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Translon: a single term for translated regions.

by

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During translation, ribosomes synthesise polypeptides using RNA molecules as templates. All cellular proteins are products of translation, and the identification of protein-coding regions is the primary goal of genome annotation. Beyond protein synthesis, translation has long been known to have regulatory functions independent of its products[1,2]. However, only with the advent of ribosome profiling, was the broad scale and complexity of translated regions fully appreciated.

Recent interest in pervasive translation has exposed a lack of general terminology for translated regions that does not depend on the properties of their products or their sequence. In the absence of such terminology, a range of inconsistently defined terms are currently used to describe them. These terms are typically variations on Open Reading Frame (ORF), for example, ***n***on-***c***anonical, ***RiboSeq***, ***alt***ernative, ***t***ranslated, ***sm***all, ***s***hort, and other ***x***ORFs-based labels. Such terms largely overlap and redundantly describe the same core concept, that the region in question is translated.

Denoting translated regions with ORF-based terms is problematic for two main reasons. First, in sequence analysis, ORFs are defined purely by the nucleotide sequence and the relevant genetic code (starts/stops; Fig. 1a). Thus, ORFs are found everywhere in the genome, including regions that are not transcribed. This ORF definition is useful for the prediction of potential protein-coding regions. However, using the same term to specify regions that are known or confidently predicted to be translated leads to confusion. Indeed, for annotated protein-coding regions, a different technical term, CDS (historically from 'Coding DNA Sequence'), is commonly used.

The second problem is that, although most known protein-coding regions in the majority of model organisms conform to an ORF, starting at an AUG and terminating at the first in-frame stop, there are numerous alternatives. In addition to AUG, other triplets can also initiate translation[3] (Fig. 1a), making it challenging to determine start codons purely from sequence. The incorporation of non-standard proteinogenic amino acids (selenocysteine/pyrrolysine) usually occurs at stop codons within the CDS, with over a hundred in CDSs encoding selenoproteins in some species[4] (Fig. 1a). Furthermore, in some organisms, termination codons are defined not only by their sequence, but also by their position within mRNA[5].

Ribosomal frameshifting (Fig. 1a), which involves translation of two different reading frames to produce a single protein, is common in viruses and also occurs in nuclear-encoded genes of most organisms, in some species, in 5-20% of the genes[6]. Because the products of translation of frameshifted CDSs cannot be derived automatically by converting nucleotide triplets to amino acids, current annotation practice is to introduce a "pseudo-intron" between two partial ORFs in the annotation of these genes (Fig. 1b). Most concerning is the practice of automatically modifying RNA sequences inferred from the genome to obtain full-length protein product via triplet translation (Fig. 1c). Such artificial fitting of well-established translation mechanisms to a simplified model reinforces a widespread fallacy that all translated regions can be represented as single ORFs. This leads to an inaccurate and oversimplified representation of genetic information and molecular composition of the cells, with potentially serious consequences for those unaware of the underlying makeshift solutions. Similar terminological confusion, such as the routine conflation of "exons" and "protein-coding regions"[7], highlights the need for precise vocabulary relating to gene expression.

The above problems can be solved or at least alleviated with the introduction of a specific term for a translated region that would be defined without reference to the product of translation or to the sequence of the region. For this purpose, we suggest using the term *translon* (short for **transl**ated regi**on**), which has previously been introduced but failed to gain traction[8]. It aligns well

with other terms describing gene structures: intron (**intr**agenic regi**on**) and exon (**ex**pressed regi**on**)[9].

The term translon denotes any region that is decoded by the ribosome. This ranges from minimal sequences with detectable translation (AUG followed by a stop) to sequences encoding long proteins in multiple reading frames, and even those disrupted by non-coding sequences as in translational bypassing[10] (Fig. 1a). It also facilitates the efforts to characterise unannotated translation: newly identified translated regions can be described as novel translons. Their biological roles, if any, can remain enigmatic until specific information is obtained. These roles can be purely regulatory, independent of the translation products, or involving those products, such as short peptides modulating functions of other proteins, signalling peptides or antigens; some translons could encode neutral or even harmful "protein junk".

Translon would fill the gap in the vocabulary used to describe units of genetic information (Fig. 1d). Unlike the existing terminology, translon is directly defined by the process it aims to capture instead of doing so indirectly, through sequence or function. We expect that this term will reduce confusion when discussing translated regions and facilitate development of more biologically realistic annotations.

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ETHICS DECLARATION

Competing interests

A.-R.C. is on the scientific advisory board of ProFound Therapeutics. G.L. & P.V.B. are co-founders and shareholders of Eirnabio Ltd. The remaining authors declare no competing interests.

