene probe and the ends of this YAC clone were used for the identification of overlapping YACs. Southern blot analysis with the ends of all YAC clones allowed to identify the minimal commonly amplified region in one pancreatic cancer tissue (no. 7). As the complete minimally amplified region was contained in the first isolated YAC, we used this clone to isolate additional candidate genes by exon trapping. This approach led to the identification of several gene fragments from the 6q24 region; however, only the proto-oncogene c-myb and eRF3b, a novel putative translation termination factor, were found to be amplified in the minimal commonly amplified region of cancer tissue no. 7.

eRF3b codes for a novel GTP-binding protein that is presumably involved in translation termination. Only a part of the restriction fragments detected with the eRF3b probe on Southern blots were found to be coamplified with c-myb. This data suggests that eRF3b is presumably located in the breakpoint of the amplification in the tissue no. 7. Expression studies revealed enhanced transcript levels of eRF3b only in the amplified pancreatic carcinoma tissue no. 1 and pancreatic cancer cell line PC2. A clear overexpression could not be found in tissue no. 7, which supports our suggestion that only parts of the gene

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**Fig. 3.** Metaphase spread of pancreatic cancer cell line PC2 after FISH with a YAC probe containing genomic DNA of the myb locus. Hybridization signals are detected with avidin-FITC and chromosomes are counterstained with propidium iodide. Small hybridization signals indicate the locus of myb on both homologous chromosomes 6 (band 6q24), and larger signals on two marker chromosomes visualize clusters of amplified myb sequences.

**Fig. 4.** a, RT-PCRs obtained with primers specific for exon 5 of the c-myb gene and cDNA from healthy pancreas, chronic pancreatitis, pancreatic cancer cell lines (no. 1, PC3; no. 2, PC2; no. 3, Patu8902; no. 4, Patu; no. 5, MiaPaca1; no. 6, Capan1; no. 7, Capan2; no. 8, Patu8988t; no. 9, Patu8988s, no. 10, DanG; no. 11, HPAF; no. 12, IMIM-PC1; no. 13, IMIM-PC2) and pancreatic cancer tissues (see Table 1) as template were size-fractionated on a 1.5% agarose gel, Southern blotted onto a nylon membrane, and probed with a 32P-labeled c-myb probe. b, ethidium bromide-stained agarose gel of the internal standard RT-PCR. The primers amplify an acidic ribosomal phosphoprotein (GenBank/NCBI data base accession no. M17885), which has been shown to be expressed at equal levels in all examined pancreatic tissues and cells.
are positioned inside the amplified region in this tissue. Therefore, of the two isolated genes found to be amplified at 6q24, eRF3b appears to be the less likely candidate oncogene. This and the finding that eRF3b is only overexpressed in tissues harboring a large 6q24 amplification suggest that this gene is not of general importance for pancreatic cancerogenesis but simply represents a gene coamplified with the relevant oncogene.

The second gene amplified in pancreatic cancer at 6q24 was the proto-oncogene c-myb, which encodes a transcriptional activator protein with repeated helix-turn-helix DNA-binding motifs. In hematopoiesis, c-myb appears to control both proliferation and differentiation (11). c-myb is known to be activated as an oncogene through amplification in several tumor cells, for example, some acute myelogenous leukemia cell lines (12), primary breast cancer (13), and, in a few additional cases, established adenocarcinoma cell lines from colon carcinoma (14) and small cell lung carcinoma (15). Our data represents the first report describing an amplification of the c-myb locus in pancreatic cancer. This amplification appears to occur at a moderate frequency of 10%, as compared to the amplification rates observed in primary breast cancer (3%; Ref. 13) and in colon cancer (23%; Ref. 16).

The selective increase of the copy number of the c-myb oncogene should result in increased RNA expression. Therefore, we examined the abundance of c-myb transcripts in different pancreatic tissues by RT-PCR with c-myb-specific primers. Using these conditions, c-myb expression was barely detectable in healthy pancreas and chronic interstitial inflammation as cancer tissue. Significantly enhanced expression was found in the pancreatic cancer tissues and cells showing amplifications at 6q24, thus confirming that DNA amplification is one of the genetic mechanisms leading to an up-regulation of c-myb gene expression. Interestingly, overexpression was found not only in the tissues and cells showing amplifications but also in 70% of the examined pancreatic cancer tissues and 54% of the examined pancreatic cancer cell lines. Therefore, we suggest that enhanced c-myb expression is an important pathogenetic factor for pancreatic cancerogenesis and that other mechanisms besides DNA amplification lead to c-myb activation. In addition to nonhematopoietic cells, c-myb expression has been detected in different cancers, for example, colon tumors (17) and breast cancer (18), and it has been suggested that c-myb be of general importance for regulating processes as, e.g., proliferation and differentiation of tumor cells (19).

Interestingly, in addition to high copy number amplifications, other genetic alterations of the c-myb locus were detectable. LOH was found in 14% of the examined pancreatic cancer tissues and 15% of the examined pancreatic cancer cell lines. Similar alterations have been described in different leukemias and lymphomas (20) and in breast cancer (21). It has been suggested that genetic imbalances of the myb locus, both amplification and deletion, might occur along the examined pancreatic cancer tissues and cell lines, we propose that it is an important pathogenetic factor for pancreatic cancerogenesis. One of the mechanisms of c-myb activation appears to be gene amplification. Data in the literature suggest that increased activity of c-myb leads to a selective advantage in tumor cell proliferation. In pancreatic cancer, this may lead to the development of more aggressive tumor phenotypes, as indicated by our data.

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6. Pellicci, P. G., and Dhanraj, P. K. High copy number amplification at 6q24 detected by cell lung carcinoma (15). Our data represents the first report describing an amplification of the c-myb locus in pancreatic cancer. This amplification appears to occur at a moderate frequency of 10%, as compared to the amplification rates observed in primary breast cancer (3%; Ref. 13) and in colon cancer (23%; Ref. 16).

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To summarize, we suggest that c-myb is the most likely oncogene harbored by the high copy number amplification at 6q24 in pancreatic cancer. In addition, because c-myb is overexpressed in the majority of the examined pancreatic cancer tissues and cell lines, we propose that it is an important pathogenetic factor for pancreatic cancerogenesis. One of the mechanisms of c-myb activation appears to be gene amplification. Data in the literature suggest that increased activity of c-myb leads to a selective advantage in tumor cell proliferation. In pancreatic cancer, this may lead to the development of more aggressive tumor phenotypes, as indicated by our data.
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