Fusion of the \textit{TBL1XR1} and \textit{HMGA1} genes in splenic hemangioma with t(3;6)(q26;p21)

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Received September 27, 2015; Accepted November 26, 2015

DOI: 10.3892/ijo.2015.3310

Abstract. RNA-sequencing of a splenic hemangioma with the karyotype 45~47,XX,t(3;6)(q26;p21) showed that this translocation generated a chimeric \textit{TBL1XR1-HMGA1} gene. This is the first time that this tumor has been subjected to genetic analysis, but the finding of an acquired clonal chromosome abnormality in cells cultured from the lesion and the presence of the \textit{TBL1XR1-HMGA1} fusion in them strongly favor the conclusion that splenic hemangiomas are of a neoplastic nature. Genomic PCR confirmed the presence of the \textit{TBL1XR1-HMGA1} fusion gene, and RT-PCR together with Sanger sequencing verified the presence of the fusion transcripts. The molecular consequences of the t(3;6) would be substantial. The cells carrying the translocation would retain only one functional copy of the wild-type \textit{TBL1XR1} gene while the other, rearranged allele could produce a putative truncated form of \textit{TBL1XR1} protein containing the LiSH and F-box-like domains. In the \textit{TBL1XR1-HMGA1} fusion transcript, furthermore, untranslated exons of \textit{HMGA1} are replaced by the first 5 exons of the \textit{TBL1XR1} gene. The result is that the entire coding region of \textit{HMGA1} comes under the control of the \textit{TBL1XR1} promoter, bringing about dysregulation of \textit{HMGA1}. This is reminiscent of similar pathogenetic mechanisms involving high mobility genes in benign connective tissue tumors such as lipomas and leiomyomas.

Introduction

Splenic hemangiomas, although infrequent, represent the most common benign neoplasms of the spleen with an incidence of 0.03-14% found in large autopsy series (1,2). In the vast majority of cases, splenic hemangiomas are incidental surgical, radiologic, or autopsy findings, made during evaluation for other disorders (1-3). Arber et al (3) reported 7 localized splenic hemangiomas all of which were discovered incidentally in surgical patients. In a large series of 32 patients with splenic hemangioma, only 6 presented with abdominal symptoms and only 4 had a palpable spleen (1).

Because of the general absence of presenting symptoms and the typically incidental nature of splenic hemangiomas, the age at presentation varies considerably. Several non-autopsy, surgical series revealed an average age at detection/presentation of between 51 and 63 years (1,3). However, examination of autopsy data reveals a much younger average patient age (4) indicating that these benign lesions are likely to be present but remain undetected for long periods of time. No gender or race predilection has been reported (1).

Splenic hemangiomas are thought to be congenital in origin, arising from sinusoidal epithelium (5). Whether they are neoplastic or represent some other type of misgrowth, remains uncertain. They typically appear as circumscribed, non-encapsulated, honeycomb-like, red-purple masses that frequently blend imperceptibly into the surrounding splenic parenchyma (4). The spaces are composed of sponge-like tissue filled with blood and separated by fibrous septa. Occasional calcification may be seen, often in association with an organized infarct (6). Microscopically, the majority of hemangiomas are cavernous in nature, consisting of large interconnected, dilated, blood-filled spaces lined by a monolayer of cytologically bland endothelial cells separated by thin fibrous septa or splenic pulp tissue. Pure capillary architecture is less common. Instead, many lesions contain varying proportions of both cavernous and capillary components (4). Immunophenotypically, splenic hemangiomas show reactivity for endothelial lining cells for CD31, von Willebrand factor, Ulex europeaus, lectin I, and CD34. This pattern raises the possibility that splenic hemangioma may derive from a combination of splenic venous structures as well as from splenic sinusoidal cells (4).

Most splenic hemangiomas tend to be small in size (<4 cm) although lesions ≤36 cm have been reported (4). They need not be entirely without complications as larger lesions may
rupture with resulting intra-abdominal hemorrhage (7-11). In some patients, they cause the Kasabach-Meritt syndrome (12).

The etiology and pathogenesis of splenic hemangiomas are unclear and no cytogenetic or molecular genetic information about the disease has been published. We here describe the cytogenetic analysis of a splenic hemangima and the fusion gene corresponding to the chromosomal translocation thus found.

Materials and methods

Ethical approval. The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (REK Sør) http://helseforskning.etikkom.no). Written informed consent was obtained from the patient. The consent included acceptance that the clinical details be published. The ethics committee's approval included a review of the consent procedure. All patient information has been anonymized and de-identified.

