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WT1 and Leukemia

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ABSTRACT

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WT1 and Physiological Function

The *Wilms' tumor1* (*WT1*) gene is located on human chromosome 11p13 and is about 50 kb in length and consists of ten exon [1,2]. It encodes a zinc-fingers transcriptional regulatory protein containing four Cys2-His2 Kruppel-like zinc-fingers on their C-terminus. *WT1* was first identified as a candidate tumor susceptibility gene for Wilms' tumor [1]. There are at least 36 WT1 isoforms have been detected in mammalian thus far, which are the result of alternative mRNA splicing, transcription start sites, translation initiation sites and RNA editing. The four major WT1 isoforms generated from alternative splicing are WT1(-17AA/-KTS), WT1(+17AA/-KTS), WT1(-17AA/+KTS), and WT1(+17AA/+KTS) also named as WT1 A, B, C and D isoforms respectively. These WT1 alternative splicing events confer functional diversity of WT1. The WT1-KTS was shown to function as a DNA binding protein whereas WT1+KTS was shown to possess RNA binding property, therefore is likely involved in post- transcriptional regulation [3]. WT1 was shown to contribute various physiological functions including cell proliferation, differentiation, survival and apoptosis. The involvement of WT1 in these cellular functions was largely mediated by transcriptional regulatory role of the WT1. Intriguingly, the function of WT1 seems to be modulated by the expression and mutational status of WT1 interactive proteins including p53 [4,5] and PAR4 [6].

WT1 and Malignancies

The role of WT1 in the carcinogenic process becomes the major topic of investigation. Although WT1 was first discovered as a tumor suppressor gene in Wilms' tumor, expression pattern of WT1 gene in certain malignancies suggested an oncogenic property [7]. Overexpression of wild type WT1 was detected in various malignancies especially breast cancer [8,9], ovarian cancer [10], hepatocellular carcinoma [11,12] and leukemia [13-15]. Moreover, overexpression of WT1 in some cancers has been shown to be correlated with poor prognosis. For example, *WT1* expression detected by immunohistochemical method on ovarian cancer specimens showed that 50% of ovarian carcinoma samples possessed high level of *WT1* expression, which was associated with shortened overall survival of this cancer [16,17].

WT1 and Leukemia

As overexpression of WT1 in leukemia is the most consistent finding, oncogenic role of WT1 has been proposed. In AML patients, the ratio of spliced WT1 isoforms A:B:C:D was shown to be 17:23:24:31% while the ratio of these isoforms was 10:16:7:39% in normal $CD34^+$ cells. The physiological relevance of the altered WT1 isoforms ratio was addressed. The preferential expression

of WT1 isoforms A, B, and C was detected in AML patients [18]. Moreover, the trend of correlation was also recapitulated in CML, in which WT1 overexpression is associated with relapse of the disease [19,14]. The role of specific WT1 isoforms in oncogenesis has been also investigated. One of the truncated-WT1 isoform was also detected in some cancer cell lines and primary patient samples, including prostate cancer cell lines, K562, MCF-7 cells and acute leukemic blood samples [20]. Interestingly, overexpression of wild type *WT1* and truncated *WT1* were detected in 94.5% and 19% of AML patients, respectively [21]. This truncated form of WT1 was generated by the use of cryptic translational start site located in intron 5 therefore consists of the C-terminal domain encoded by exon 6-10 only [20]. Recently, another novel truncated called Ex4a(+) WT1 isoform was detected in some cancers [22]. Interestingly, overexpression of Ex4a(+) WT1 suppressed of *Bcl-xl* gene expression and induced mitochondrial damage and apoptosis. This truncated isoform likely had an ability to modify the function of wild type WT1 via protein-protein interaction [22].

The functional studies to dissect the molecular pathway underlying WT1-mediated leukemogenesis have been reported. Downregulation of *WT1* gene resulted in reduced cell proliferation with G0/G1 arrest of cell cycle in myeloid leukemia cells [23]. Moreover, suppression of WT1 by curcumin inhibited growth and induced G2/M arrest in myeloid leukemia cells [24]. Furthermore, *WT1* silencing by shRNA resulted in increased fraction of cells in G0/G1 phase and reduced proportion of cells in S-phase in this cancer cells [24]. Although most of the studies indicated the oncogenic property of WT1 in leukemia, some conflicting evidences were demonstrated. Overexpression of *WT1* induced differentiation of myeloblastic leukemia M1 cells [25]. Moreover, low level of W1 protein expression was reported in T-ALL cell lines and primary T-ALL cells from the patients. In addition, induced WT1expression in this T-ALL cell resulted in upregulation of CD95L expression and enhancement of CD95L-mediated cell death [26]. Recently, WT1 was shown to interact with TET2 and this interaction is critical for growth inhibition of leukemia cells [27]. These discrepancy results likely addressed the cellular context dependent role of WT1.

The studies using Anti-WT1 strategies show that downregulation of WT1 by using antisense oligonucleotides led to inhibition of cellular proliferation of K562 and fresh leukemia cells from AML and CML patients [28]. Moreover, it has been shown that in cell culture condition, the reduction in serum level or the decreased pH in culture media led to growth inhibition of CML and AML primary cells obtained from leukemia patients. Interestingly, this growth suppressive effect was shown to be mediated by WT1 downregulation [23]. Using Anti-WT1 strategy using plant extract, curcumin, resulted in reduced K562 cell proliferation by dose- and time-dependent manners via the inhibition of protein kinase C (PKC) pathway [29]. Moreover, overexpression of WT1(+17AA/+KTS) and WT1(-17AA/-KTS) isoforms resulted in delay differentiation of K562 cells induced by 12-o-tetradecanoylphorbol 13-acetate [30]. On the other hand, WT1(+KTS) overexpression induced monocytic differentiation in murine promyolocytic leukemia M1 [31].

Regading to apoptosis, specific knockdown of WT1(+17AA) by siRNA induced apoptosis via activation of caspase-3 and -9 in leukemia cells [32]. With regard to cell cycle regulation, the inhibition of WT1 expression caused G2/M arrest in leukemic cells [33]. Additionally, downregulation of WT1 resulted in reduced S-phase progression on K562 cells [24]. In contrast, overexpression of WT1 in murine myeloblastic leukemia (M1) cell line, the cells exhibited G1 arrest and apoptosis [34]. Therefore, role of WT1 in cell cycle is likely depended on cellular context [30]. Recently, by using Lentiviral-based RNAi system WT1 has been shown to the RNA expression of IL-2, IL-2RB and IL-2RG in the myeloid leukemia cells [35]. In this study, WT1 silencing led to growth inhibition and enhanced apoptosis and decreased S-phase fraction as well as downregulation of the RNA expression of IL-2, IL-2RB, IL-2RG. This study supported the oncogenic role of WT1 in myeloid leukemia and the discovery of new WT1 target genes; IL-2, IL-2RB and IL-2RG which are likely involved in WT1-mediated leukemogenesis [36].

Conclusion

The large pieces of evidence in the literature supported the oncogenic role of WT1 in leukemia. WT1 has been already used for tumor marker and/or prognostic indicator of some type of leukemia. Molecular mechanism underlying the WT1 mediated leukemic transformation process has been actively investigated. As WT1 been shown to possess different roles largely depending on cellular context, the understanding about the molecular network of signaling pathway initiated by WT1 in the specific subtypes of leukemia would be beneficial to design tailored molecular-based therapy suitable for each leukemic subtypes.

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