UAG readthrough in mammalian cells: Effect of upstream and downstream stop codon contexts reveal different signals

ABSTRACT

Our findings indicate that readthrough in mouse cells is influenced by both upstream and downstream stop codon contexts, leading to intricate interactions between the mRNA and the translation termination machinery components. A comparison of our findings with those carried out in plant cells and yeast suggests that the mechanisms for recognizing stop codons are conserved across all eukaryotes.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a disease that involves multiple organs, including humans. It has an important genetic component, but it is predominantly caused by the MHC located on the short arm of chromosome 6, which is also affected by several other inherited phenotypes. A range of methods has been employed to pinpoint T1DM susceptibility regions, including case-control studies of candidate genes, combined linkage and association-based studies, and systematic total genome searches in addition to analyses of individual chromosomal regions. Immunogenetic predisposition to T1DM differs markedly from country to country, and disease incidence also appears to vary along with these discrepancies. For instance, the incidence of T01DM is comparable in Southern India (10.4/100000 cases per year) to the number of cases reported in Asian children in the UK and white children of European descent. The presence of an MHC component in T1DM susceptibility is apparent in Southern India, but no correlation has been observed with the insulin gene or ILIR1 in case-control studies. This implies that there may be differences in the non-MHC T1/DM component between Southern Indians and Caucasians of European descent. An association with the insulin gene has been reported universally in the latter population, and some Northern Europeans have reported an IL1R1 association to T1DM. Allelic variation in VDR also increases the susceptibility of Indian Asians, Germans and Taiwanese to T1DM. In the VDR locus, there are six known polymorphisms: FokI restriction enzyme detects an initiation codon polymer (exon 2), BsmI, Tru9I and ApaI ("reflection fragment length polymers") between exons 8 and 9 in the vector flyer type (VDR) loci, and a poly A polyphenystym downstream of the 3' untranslated region. The FokI polymorphism does not seem to have a significant impact on the BsmI, ApaI and TaqI (the three major immune depressive genes): in Japanese patients with T1DM, we studied the exon 2 initiation codon (VDR-FokI) gene polyfomi and found no association with GAD65 antibody (Ab) status.

CONCLUSION

Specifically, we describe how the mouse RPTP (mouse phage-tumor-like) cDNA is cloned into the human skeletal muscle, the way in which the mice and humans are genetically expressed through alternative splicing of their respective genes, and the presence of an 8 kb 3'UTR in human "RPTTP" (human minus 2), The largest PCRTA gene known to date, spanning over 1 megabase pairs of genomic DNA, with its considerable length, mostly due to expanded introns in this region). Encoding the protein domains in the extracellular segment consist of modules that are flanked by phase 1 introns, while the majority of intracellular segments are phase 0 and relatively small. These data indicate that the ectodomain originated from exon shuffling and duplication and eventually fused with another

phosphatase domain at a later time. The MAM domain, which is the region defining type IIB phosphatases, has a genomic structure that is typical of all these domains when located at the N-terminus. Additionally, three exons encode the fourth fibronectin repeat in RPTP, an extra property present in only type I ATPaSeq. At least two spliced exons flank the transmembrane domain, which is the region of greatest variation between the four IIB phosphatases; another resembling an alternatively arranged exonet precedes the catalytic core of the first ATPase. The genomic structure of representative members of the RPTP family (types I-V) shows that the intron/exon organization of both phosphatase domains is highly conserved. Significant variation exists in the length of their 3' UTRs; the longest known record of a regulated transcriptional region at 8 kb is characterized as 3'UTR, or "under regulation" UTM. We have achieved the first-ever characterization of the genomic structure of an RPTP type IIB gene. This knowledge will assist in future research on the regulatory factors that influence tissue specificity of gene expression.