Patient. A twenty-nine-year-old woman was incidentally diagnosed with a splenic hemangima during an ultrasound examination for cholecystitis. She had been without symptoms attributable to the splenic lesion, possibly except some pressure in the upper left abdomen. Because of continuous growth of the hemangima, it was decided to do a splenectomy. Histological examination (Fig. 1) showed that the lesion was composed of large, blood-filled vessels lined by flat endothelium and separated by thin fibrous septa or splenic pulp. Immunohistochemical analysis showed positivity for CD31 and ERG.

Control sample. The control sample was FirstChoice human spleen total RNA (Life Technologies, Carlsbad, CA, USA).

G-banding and karyotyping. Fresh tissue from a representative area of the tumor was received and analyzed cytogenetically as part of our diagnostic routine. The sample was disaggregated mechanically and enzymatically with collagenase II (Worthington, Freehold, NJ, USA). The resulting cells were cultured and harvested using standard techniques. Chromosome preparations were G-banded with Wright stain and examined. Peripheral blood lymphocytes stimulated with phytohemagglutinin (PHA) for 72 h were also karyotyped. The karyotypes were written according to the International System for Human Cytogenetic Nomenclature (ISCN) 2009 guidelines (13).

RNA and DNA extraction. Tumor tissue adjacent to that used for cytogenetic analysis and histologic examination had been frozen and stored at -80°C. Total RNA was extracted using miRNasy Mini kit according to the manufacturer's instructions (Qiagen Nordic, Oslo, Norway). Tumor tissue was disrupted and homogenized in Qiazol Lysis Reagent (Qiagen) using a 5-mm stainless steel bead and TissueLyser II (Qiagen). Subsequently, total RNA was purified using QIAcube (Qiagen). The RNA quality was evaluated using the Experion Automated Electrophoresis system (Bio-Rad Laboratories, Oslo, Norway). The RNA quality indicator (RQI) was 9.0. Genomic DNA was extracted using the Maxwell 16 Instrument System and the Maxwell 16 Tissue DNA Purification kit (Promega, Madison, WI, USA), and the concentration and purity of DNA were measured using NanoVue Plus Spectrophotometer (GE Healthcare Life Sciences, Oslo, Norway).

High-throughput paired-end RNA-sequencing. Three micrograms of total RNA were sent for high-throughput paired-end RNA-sequencing at the Norwegian Sequencing Centre, Ullevål Hospital (http://www.sequencing.uio.no/). The RNA was sequenced using an Illumina HiSeq 2000 instrument and the Illumina software pipeline was used to process image data into raw sequencing data. The regular TruSeq library preparation protocol (http://support.illumina.com/downloads/truSeq_rna_sample_preparation_guide_15008136.pdf) was used. The reads obtained had a length of 100 base pairs (bp). A total of 74 million reads were obtained. The quality of the raw sequence data was assessed using FastQC software (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/). The software TopHat-Fusion was used for the discovery of fusion transcripts (14,15). To verify further the fusion gene which was found by TopHat-Fusion, the ‘grep’ command (http://en.wikipedia.org/wiki/Grep) was used to search the fastq files of sequence data (http://en.wikipedia.org/wiki/FASTQ_format). Our ‘specific expression’ was a sequence of 20 nucleotides at the fusion point, 10 bases upstream (5’-end gene), and 10 bases downstream from the junction (3’-end gene). The expression was ‘CGACCAATAGGTCCCCAAGT’. The sequences obtained by ‘grep’ were blasted against the human genomic plus transcript database (http://blast.ncbi.nlm.nih.gov/Blast.cgi) as well as the sequences with accession numbers NM_024665.4 (TBL1XR1) and NM_002131.3 (HMGA1) and DB051170.1 (TESTI2 Homo sapiens cDNA clone TESTI2040990, 5’, mRNA sequence).

RT-PCR and genomic PCR analyses. The primers used for PCR amplification and Sanger sequencing are listed in Table I. For RT-PCR, 1 µg of total RNA was reverse-transcribed in a 20-µl reaction volume using iScript Advanced cDNA Synthesis kit for RT-qPCR according to the manufacturer’s instructions (Bio-Rad Laboratories). The 25 µl PCR volume contained 12.5 µl Premix Ex Taq™ DNA Polymerase Hot Start Version (Takara Bio Europe/SAS, Saint-Germain-en-Laye, France), 1 µl of cDNA, and 0.4 µM of each of the forward and reverse primer. The primer sets TBL1XR1-229F1/DB051170-Intr2R1 and TBL1XR1-229F1/HMGA1-324R1 were used to detect possible TBL1XR1-HMGA1 fusion transcripts. The quality of the cDNA synthesis was examined by amplification of a cDNA fragment of the ABL1 gene using the primers ABL1-91F1 and ABL1-404R1 (16).

