Genomic copy number gain of the human 8q24 region is found in all major cancers. The 8q24 region is a ‘gene desert’ that contains the v-myc avian myelocytomatosis viral oncogene homolog (MYC), an obvious candidate locus. However, gain/amplification of 8q24 frequently includes MYC and the adjacent regions, which contain additional genetic elements whose potential role in the induction of cancer is underinvestigated. Adjacent to MYC is plasmacytoma variant translocation 1 (PVT1), a long non-coding RNA (lncRNA) that was originally identified as a cluster of breakpoints for viral integration and translocation in T- and B-cell lymphomas. The PVT1 locus is syntenically conserved between the human and mouse. Although PVT1 is a mutational hotspot and frequently overexpressed in cancers, its role in tumorigenesis is poorly understood.

Despite the existence of several mouse models of Myc, lack of an in vivo system that links MYC with additional elements in the 8q24 region has been an impediment to understanding the contribution of additional genetic elements in this region to the pathophysiology of cancer. We sought to functionally determine whether gain of MYC alone is sufficient to drive tumor formation, or whether other elements in this gene-desert region also play a role in malignancy. We used chromosome engineering of mouse ES cells to develop mice with a single-copy gain of the following regions: (1) an ~1.9 Mb genomic interval that is syntenic to Hu 8q24.21 encompassing Myc, Pvt1, coiled-coil domain containing 26 (Ccdc26), and gasdermin-C (Gsdmc); (2) Myc only, and (3) Pvt1, Ccdc26, and Gsdmc.

Our first surprise came when mammary glands of mice with gain of Myc/Pvt1/Ccdc26/Gsdmc, MMTVNeu/+ cells and human breast cancer cell lines with 8q24 amplification (SK-BR-3 and MD-MBA-231) confirmed that MYC and PVT1 may share the same oncogenic pathway in these cells.

SiRNA mediated knockdown of PVT1 in SK-BR-3 and MDA-MB-231 resulted in significant reduction of MYC protein, but, interestingly, not transcript levels. This suggested that PVT1 might regulate MYC protein stability. A chase experiment using the protein synthesis inhibitor cycloheximide in cells with and without PVT1 confirmed that PVT1 confers increased stability on MYC protein. Further analysis revealed that PVT1 decreases phosphorylation of MYC at the Threonine 58 residue (MYC\(^{T58}\)), a post-translational modification that licenses MYC degradation. We also found that PVT1 and MYC preferentially co-localize in the nucleus, and co-immunoprecipitation using antibody against MYC can enrich for the PVT1 transcript, suggesting that PVT1 and MYC might be a part of a ribonucleo–protein complex in which PVT1...
attenuates phosphorylation at MYC\textsuperscript{T58}, thus increasing its stability.

We investigated whether PVT1/MYC co-operation is a fundamental feature in all 8q24 gain cancers by analyzing genomic data from the cancer genome atlas (TCGA) and the Progenetix database. We identified the subset of cancers with 8q24 gain/amplification, and compared how many of those amplicons contained only MYC or PVT1 or both MYC and PVT1. We hypothesized that if PVT1 and MYC co-operate in human cancers with 8q24 gain, the majority of these amplicons should contain both MYC and PVT1. Indeed, 98% of the 8q24 amplicons contained both MYC and PVT1, confirming that both loci are preferentially amplified/gained concurrently in these cancers.

Finally, we examined whether MYC-driven cancer cells are dependent on PVT1. The driver mutation in the colorectal cancer cell line HCT116 is a mutant \(\beta\)-catenin gene. A stable \(\beta\)-catenin protein recruits TCF4 to upregulate MYC transcription in these cells. Using the CRISPR/Cas9 system,\(^6\) we deleted PVT1 in these cells. PVT1-deficient HCT116 cells are impaired in their tumorigenic potential compared to their wild-type controls. Importantly, we noticed \(\sim 50\%\) reduction in MYC protein levels in these PVT1-deficient cells. Thus, multiple lines of evidence suggest that PVT1 plays a crucial role in augmenting MYC protein in 8q24 gain cancers. Similarly, a recent study implicates another frequently amplified oncogenic lncRNA called FAL1 at 1q21 in the stabilization of BMI1 in ovarian cancers, suggesting a broader role of lncRNAs in the fine tuning of oncoproteins in cancer.\(^7\)

We have identified a novel regulation of MYC via the lncRNA PVT1, at least in cancers where these loci are co-amplified (Fig. 1). Whether PVT1 plays a role in MYC regulation in 8q24 non-supernumerary cancers remains to be investigated. Additionally, a detailed mechanistic understanding of how PVT1 RNA regulates MYC protein in cancer cells can be exploited therapeutically. It has been shown that MYC ablation causes regression of K-Ras-mediated lung cancer in mice,\(^8\) suggesting the central importance of MYC in cancers. However, so far it has not been possible to target MYC directly.\(^9\) JQ1, a small molecule inhibitor of bromodomain 4 (Brd4) has recently been shown to indirectly inhibit MYC transcription in hematological malignancies.\(^10\) Inhibition of PVT1, thereby fine tuning MYC stability in cancers to precancerous levels with less toxic side effects, could be therapeutically exploited for patients with gain of 8q24.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Funding**

This work was supported by the Masonic Cancer Center Laboratory start-up funds (A.B.), and by grants from the Masonic Scholar Award (A.B.), Karen Wyckoff Rein in Sarcoma Fund (A.B.), Translational Workgroup Pilot Project Awards by Institute of Prostate and Urologic Cancer, University of Minnesota (A.B.), American Cancer Society Research Scholar Grant Award# RSG-14-074-01-TBG (A.B.).
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