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SRY is a target of WT1

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Abstract

The *SRY* gene has been shown to be a direct transcriptional target of the WT1 transcription factor.

Significance and context

WT1 is an important gene with several functions in the developing embryo. It is expressed in the developing urogenital system, where it is critical for development of the kidneys and gonads. The *WT1* transcript has more than 16 different isoforms as a result of different transcription initiation sites, RNA editing and alternative splicing. Four major isoforms of WT1 result from alternative splicing at two different splice sites: the presence or absence of a 17-amino-acid region encoded by exon 5 is coupled with the presence or absence of three amino acids (KTS) in the zinc-finger region of the WT1 protein.

Early studies indicated that WT1 is a tumor suppressor, as damage to both alleles results in Wilms' tumor. This tumor of the kidney seems to originate from a single mesenchymal stem cell whose proliferation should normally be switched off, but which instead apparently tries to reiterate the normal processes of kidney development. More recent studies suggest that WT1 is both a transcription regulator and a splicing factor, depending on the absence or presence, respectively, of the KTS region. WT1 may also have a role in post-transcriptional regulation. Thus, *WT1* is a single gene with multiple functions depending on where, when and how it is expressed and processed.

The expression of *WT1* in the developing urogenital system, coupled with the timing of its expression in the early embryo, and its involvement in sex-reversal in some cases, prompted Hossain and Saunders to investigate whether there might be a direct interaction between this gene and the sex-determining gene, *SRY*. *SRY* is the major genetic switch that causes the developing embryo to change course from the default female developmental pathway into the male pathway, and little is known about its regulation.

Hossain and Saunders used plasmid constructs of the *SRY* promoter to drive expression of the luciferase gene and cotransfected these together with *WT1* expression constructs into various cell lines to discover whether the presence of one of the four isoforms of WT1 mentioned above could activate the *SRY* promoter. They also investigated whether any of the *WT1* constructs could activate the endogenous *SRY* promoter in certain cell lines.

Key results

Activation of the *SRY* promoter was achieved by the *WT1* constructs lacking KTS (-KTS), consistent with the proposed transcriptional activator activity of the -KTS isoforms. By assessing the transactivation of various *SRY* deletion constructs, the authors showed that the WT1-responsive element lay within the *SRY* promoter itself. To identify nucleotides essential for transactivation, they then altered nucleotides within the one putative WT1-responsive element found within the *SRY* promoter, and backed this up by gel-shift assays. They showed that this WT1-responsive element was essential for WT1 to bind to and transactivate the *SRY* promoter. They then made *WT1* mutant constructs containing single point mutations known to cause Denys-Drash syndrome (DDS), and found that the most common mutations within the zinc-finger domain resulted in failure to transactivate the *SRY* promoter, whereas those outside this domain transactivated to the same degree as wild-type WT1. Finally, they showed that these mutants did not act in a dominant-negative fashion.

Conclusions

Using a candidate gene approach, Hossain and Saunders showed that *SRY* is a direct target of the WT1 protein. Many other genes have recently been shown to be upregulated by WT1, and none appears to be downregulated, suggesting that WT1 has a major role in upregulating gene expression *in vivo*. The hypothesis that single mutations resulting in DDS operated in a dominant-negative fashion is thrown into doubt by this work. The authors suggest a new model for the mechanism underlying DDS, in which haploinsufficiency reduces the ability of WT1 to activate transcription, thus affecting expression of critical downstream targets.

Reporter's comments

WT1 is a gene with several functions, depending on the context and manner of its expression. This work is therefore particularly topical, given the recent discovery that the human genome contains fewer genes than expected.

Table of links

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References

1. Hossain A, Saunders GF: The human sex-determining gene *SRY* is a direct target of WT1. J Biol Chem. 2001, 276: 16817-16823. 0021-9293

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