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PERSPECTIVE ARTICLE OPEN ACCESS

WTX beyond WNT signaling pathway

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Abstract – Gastric cancer (GC) is a major malignancy in many developing countries with low early detection rate. As a tumour suppressor gene, *WTX* inhibits PI3K/AKT/mTOR pathway activity by inhibiting PI3K phosphorylation. *WTX* loss of WTX protein associates with tumor metastasis and poor survival of GC patients. During GC progression, an aberrantly elevated miR-20a-5p expression has been found, which inhibits *WTX* expression and induces PI3K phosphorylation, thereby activating the PI3K/AKT/mTOR pathway and promoting cellular proliferation and migration. A new mechanism in which miR-20a-5p promotes GC progression by regulating *WTX* expression to control PI3K/AKT/mTOR pathway activity has been recently discovered. These findings might be useful for developing novel therapeutics to inhibit the progression of GC.

Key words: Gastric cancer, PI3K/AKT, WTX/AMER1, miR-20a-5p.

Gastric cancer (GC) is the fifth most common cancer incidence and the third most common cause of cancer death worldwide. About half of the GC patients come from China, most of whom were in the late stages with lymph node or distal metastasis at the time of diagnosis, resulting in only 16.35% of the diseases at stages I and II [1–3]. It is, therefore, critical to elucidate the underlying mechanisms for GC promotion and progression by which novel therapeutics could be developed.

Initially found in Wilms tumor, *WTX* (Wilms tumor gene on the X chromosome, also called *AMER1*) is an X-linked tumor suppressor located on chromosome Xq11.2. This gene has 1 transcript (splice variant), 189 orthologues, 2 paralogues and is associated with phenotypes. The full-length WTX protein resides at the plasma membrane and cytoplasm and possesses three adenomatous polyposis coli (APC) binding domains [4, 5]. The short isoform localizes primarily to the nucleus. Nuclear WTX forms a complex with β-catenin and the destruction complex (AXIn1, β-transducin repeat-containing protein 2, and APC) and promotes ubiquitylation and degradation of β-catenin. The short isoform negatively regulates the Wnt/β-catenin signaling pathway [6].

The inactivation of the *WTX* gene just needs a monoallelic "single-hit" that targets the single X chromosome in tumors from males and the active X chromosome in tumors from females [7]. The loss of WTX is also linked to a predisposition for nephroblastoma [8]. Mechanistic research has revealed that WTX can inhibit Wnt/β-catenin signaling pathway activation by binding β-catenin and promoting β-catenin ubiquitination and degradation [9, 10]. The interaction between WTX and p53 affects nuclear proteins. The loss of WTX accelerates CBP/p300 protein turnover and attenuates this modification of p53. In p53-reconstitution experiments, cell-cycle arrest, apoptosis, and p53 target-gene expression are suppressed by the depletion of WTX. Together, these results suggest that WTX modulates the p53 function partly by regulating its activator CBP/p300 [11].

According to previous studies, WTX was generally lost in GC, and the stomach was identified as another important target organ of the *WTX* gene [12]. Different from the high mutation rate (16.3%–30%) and high loss rate in Wilms tumor [13], *WTX* mutations and high methylation levels of *WTX* promoters are rare among GC, which suggests that there may be other mechanisms leading to the silencing of *WTX* gene. Li and colleagues report in the *Journal of Experimental & Clinical Cancer Research* that using three published target prediction databases, they selected miR-20a-5p as the top candidate regulator of WTX expression in GC. The following luciferase assay experiments confirmed that miR-20a-5p could directly bind to the *WTX* 3'UTR. After that, the authors established gastric tumor mouse models to determine the effect of WTX on tumor formation and growth in vivo. Additional cellular functional tests in GC cell lines showed that WTX significantly inhibited

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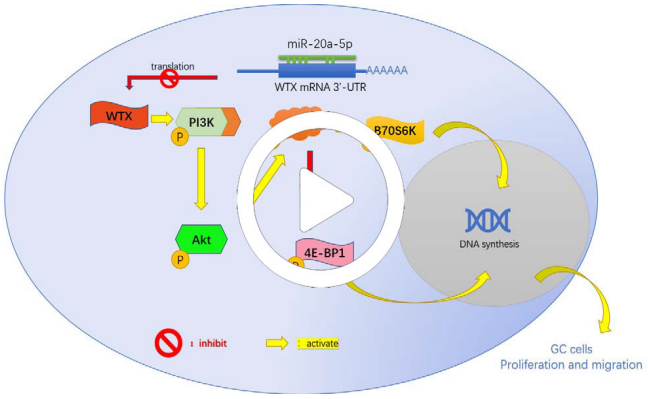

Video 1. WTX inhibits PI3K/AKT/mTOR pathway. https://vcm.edpsciences.org/10.1051/vcm/2022006#V1.

the proliferation, migration, and invasion abilities of GC cells. Over-expression of WTX in AGS cells significantly inhibited the activity of PI3K/AKT signaling. Mechanistically, WTX expression suppresses PI3K/AKT/mTOR pathway activity by inhibiting PI3K phosphorylation (Video 1). Finally, miR-20a-5p was found to positively regulate PI3K/AKT pathway activation by inhibiting *WTX* expression, thereby promoting GC progression [14].

It has been reported that WTX plays a major role in organ development and tumor suppression, but its functions have not been well elucidated. The clinical significance and specific mechanism of the *WTX* gene in different tumor types still need further study. Li' s article first reveals the clinical significance of the *WTX* gene in GC, and the clinicopathological consequences showed that WTX loss is associated with poorer GC differentiation, more invasion, increased tumor cell proliferation, increased lymph node metastasis, and poorer GC patient prognosis. These findings suggest that WTX loss could be used as a prognostic marker for GC patients.

The mechanism of inhibiting PI3K phosphorylation by WTX to suppress PI3K/AKT/mTOR signaling in GC might also work in other type of malignancies. Further explorations are warranted to identify the specific protein binding sites of miR-20a-5p on the promoter regions of *WTX* and the phosphorylation sites of PI3K.

Conflict of interest

The authors have nothing to disclose.

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