For genomic PCR, the 25 µl PCR volume contained 12.5 µl Premix Ex Taq™ DNA Polymerase Hot Start Version, 100 ng DNA, and 0.4 µM of each of the forward and reverse primers TBL1XR1-intron4-F1 and DB051170-intr2R1.

The PCR amplifications were run on a C-1000 Thermal cycler (Bio-Rad Laboratories) with an initial denaturation at 94°C for 30 sec, followed by 35 cycles of 7 sec at 98°C, 30 sec at 55°C (58°C for genomic PCR), 1 min at 72°C, and a final extension for 5 min at 72°C. For amplification of the ABL1 cDNA fragment, the PCR cycling was an initial denaturation at 94°C for 30 sec followed by 35 cycles of 7 sec at 98°C and 2 min at
Three microliters of the PCR products were stained with GelRed (Biotium, Hayward, CA, USA), analysed by electrophoresis through 1.0% agarose gel, and photographed. The remaining 22 µl PCR products were purified using the MinElute PCR purification kit (Qiagen Nordic) and sequenced at GATC Biotech.
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(Germany, http://www.gatc-biotech.com/en/home.html). The BLAST software (http://blast.ncbi.nlm.nih.gov/Blast.cgi) was used for computer analysis of sequence data.

Results

G-banding. The G-banding analysis of the splenic hemangioma yielded a karyotype with a single clonal chromosome abnormality: 45~47,XX,t(3;6)(q26;p21)[cp22] (Fig. 2). The G-banding analysis of PHA-stimulated peripheral blood cells yielded a normal 46,XX karyotype. Thus, the translocation t(3;6)(q26;p21) was found in cells of the splenic hemangioma only.

High-throughput paired-end RNA-sequencing analysis. Using the TopHat-Fusion on the raw sequencing data obtained by Norwegian Sequencing Centre, four fusions were found between chromosome bands 3q26 and 6p21 (Table II). Among them was a fusion between TBL1XR1 (from 3q26) and the sequence with accession number DB051170 which is an alternative splicing transcript of HMGA1 found in testis (17).

In order to verify this fusion, we used the ‘grep’ command utility to search for expressions composed of 10 nt of TBL1XR1 and 10 nt of HMGA1 upstream and downstream of the fusion point (Table III). Using the expression ‘CGACCAATAAGGTCCCCAAGT’, which is composed of 10 nt, ‘CGACCAATAAG’, from TBL1XR1 and 10 nt, ‘GTCCCCAAGT’, from HMGA1, 16 sequences were retrieved. BLAT of these sequences on the human genome browser-hg19 assembly (http://genome-euro.ucsc.edu/cgi-bin/hgGateway) showed that they were chimeric cDNA fragments composed of nucleotides which mapped on 3q26 in the coding region of TBL1XR1 and nucleotides mapped on chromosome band 6p21, circa 700 bp upstream of the HMGA1 sequence with accession number NM_002131 and within the sequence with accession number DB051170 which is an alternative splicing transcript of HMGA1 found in testis (17). The fusion had occurred between nt 496 of TBL1XR1 mRNA reference sequence NM_024665.4

Table II. Fusions between chromosome bands 3q26 and 6p21 which were found with the TopHat-Fusion program.a

| 3q26-fusion point | 6p21-fusion point | Fifty bases on the left side of the fusion (3p21) | Fifty bases on the right side of the fusion (6p21) |
|-------------------|-------------------|---------------------------------------------------|---------------------------------------------------|
| 166196913          | 3093594           | GGGATTACAACTCCTCCTGGCATTA                        | TCTCTTCCCAGTCTACAGCTCCTACAGAGCACTCTGAGGGCCTGTCTGCGAGGAGTGAGCCACCATGCCTGGCC |
| 176799652          | 3420389               | CACAATTTTCCAAATCCAGGATGG                      | GTCCCCAAGTGGGCCTGCGTATCTCCAGAACACATCTAAGTCACCTCAA |
| 176799483          | 3544154               | TCTTTAGTCAGTATAATTACAGT                      | CCTAGGTGGGGTTTGGAGGTGGCCTGAGCGATATGCAAACAGTGAGGACC |
| 166196867          | 3915735               | TTGGGTTTGAGACTATAGCTAAA                       | CATTCAGGACACAGTGGGCCAGCCCCAGGGTGAACATCATGGAGAACCCAATATAATAAAACAAAAATAACAAATA |

aThe sequences corresponding to TBL1XR1-HMGA1 fusion are in bold.

