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Review

The development of Wilms tumor: From WT1 and microRNA to animal models

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ABSTRACT

Wilms tumor recapitulates the development of the kidney and represents a unique opportunity to understand the relationship between normal and tumor development. This has been illustrated by the findings that mutations of Wnt/β-catenin pathway-related WT1, β-catenin, and WTX together account for about one-third of Wilms tumor cases. While intense efforts are being made to explore the genetic basis of the other two-thirds of tumor cases, it is worth noting that, epigenetic changes, particularly the loss of imprinting of the DNA region encoding the major fetal growth factor IGF_2, which results in its biallelic over-expression, are closely associated with the development of many Wilms tumors. Recent investigations also revealed that mutations of Drosha and Dicer, the RNases required for miRNA generation, and Dis3L2, the 3′–5′ exonuclease that normally degrades miRNAs and mRNAs, could cause predisposition to Wilms tumors, demonstrating that miRNA can play a pivotal role in Wilms tumor development. Interestingly, Lin28, a direct target of miRNA let-7 and potent regulator of stem cell self-renewal and differentiation, is significantly elevated in some Wilms tumors, and enforced expression of Lin28 during kidney development could induce Wilms tumor. With the success in establishing mice nephroblastoma models through over-expressing IGF_2 and deleting WT1, and advances in understanding the ENU-induced rat model, we are now able to explore the molecular and cellular mechanisms induced by these genetic, epigenetic, and miRNA alterations in animal models to understand the development of Wilms tumor. These animal models may also serve as valuable systems to assess new treatment targets and strategies for Wilms tumor.

Contents

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1. Wnt/β-catenin pathway and the development of Wilms tumor

1.1. Introduction

Wilms tumor, also known as nephroblastoma, is the most common childhood kidney tumor. It affects ~1 in 10,000 children and accounts for ~8% of pediatric cancers. The tumor is usually discovered before the age of 6 years old and is regarded as a prototype of tumors originated from abnormal differentiation and development [1]. Though the overall survival rate for Wilms tumor has reached 90%, a significant portion of the patients have survival rate less than 70%, and up to 25% of the survivors suffer from serious chronic health conditions 25 years after diagnosis, underscoring the importance for exploring the molecular and cellular mechanisms of the tumor [2]. The cancer genome project has revealed that, while adult human cancer genomes often contain more than 100 genetic mutations, pediatric cancers such as neuroblastomas and acute lymphocytic leukemia usually have only ~10 mutations [3]. Although the whole genome studies of Wilms tumor remain to be completed, it is conceivable that Wilms tumor might harbor a similar small number of genetic alterations that are responsible for the development of the tumor.

The development of the mammalian kidney depends on the reciprocal interactions between the ureteric bud and metanephric mesenchyme (blastema), which undergoes mesenchymal-to-epithelial transition (MET) to form the epithelial and stromal components of the kidney [4]. It is evident that Wnt9b generated from the ureteric bud and Wnt4 in the mesenchyme play critical roles in the survival, self-renewal, and differentiation of mesenchymal progenitor cells. Recent studies also indicated that signals from the stromal fibroblasts, including Fat4-mediated modulation of the Hippo pathway, cooperate with Wnt9b to promote differentiation of the progenitors in the developing kidney [5]. Most Wilms tumors have a triphasic histology composed of blastema, stroma, and epithelium, recapitulating the kidney development. As a further indication of aberrant differentiation, heterologous elements, such as cartilage and smooth muscle, are observed in some Wilms tumors. Pathological examination also found that clusters of embryonic cells (nephrogenic rests, NR) present in developed kidneys are often precursors of Wilms tumor cells [6]. Microarray analysis found that genes corresponding with the early stage of metanephric development are highly expressed in Wilms tumor, whereas genes corresponding with later kidney development stages are expressed at lower levels [7]. Similar phenomena were observed at protein level using selected markers. A recent study showed that Six2 (a homeodomain transcription factor)-positive progenitor cells, which normally reside adjacent to the ureteric tips in the nephrogenic zone of developing kidney and are largely absent in mature kidney, are extensively present at significantly increased numbers in Wilms tumor tissue [8]. It has also been found that Six2 acts together with the zinc-finger protein Osr1 to maintain nephron progenitor cells in the developing kidney [9]. Notably, it has been shown recently that transient expression of iPS reprogramming transcription factors in mice can induce kidney tumors which consist of undifferentiated dysplastic cells and share a number of characteristics with Wilms tumor [10]. These observations at both morphological and molecular levels led to the general belief that Wilms tumor originates from embryonic mesenchymal progenitors that fail to undergo normal differentiation. Furthermore, it is evident that the tumor may arise from different development stages of the progenitors and manifest as a number of heterogeneous groups [11].