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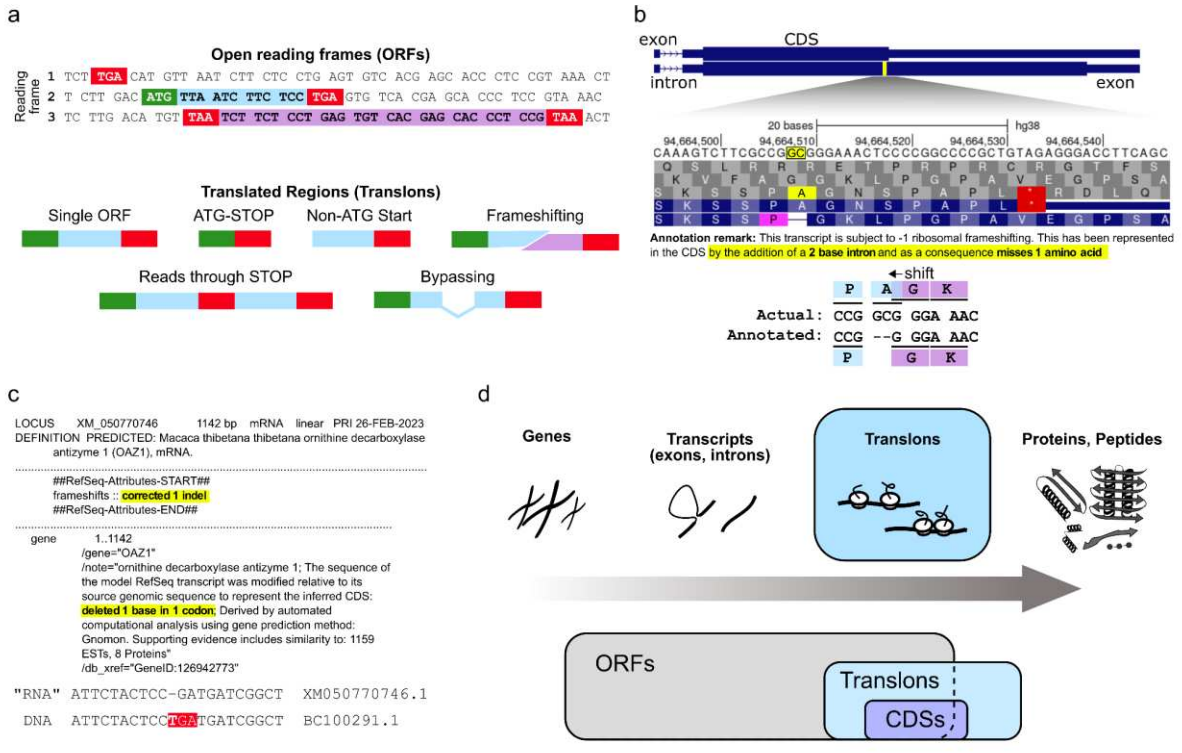
FIGURE LEGEND

Figure 1| Open Reading Frames (ORFs) and translated regions. **a.** Any nucleotide sequence can be represented as three sequences of nucleotide triplets (codons), i.e. triplets read in three different reading frames. An ORF is defined as a sequence of sense codons bounded by a stop codon (purple bar) or from a start (most commonly ATG) to a stop (light blue bar). Below are examples of how different translated regions (translons) relate to ORF. **b.** Graphical representation of human PEG10 annotation zoomed in the area of ribosomal frameshifting site. Two different transcripts are used to represent two different proteins synthesised during translation of PEG10 mRNA. The one representing the full-length protein is artificially modified with a two-nucleotide "pseudo-intron". As a result of this modification, the product of conceptual translation differs from the full-length product of actual translation by one amino acid **c.** A fragment of macaca *OAZ1* gene transcript (XM_050770746.1) annotation illustrating automatic "correction" of mRNA sequences relative to the genomic sequence. The alignment of predicted RNA and genomic source is shown below, with the conserved stop codon at the *OAZ1* frameshifting site shown in red and deleted T in bold. **d.** Relationship of the translon to other terms used when interpreting genome information. Translon fills a missing step in the description of genetic information flow in the cells. Below is a relationship of translon to ORFs and CDSs: most ORFs are not transcribed. Of those that are, most are not translated; all CDSs are translons, but not all translons and CDSs are ORFs.


a
Open reading frames (ORFs)
Reading frame
1 TCT TGA CAT GTT AAT CTT CTC CTG AGT GTC ACG AGC ACC CTC CGT AAA CT
2 T CTT GAC ATG TTA ATC TTC TCC TGA GTG TCA CGA GCA CCC TCC GTA AAC
3 TC TTG ACA TGT TAA TCT TCT CCT GAG TGT CAC GAG CAC CCT CCG TAA ACT
Translated Regions (Translons)
Single ORF
ATG-STOP
Non-ATG Start
Frameshifting
Reads through STOP
Bypassing
b
exon
CDS
intron
exon
20 bases
hg38
94,664,500
94,664,510
94,664,520
94,664,530
94,664,540
CAAAGTCTTCGCCGGCGGGAAACTCCCCGGCCCCGCTGTAGAGGGACCTTCAGC
Annotation remark: This transcript is subject to -1 ribosomal frameshifting. This has been represented in the CDS by the addition of a 2 base intron and as a consequence misses 1 amino acid
shift
P A G K
Actual: CCG GCG GGA AAC
Annotated: CCG --G GGA AAC
P G K
c
LOCUS XM_050770746 1142 bp mRNA linear PRI 26-FEB-2023
DEFINITION PREDICTED: Macaca thibetana thibetana ornithine decarboxylase antizyme 1 (OAZ1), mRNA.
##RefSeq-Attributes-START##
frameshifts :: corrected 1 indel
##RefSeq-Attributes-END##
gene 1..1142
/gene="OAZ1"
/note="ornithine decarboxylase antizyme 1; The sequence of the model RefSeq transcript was modified relative to its source genomic sequence to represent the inferred CDS: deleted 1 base in 1 codon; Derived by automated computational analysis using gene prediction method: Gnomon. Supporting evidence includes similarity to: 1159 ESTs, 8 Proteins"
/db_xref="GeneID:126942773"
"RNA" ATTCTACTCC-GATGATCGGCT XM050770746.1
DNA ATTCTACTCCTGATGATCGGCT BC100291.1
d
Genes
Transcripts (exons, introns)
Translons
Proteins, Peptides
ORFs
Translons
CDSs