Figure 2. Partial karyotype showing the der(3)t(3;6)(q26;p21) and der(6)t(3;6) (q26;p21) together with the corresponding normal chromosome homologs; breakpoint positions are indicated by arrows.
and nt 215 of the sequence with accession number DB051170.1 (Table III). We therefore decided to investigate the tumor further for the presence of the TBL1XR1-HMGA1 fusion transcript using molecular techniques. No other fusions were examined.

**Molecular genetic confirmation of the TBL1XR1-HMGA1 fusion.** A 338-bp ABL1 cDNA fragment was amplified indicating the good quality of the synthesized cDNA (Fig. 3A).

To verify the data obtained with the RNA-sequencing/TopHat-Fusion software and ‘grep’ command, PCR amplifications were performed using forward TBL1XR1 and reverse HMGA1 primers corresponding to sequences located upstream and downstream of the putative breakpoint, respectively. PCR with the two primer combinations, TBL1XR1-229F1/DB01170-intr2R1 and TBL1XR1-229F1 and HMGA1-324R1, amplified fragments from the cDNA of splenic hemangioma but not from cDNA of the normal spleen. The results strongly suggested the presence of TBL1XR1-HMGA1 chimeric transcript in splenic hemangioma (Fig. 3A). Direct Sanger sequencing of the amplified fragments showed that both were TBL1XR1-HMGA1 chimeric cDNA fragments with the fusion point identical to that found with TopHat-Fusion and the ‘grep’ command, i.e., the fusion had occurred between nt 496 of TBL1XR1 mRNA reference sequence NM_024665.4 and nt 215 of the sequence with accession number DB051170.1 (Fig. 3B).

Genomic PCR with the primer combination TBL1XR1-intron4-F1/DB051170-intr2R1 amplified a fragment from the DNA of the splenic hemangioma. Direct Sanger sequencing showed that it was a genomic hybrid DNA fragment with sequences from the TBL1XR1 and HMGA1 genes (Fig. 4B). The junction point was identical to the fusion point found with TopHat-Fusion and the ‘grep’ command and with RT-PCR.

**Discussion**

We describe the first cytogenetic and molecular genetic analysis of a splenic hemangioma. The tumor had an acquired chromosomal translocation, t(3;6)(q26;p21), which resulted in fusion of the TBL1XR1 (from 3q26) and HMGA1 (from 6p21) genes. The fact that an acquired genetic aberration was found in the splenic hemangioma cells argues strongly that the disease is neoplastic.

The protein encoded by the TBL1XR1 gene has sequence similarity with members of the WD40 repeat-containing protein family (18). The WD40 group is a large family of proteins which appear to have a regulatory function (19-21). WD40 repeats mediate protein-protein interactions and members of the family are involved in signal transduction, RNA processing, gene regulation, vesicular trafficking, cytoskeletal assembly, and they may also play a role in the control of cytotypic differentiation (19-21). TBL1XR1 is a core component of NCoR (nuclear receptor corepressor) and SMRT (silencing mediator of retinoic acid and thyroid hormone receptors) repressor complexes and is essential in targeting SMRT/NCoR corepressor complexes to the promoter of target genes. It is also required for transcriptional activation by nuclear receptors and other regulated transcription factors (18). TBL1XR1 is further essential in the activation of Wnt-β-catenin and NF-κB signaling pathways (18). *De novo* deletions
Figure 3. RT-PCR analyses of splenic hemangioma (H) together with normal spleen (S). (A) Amplification of an ABL1 cDNA fragment using the primers ABL1-91F1 and ABL1-404R1. (B) Amplification of a cDNA fragment using the primers TBL1XR1-229F1 and DB051170-Intr2R1. (C) Amplification of a cDNA fragment using the primers TBL1XR1-229F1 and HMGA1-324R1. M, 1 kb DNA ladder (GeneRuler, Fermentas); Bl, blank, water in cDNA synthesis. (D) Partial sequence chromatogram of the cDNA fragment showing the fusion (arrow) of TBL1XR1 with HMGA1 (sequence with accession number DB051170).