1.2. WT1

The association of Wilms tumor with development is further strengthened by the greatly increased risk of developing Wilms tumor in a number of rare abnormal development-associated syndromes, such as WAGR syndrome, Denys–Drash syndrome, Perlman syndrome, and Beckwith–Wiedemann syndrome. The rate of developing Wilms tumor ranges from 95% in WAGR syndrome to 5% in Beckwith–Wiedemann syndrome. WAGR syndrome is characterized by developing Wilms tumors, Aniridia, Genitourinary abnormalities, and mental Retardation. Mutations in the WT1 gene were found to be responsible for the development of Wilms tumor in WAGR patients and also in ~20% of sporadic cases [12]. Further studies revealed that, depending on the cell line used, WT1 may act as both activator and repressor of certain genes, such as c-myc and bcl-2. It appears that these variations in WT1 transcription activities are due to post-translational modifications, such as phosphorylation and interaction with other proteins and RNAs [13]. As suggested by its expression in gonads, spleen, and the lining of the abdominal cavity, loss-of-function mutations of WT1 were also found in Frasier syndrome, mesothelioma, and some adult myeloid leukemia. However, many investigations found that wild type WT1 is highly expressed in a variety of human cancers, including brain tumors, carcinomas, adenocarcinomas, sarcomas, and leukemia, which led to a clinical trial using peptides derived from WT1 as antigens for immunotherapy [14]. It has also been shown that WT1 promotes the survival of cancer cells in culture and may confer resistance on them to chemotherapeutic agents, and increased expression of WT1 in tumors is associated with poor prognosis following chemotherapy [15]. Furthermore, a recent study using primary Wilms tumor cell lines found that mutated WT1 is required for the proliferation of these cells, likely due to its ability to interact and antagonize the suppressive function of p53 [16]. Thus, WT1 has a complicated role in tumorigenesis. It may act as tumor suppressor or oncogene under different circumstances, and mutation of WT1 could result in gain-of-function to promote the growth of tumor.

The expression and function of WT1 during kidney development have been investigated extensively. WT1 is first expressed at low levels in intermediate mesoderm of E9 embryo and later in the metanephric mesenchyme. Its expression level is significantly increased in the condensed mesenchymal cells that surround the ureteric bud, suggesting that it may play an important role in the differentiation of these cells. It is also expressed in the renal vesicle and in the proximal segment of the comma and S-shaped bodies. In the mature kidney, WT1 expression is mainly restricted to the glomerular podocytes, a highly specialized visceral epithelial cell essential for maintaining the glomerular filtration barrier [17]. The importance of WT1 in kidney development has been clearly demonstrated by the finding that WT1 deficient mice fail to develop kidneys [18], and conditional deletion of WT1 after E11.5 caused the disruption of metanephric mesenchyme differentiation and almost no mature nephrons were generated in the mice [17,19]. It was also found that knockdown of WT1 with siRNA in explant culture of E11.5 kidney resulted in blockage of nephron development at the pre-epithelial stage [20]. Therefore, WT1 is required for the survival and differentiation of kidney progenitors. It is worth noting that the expression of WT1 in podocytes of mature kidney is also essential for the function of glomerulus. Altered WT1 expression in mice podocytes, and mutations of WT1 in Denys–Drash syndrome and Frasier syndrome, all lead to glomerulosclerosis and eventually renal failure [21,22].

To understand how WT1 regulates kidney progenitor cell survival and differentiation, extensive efforts have been made to find genes regulated by WT1. Based on studies using degenerate oligonucleotides