PVT1: A Cancer-associated Non-coding Gene Revisited

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Abstract

PVT1 was originally identified as a transcriptional unit from a human homologous sequence to Pvt1, which was cloned from murine plasmacytoma with t(6;15). Previous studies have revealed various genetic alterations in the PVT1 locus, including chromosome translocation, amplification, chromothripsis, and single nucleotide polymorphisms in human diseases, suggesting important roles of PVT1 in the pathogenesis. However, because this locus does not produce protein coding sequences, its functional properties have not been characterized and its biological significance remains unclear. Recent studies have shown that the PVT1 locus encodes lincRNAs and microRNAs. Therefore, current investigations are being performed focusing on the biological features of this long-standing puzzle gene as a non-coding gene.

Keywords: PVT1; Genetic alterations; microRNA; lincRNA

Introduction

Majority of cancer cells show chromosome abnormalities, including amplifications, deletions, and translocations, and these are caused by genetic alterations during tumor development. Identification of genes that are responsible for these chromosome abnormalities has elucidated important tumorigenic mechanisms.

In human B cell malignancies, chromosome translocations, involving one of three immunoglobulin gene (IG) loci (heavy chain gene, IGH/14q32; kappa chain gene, Igk/2p12; lambda chain gene, Igλ/22q11), are frequently observed and are strongly associated with tumorigenesis. Among these IG loci, IGH/14q32 is the most common target, and chromosome translocations involving Igk/2p12 or Igλ/22q11 are less common, thus those are called as “variant” IG-translocations. Molecular cloning of the breakpoints of IG translocations has revealed several oncogenic sequences that play crucial roles in tumor cell development [1]. The gene targeted by IG translocations becomes closely associated with IG transcriptional elements, resulting in deregulated expression. Most of these targeted genes physiologically involves in the cell cycle, differentiation, apoptosis, or signal transduction in B cells. Thus, deregulation of their expression impairs biological functions and leads to B cell tumorigenesis.

The plasmacytoma variant translocation 1 (Pvt1) gene was originally cloned in early 1980s from a variant translocation breakpoint of t(6;15), which involves the Igκ locus, observed in murine plasmacytoma [2]. Thereafter, a homologous human sequence (human Pvt1) was identified from the equivalent translocation t(2;8)(p12q24) observed in human Burkitt lymphoma [3], and a transcriptional unit encompassing this sequence was cloned and defined as PVT1 [4]. Thus, PVT1 was one of the first genes to be cloned from IG translocations. Although several studies have investigated the functional roles of PVT1 since its molecular identification, similar to other genes cloned from IG translocations, the functional aspects still remain unclear.

In addition to chromosome translocations, it is well known that PVT1 is a target of genetic gains and amplifications in various cancers [5–7]. Moreover, recent genome-wide screening experiments indicated that Single Nucleotide Polymorphisms (SNPs) around the PVT1 locus are predictive of susceptibility to malignant or non-malignant diseases [7–12]. Therefore, observations of these genetic alterations (translocation, amplification, and SNPs) in the PVT1 locus in various diseases suggest that it plays important roles in pathogenesis.

The PVT1 locus produces various alternative transcripts [4], although no protein coding sequences have been determined thus far [7]. Several microRNAs (miRs) from both human and mouse PVT1/Pvt1 loci have recently been validated [13,14]. In addition, transcripts from the PVT1 locus have been identified as large interceding non-coding RNA lincRNA [15]. Although the biological significance of these RNAs is under investigation, the functional characteristics of PVT1 are being analyzed as non-coding RNAs.

This review summarizes on the current knowledge of the structures, genetic alterations, and functions of PVT1.

Structure

The PVT1 region is located 57 kb downstream of MYC on 8q24 and covers approximately 300 kb up to the telomeric end (Figure 1). This gene comprises at least nine annotated exons and encodes at least six alternative transcripts of 2.7–3.3 kb length [7]. Nonetheless, no protein-coding sequences have been identified in these alternative mRNAs.