Figure 4. Genomic PCR analysis of splenic hemangioma (H). (A) Amplification of genomic DNA fragment using the primers TBL1XR1-intron4-F1 and DB051170-intr2R1. (B) Direct Sanger sequencing showed that the amplicon is a genomic hybrid DNA fragment with sequences from TBL1XR1 and HMGA1. The primers are shown in boxes. Arrow indicates the genomic breakpoint. Capital letters show part of exon 5 of TBL1XR1. (C) The TBL1XR1 gene. The location of TBL1XR1 on chromosome 3 (vertical line) and the reference sequence NM_024665 are shown. (D) The HMGA1 gene. The location of HMGA1 on chromosome 6 (vertical line), the 6 reference sequences, and the sequence with the accession number DB051170 are shown.
and recurrent mutations have been identified in the TBL1XR1 gene and are linked to intellectual disability (18). TBL1XR1 plays an important role in tumorigenesis, invasion, metastasis, and the development of therapy resistance (18). TBL1XR1 is overexpressed in primary lung squamous cell carcinoma, breast cancer, cervical cancer, nasopharyngeal carcinoma, esophageal squamous cell carcinoma, and invasive prostate cancer (reviewed in ref. 18). Mutation of TBL1XR1 was found in primary central nervous system lymphomas (22,23). Deletions of TBL1XR1 were described in 15% of ETV6-RUNX1 positive acute lymphoblastic leukemias (24). In frame TBL1XR1 chimeric transcripts which code for chimeric proteins, were found in different neoplasias. A recurrent TBL1XR1-TP63 fusion gene was reported in diffuse large B-cell lymphoma, peripheral T-cell lymphoma, and follicular lymphoma which was the result of a chromosomal rearrangement between 3q26 (TBL1XR1) and 3q28 (TP63) (25,26). In most of the cases, the exons 1-7 of TBL1XR1 were fused in frame to exons 4-8 or 4-10 of TP63. Exon 14 or exon 4 of TBL1XR1 was involved in the remaining cases (25,26).

TBL1XR1 is fused to RARA in an acute promyelocytic leukemia carrying a variant t(3;17)(q26;q21) translocation (27). The TBL1XR1-RARA fusion protein was predominantly localized in the nucleus, formed homodimers or heterodimers with retinoid X receptor α, and acted as transcriptional activator in the presence of ligand. In the presence of pharmacologic doses of ATRA, TBLR1-RARA protein could be degraded, and its homodimerization was abrogated (27).

Fusions of TBL1XR1 resulting in promoter swapping were also found (28,29). In the breast carcinoma MCB7 cell line, the untranslated (5′-UTR) exon 1 of TBL1XR1 is fused with the start codon-bearing exon 2 of RGS17, generating a fusion gene that encodes the full-length RGS17 protein under the control of TBL1XR1 gene promoter (28). The same 5′-UTR exon 1 of TBL1XR1 was also found to be fused with the PIK3CA gene in breast cancer and prostate adenocarcinomas. The result was again the expression of PIK3CA which came under the control of the TBL1XR1 promoter (29).

The HMGA1 gene encodes a non-histone protein involved in many cellular processes, including regulation of inducible gene transcription, integration of retroviruses into chromosomes, and the metastatic progression of cancer cells (30-32). The encoded protein preferentially binds to the minor groove of A+T-rich regions in double-stranded DNA. It has little F-box-like domains, could participate in protein dimerization, and act as an oncogenic protein involved in the development of cancer. The truncated form of TBL1XR1, through the LisH and F-box-like domains (NP_078941; LiSH domain: 4-32, F-box-like domain: 41-86), would have molecular consequences for both TBL1XR1 and HMGA1. The TBL1XR1 gene would have only a single functional copy of the gene left in the cell, while the other, rearranged allele would produce a putative truncated form of TBL1XR1 protein containing the LiSH and F-box-like domains (NP_078941; LiSH domain: 4-32, F-box-like domain: 41-86). Thus, the truncated form of TBL1XR1, through the LiSH and F-box-like domains, could participate in protein dimerization, affect protein half-life, and could influence specific cellular localizations (53,54).

With regard to HMGA1, the TBL1XR1-HMGA1 fusion transcript leads untranscribed exons of HMGA1 to be replaced by the first 5 exons of the TBL1XR1 gene. The result is that the entire coding region of HMGA1 comes under the control of the TBL1XR1 promoter leading to dysregulation of HMGA1.

Acknowledgements

This study was supported by grants from the Norwegian Radium Hospital Foundation.

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