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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 tumoriogenic mechanisms.

In human B cell malignancies, chromosome translocations, involving one of three immunoglobulin gene (*IG*) loci (heavy chain gene, *IGH*/14q32; kappa chain gene, *IGκ*/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 *IGκ*/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)(p12;q24) 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 intervening 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 upto 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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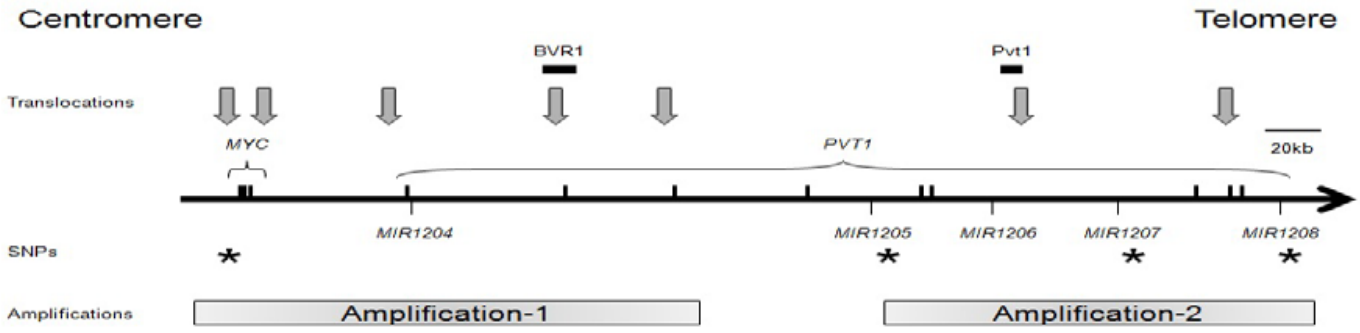

Figure 1: Relative positions of *MYC* (three exons), *PVT1* (nine exons), microRNAs, translocation breakpoints, SNPs and amplification regions are shown. This figure is modified from previously published manuscripts [7,20,24-26]. The direction of the bold arrow indicates centromere to telomere.

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 *IGλ*/22q11 and *IGκ*/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*s, 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 of 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.

Huppi 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 meduloblastomas revealed that *PVT1* fusion genes are highly recurrent and are generated through a chromothripsis-like process in group 3-type meduloblastomas [26]. One of the *PVT1* fusions, 5'-*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

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 p^{53}-dependent manner and that ectopic miR1204 expression leads to increased p^{53} levels and cell death, controversially suggesting pro-apoptotic activities of *PVT*. 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 mesangeal 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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