Huppi et al. [13] recently identified and observed miR1204, miR1205, miR1206, miR1207-5p, miR1207-3p, and miR1208 expression, which reside within the PVT1 region, but do not overlap any PVT1 exons [13]. Although human and mouse PVT1 (Pvt1) transcripts are encoded in significantly different positions in annotated exons, relative positions of miRs are highly conserved between species [7,13,14], indicating fundamental roles of these miRs across diverse species. Transcripts produced from PVT1 are presently considered to be lincRNAs [7,16], which are non-coding transcripts of more than 200 nucleotides that may be involved in several biological processes. Moreover, gene expression profiling using lincRNA probes recently revealed that PVT1 encoded transcripts are among the top 30 lincRNAs expressed in gastric cancers [15], suggesting functions of PVT1 as lincRNAs in carcinogenesis. Therefore, PVT1 is believed to be a host gene for lincRNAs and miRs, rather than a protein coding gene.

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Genetic Alterations in Human Diseases

Chromosome translocation

Chromosome translocations involving the 8q24 locus are observed in all cases of Burkitt lymphoma, some cases of non-Hodgkin lymphoma, and advanced cases of multiple myeloma [17,18]. Among 8q24-translocation partners, IGH/14q32 is the most common, followed by IGK/22q11 and IGKV/2p12. These result in t(8;14)(q24;q32), t(8;22) (q24;q11), and t(2;8)(p12;q24) translocations, respectively [17]. In addition to Ig, various non-IG partners are translocated with the 8q24 region [18-20]. Lymphoma or multiple myeloma with the 8q24 translocations shows rapid clinical progression irrespective of tumor types. Therefore, identification of the genes responsible for 8q24 translocations is critical for understanding these aggressive cancer phenotypes.

In t(8;14)(q24;q32) translocation, 8q24 breakpoints are to the 5’-end of MYC or its first intron. No transcriptional units have been identified from the intervened sequence between the 8q24 breakpoint and MYC, and the oncogenic actions of MYC are well characterized. Therefore, MYC is believed to be responsible for the t(8;14)(q24;q32) translocation. In contrast, breakpoints of other variants or non-IG 8q24 translocations are to the 3’-end of MYC, or within or downstream of PVT1. Because MYC is a strong cancer-associated gene and PVT1 is a non-coding gene, it is more likely that MYC would be responsible for those translocation rather than PVT1.

Although few breakpoints within PVT1 have been cloned, some putative breakpoint clusters have been found near PVT1 exon 1, Burkitt’s Variants’ Rearranged Region 1 (BVR1), and the human homologous region of PVT1 (Figure 1) [21-24]. However, the relationship between clinicopathological observations and these breakpoint clusters remains unknown.

Chromosome translocations targeted to the PVT1 region often create chimeric transcripts, comprising PVT1 exon 1 and partner genes [18,25,26]. As discussed below, PVT1 exon 1 is also co-amplified with MYC in various cancers, potentially indicating its pathological significance.

PVT1 amplification

Gains in copy numbers or amplification of 8q24 have been noted in various cancer cell types and are often associated with poor prognosis or drug resistance [7]. High-resolution analyses of somatic copy-number alterations indicate that the 8q24 region is one of the most frequently amplified regions across human cancers [27]. The prominent oncogene MYC is located on this locus, and no protein coding sequence has been identified in the surrounding 1.8 Mb [7]. Therefore, MYC has long been considered responsible for 8q24 gains and amplifications in cancers. However, recent studies indicate that MYC is not always the target of 8q24 amplification. For example, Guan et al. [6] reported that MYC and PVT1 independently contribute to ovarian and breast cancer development in cell lines bearing 8q24 amplifications.

Hoppi et al. described two types of the 8q24 amplification, designated amplification 1 and amplification 2 (Figure 1) [7]. Amplification 1 includes MYC, PVT1 exon 1, and miR1204, whereas, amplification 2 comprises the region distal of PVT1 and miR1208. Amplification 1 is often co-amplified with MYC and PVT1 exon 1, and upregulation of both transcripts has been described in colon cancers, small cell lung cancers, and neuroepithelioma. However, the biological and pathological significances of these two amplification regions remain unclear.

