Guide RNA

Guide RNAs (a.k.a. **gRNA**) are the RNAs that guide the insertion or deletion of uridine residues into mitochondrial mRNAs in kinetoplastid protists in a process known as RNA editing.

The phrase “guide RNA” and “gRNA” are also used in DNA editing in the case of Cas9.

1 Overview of gRNA-directed editing

Trypanosomatid protists and other kinetoplastids have a novel post-transcriptional mitochondrial RNA modification process known as “RNA editing”. The mitochondrial genome in these cells consists of 20-50 maxicircles that encode genes and "cryptogenes" (and some gRNAs) and 10-20,000 minicircles that encode gRNAs. All of these molecules are catenated into a giant network of DNA that is situated at the base of the flagellum in the inner compartment of the single mitochondrion.

A majority of the maxicircle transcripts can not be translated into proteins due to multiple frameshifts in the sequences. These frameshifts are corrected after transcription by the insertion and deletion of uridine residues at precise sites which create an open reading frame that is translated into a mitochondrial protein homologous to mitochondrial proteins from other cells. The insertions and deletions are mediated by short guide RNA (gRNAs) which encode the editing information in the form of complementary sequences (allowing GU as well as GC base pairs). The gRNAs are transcribed from both the maxicircles and the minicircles.

The presence of two genomes in the mitochondrion, one of which contains sequence information that corrects errors in the other genome, is novel. Editing proceeds generally 3' to 5' on the mRNA. The initial editing event occurs when a gRNA forms an RNA duplex with a complementary mRNA sequence just downstream of the editing site. This then recruits a number of ribonucleoprotein complexes that direct the precise insertions and deletions of uridine residues, thereby extending the duplex upstream. The adjacent upstream editing site is then modified in the same manner. A single gRNA usually encodes the information for several editing sites (an editing “block”), the editing of which produces a complete gRNA/mRNA duplex.

In the case of “pan-edited” mRNAs, the duplex unwinds and another gRNA then forms a duplex with the edited mRNA sequence and initiates another round of editing. The overlapping gRNAs form an editing “domain”. In some genes there are multiple editing domains. The extent of editing for any particular gene varies between trypanosomatid species. The variation consists of the loss of editing at the 3' side, probably due to the loss of minicircle sequence classes that encode specific gRNAs. A retroposition model has been proposed to account for the partial, and in some cases, complete, loss of editing in evolution. Loss of editing is lethal in most cases, although losses have been seen in old laboratory strains. The maintenance of editing over the long evolutionary history of these ancient protists suggests the presence of a selective advantage, the exact nature of which is still uncertain.

It is not clear why trypanosomatids utilize such an elaborate mechanism to produce mRNAs. It may have originated in the early mitochondrion of the ancestor of the kintoplastid protist lineage, since it is present in the bodonids which are ancestral to the trypanosomatids, and may not be present in the euglenoids, which branched from the same common ancestor as the kinetoplastids.

In the protozoan *Leishmania tarentolae*, 12 of the 18 mitochondrial genes are edited using this process. One such gene is Cyb.[1] The mRNA is actually edited twice in succession. For the first edit, the relevant sequence on the mRNA is

mRNA 5' AAAGAAAAGGCUUUAACUUCAGGUUGU 3'

The 3' end is used to anchor the gRNA (gCyb-I gRNA in this case) by basepairing (some G/U pairs are used). The 5' end does not exactly match and one of three specific endonucleases cleaves the mRNA at the mismatch site.

gRNA 3' AAUAAUAAAUUUUUAAAUAUAAUAGAAAAUUGAAGUUCAGUA 5' mRNA 5' A A AGAAA A G G C UUUAACUUCAGGUUGU 3'

The mRNA is now “repaired” by adding U’s at each editing site in succession, giving the sequence

gRNA 3' AAUAAUAAAUUUUUAAAUAUAAUAGAAAAUUGAAGUUCAGUA 5' mRNA 5' UUAUUAUUUAGAAAUUUAUGUUGUCUUUUAACUUCAGGUUGU 3'

This particular gene has two overlapping gRNA editing sites. The 5' end of this section is the 3' anchor for another gRNA (gCyb-II gRNA).

2 References

[1] Simpson, Larry (2009-08-12). "Uridine insertion/deletion RNA editing". UCLA. Retrieved 2006-05-19.

- Vargas-Parada, L. (2010). "Kinetoplastids and their networks of interlocked DNA". *Nature Education*. **3** (9): 63. Retrieved 2015-11-26.

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