The Wilms’ tumor suppressor gene (WT1) has potential to produce 36 different protein isoforms resulting from combinations of alternative splicing, RNA editing and use of alternative translational initiation codons (Hohenstein and Hastie 2006). WT1 has three sites of translational initiation giving rise to protein products with contradictory biological functions (Scharnhorst et al. 1999; Hossain et al. 2006). This talk will showcase the complexities of eukaryotic translational initiation events as illustrated by WT1.

The predominant WT1 protein isoform is a transcriptional regulator with both activator and repressor activities and is involved in urogenital development. Given the importance of this isoform in normal mammalian growth and development, it is essential that it is initiated from the correct AUG in the mRNA (Discenza and Pelletier 2004; Bor et al. 2006). Translation from a major AUG involves a scanning mechanism by the 43S complex. The 43S complex scans downstream on the mRNA until it encounters an AUG triplet in the context of a Kozak sequence (GCC(A/G)CCAUGG) (Pisarev et al. 2006; Lomakin et al. 2006). Assembly of a functional translational initiation complex capable of beginning translation at the correct codon in the mRNA involves the concerted activities of at least 12 initiation factors (eIFs) (Maag et al. 2005). Several studies have demonstrated the importance of eIF1 in cognate AUG selection processes (Pestova and Kolupaeva 2002; Maag et al. 2005; Lomakin et al. 2006; Pisarev et al. 2006). It has been proposed that eIF1 may trigger a conformational change that is important in regulating the start codon recognition event (Maag et al. 2005).

An N-terminally truncated WT1 isoform is derived from translational initiation at a downstream, in-frame AUG. This isoform has greater transcriptional activation potential than the predominant WT1 protein but does not act as a transcriptional repressor. It is unclear how or when translation is initiated from the second in-frame AUG, but aberrations from a normal ratio between the predominant and truncated WT1 isoforms may contribute to disease (Scharnhorst et al. 1999).

WT1 also initiates translation from an upstream, in-frame, non-AUG codon and the function of the protein product remains unclear (Bruening and Pelletier 1996; Touriol et al. 2003; Tikole and Sankararamakrishnan 2006). Although it is uncertain how the 43S ribosomal subunit is able to initiate translation at a non-AUG codon, the majority of mRNAs initiating at non-AUG sites can be predicted from genomic sequences and therefore sequence context appears to be important for the process (Tikole and Sankararamakrishnan 2006).

While the WT1 tumor suppressor gene was cloned over 15 years ago, its normal and tumorigenic functions are complex and understudied. Investigations into the translational regulation of this gene are essential contributions to solving the WT1 conundrum (Hohenstein and Hastie 2006).
References