Chromothripsis

In addition to chromosome translocations and amplification, the PVT1 locus has been shown to be the target of chromothripsis, which is a process by which distinct chromosomes or chromosomal regions become fragmented into numerous segments during catastrophic events, and the segments are then inaccurately reassembled by DNA repair mechanisms [28-30]. Recently, large-scale genome wide screening studies of numerous medulloblastomas revealed that PVT1 fusion genes are highly recurrent and are generated through a chromothripsis-like process in group 3-type medulloblastomas [26]. One of the PVT1 fusions, S’-PVT/MYC-3’, has also been found in a colon cancer cell line containing double-minute chromosomes derived from 8q24 [5].

Single-Nucleotide Polymorphism (SNP)

Previous studies have revealed that the 8q24 region is important for susceptibility to several malignancies and to some non-malignant diseases [7-12]. This risk is primarily associated with SNP variants at the proximal end of MYC, although a few susceptibility variants have been identified in the PVT1 region (Figure 1) [7]. Whereas most risk variants have been analyzed in relation to MYC, Myer et al. [9] recently identified a functional SNP variant that reduces binding of the transcription factor YY1 and is associated with increased PVT1 expression in prostate cancers.

PVT1 has also been linked with susceptibility to non-malignant diseases, including end-stage diabetic renal disease [10,11]. The associated-risk SNPs are located within the PVT1 locus, and one of

Figure 1: Relative positions of MYC (three exons), PVT1 (nine exons), microRNAs, translocation breakpoints, SNPs and amplification regions are shown. This figure is modified from previously published manuscripts [7,20,24-26]. The direction of the bold arrow indicates centromere to telomere.
the resulting variant transcripts is expressed in kidney cells. Therefore, PVT1 may be implicated in the development and progression of diabetic nephropathy, through mechanisms involving Extracellular Matrix (ECM) accumulation [31]. In addition, a genome-wide association study of 9,772 patients with multiple sclerosis identified PVT1 as one of 29 novel susceptibility loci [12].

Function

Although previous studies of genetic alterations around the PVT1 locus implicate PVT1 in the pathogenesis of the human diseases mentioned above, little is known of its function, and contrasting effects on cell survival have been reported [6,32-34]. Guan et al. [6] showed that inhibition of PVT1 but not of MYC induces apoptotic responses in breast and ovarian cell lines with amplified and over-expressed MYC and PVT1. This result indicated that PVT1 is an anti-apoptotic molecule [6]. In contrast, Barsotti et al. [32] reported that PVT1 and mir1204 are induced in a p53-dependent manner and that ectopic mir1204 expression leads to increased p53 levels and cell death, controversially suggesting pro-apoptotic activities of PVT1. However, differences between these observations may reflect differing materials and methods and may also be due to functional differences between PVT1 lincRNA and miR1204. Alvarez and DiStefano [31] observed that PVT1 locus. Although previous studies of genetic alterations around the PVT1 locus implicate PVT1 in the pathogenesis of the human diseases mentioned above, little is known of its function, and contrasting effects on cell survival have been reported [6,32-34]. Guan et al. [6] showed that inhibition of PVT1 but not of MYC induces apoptotic responses in breast and ovarian cell lines with amplified and over-expressed MYC and PVT1. This result indicated that PVT1 is an anti-apoptotic molecule [6]. In contrast, Barsotti et al. [32] reported that PVT1 and mir1204 are induced in a p53-dependent manner and that ectopic mir1204 expression leads to increased p53 levels and cell death, controversially suggesting pro-apoptotic activities of PVT1. However, differences between these observations may reflect differing materials and methods and may also be due to functional differences between PVT1 lincRNA and miR1204. Alvarez and DiStefano [31] observed that PVT1 expression was significantly up-regulated after treatment of human mesangial cells with glucose and suggested that the resulting ECM accumulations cause diabetic nephropathy.

Further studies on the biological functions of non-coding RNAs may facilitate understanding of the pathogenic and physiological functions of PVT1.

Conclusion

Numerous previous reports have identified various genetic alterations within or surrounding the PVT1 locus. Although PVT1 appears to play pivotal roles in human disease, little is known of the associated biological characteristics. Recently, it was recognized that the PVT1 locus contains sequences for lincRNAs and microRNAs [7]. Future functional analyses are warranted to clarify the biological significance of PVT1, a long-standing puzzle gene.

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References


