TECHNOLOGY

Xv1 Inhibition As A Novel Antimitotic Cancer Therapy

OVERVIEW

Mitosis has been an attractive target for anti-cancer therapies given that uncontrolled cell division is one of the key hallmarks of cancer. However, some normal cells like hematopoietic progenitor cells (HPCs), also undergo rapid cell division. Therefore, nearly all current cell cycle-targeted drugs are limited by their severe toxicity to such normal cells. UMB investigators recently identified a novel X-box binding protein 1 variant (Xv1)- tubulin tyrosine ligase like 6 (TTLL6) pathway that has been shown to be specifically required for mitotic progression of cancer cells, but not normal cells. This mRNA variant and protein, named Xv1, is expressed by the majority of cancer cells but absent in the normal tissues. Knockdown of Xv1 induces mitotic arrest in cancer cells and slow tumor growth. The present invention provides a valuable opportunity to overcome the shortcomings of current anti-mitosis therapies by developing inhibitors to this cancer-specific pathway and is applicable to a broad range of cancers.

TECHNOLOGY

Alternative start sites, alternative splicing, and alternative promoters are frequently used to regulate tissue or cancer-specific transcription. Recently discovered Xv1, an alternatively spliced variant of the bZiP transcription factor XBP1, has been shown to be a mediator of the endoplasmic reticulum's stress-activated unfolded protein response (UPR) (Figs. 1A). Surprisingly, Xv1 is not involved in UPR, instead regulating a pathway that is seemingly unique to cancer. While variable levels of Xv1 transcript are seen in over two dozen cancer cell lines, it is not detected in primary human fibroblasts or non-transformed MCF10A cells (Figs. 1B). Analysis of TCGA data revealed that Xv1 is the most abundant transcript variant of XBP1 in about two-thirds of 10,535 different cancer tissues. Small interfering RNAs (siRNAs) to target a unique exon of Xv1 (Fig. 1A, red) can knock down Xv1 message without affecting other XBP forms. In vitro, the siRNAs induce apoptosis in cancer cells, without affecting primary cells (Fig. 1C). Additionally, when human breast cancer cells were treated with Xv1 siRNA before injection as xenografts in mice, tumor growth was significantly slowed (Fig. 1D). Further studies have shown that Xv1 upregulates Xv1 upregulates the polyglutamylase tubulin tyrosine ligase-like 6 (TTLL6) and promotes mitosis of cancer cells.

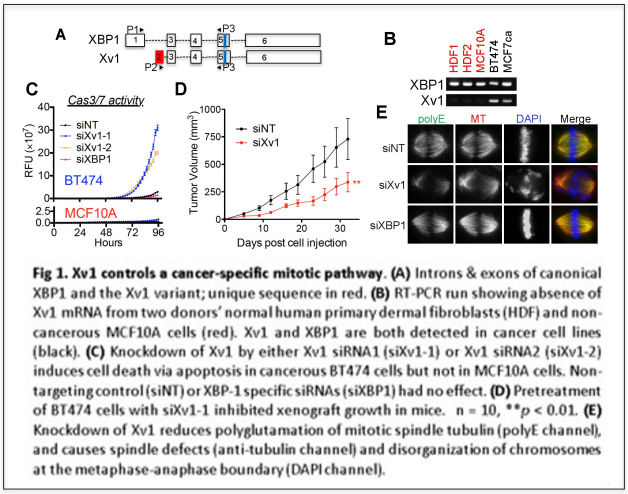

Fig 1. Xv1 controls a cancer-specific mitotic pathway. **(A)** Introns & exons of canonical XBP1 and the Xv1 variant; unique sequence in red. **(B)** RT-PCR run showing absence of Xv1 mRNA from two donors' normal human primary dermal fibroblasts (HDF) and non-cancerous MCF10A cells (red). Xv1 and XBP1 are both detected in cancer cell lines (black). **(C)** Knockdown of Xv1 by either Xv1 siRNA1 (siXv1-1) or Xv1 siRNA2 (siXv1-2) induces cell death via apoptosis in cancerous BT474 cells but not in MCF10A cells. Non-targeting control (siNT) or XBP-1 specific siRNAs (siXBP1) had no effect. **(D)** Pretreatment of BT474 cells with siXv1-1 inhibited xenograft growth in mice. n = 10, $^{**}p < 0.01$. **(E)** Knockdown of Xv1 reduces polyglutamation of mitotic spindle tubulin (polyE channel), and causes spindle defects (anti-tubulin channel) and disorganization of chromosomes at the metaphase-anaphase boundary (DAPI channel).

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PATENT STATUS

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ATTACHMENTS

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EXTERNAL RESOURCES

- Zhong Y., et al. (2022)

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