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C/EBPα enters the nucleolus

Christine Müller and Cornelis F. Calkhoven*

Leibniz Institute for Age Research; Fritz Lipmann Institute; Jena, Germany

Cell growth, in terms of increase in cell mass, is a prerequisite for cell division. If cells would not grow before they divide, their progeny would become smaller and smaller. As most of the cell's dry mass consists of protein, a high protein biosynthesis rate and therefore a high ribosome production rate are required in rapidly growing cells. The rate-limiting step in ribosomal biogenesis is the transcription of the ribosomal RNA (rRNA) precursor, which is further processed into the 28s, 18s and 5.8S rRNAs that are then incorporated into the ribosomal subunits. Transcription of the rRNA precursor from the rDNA genes takes place within the nucleoli and is performed by RNA-polymerase I (Pol I). The rate of rDNA transcription is modulated either by the epigenetic change of the number of active rDNA loci or by enhancing the efficiency of pre-initiation complex formation achieved mainly through post-translational modifications of involved Pol I-specific factors.[1] In recent years it became clear that this is not the whole story. Apparently, transcription factors that were thought to act exclusively in combination with RNA polymerase II (Pol II) are also directly involved in the regulation of Pol I-mediated rDNA transcription. The most prominent example is the proto-oncogene c-Myc, which stimulates both Pol II- and Pol I-specific transcription.[2,3] Most other transcription factors, however, including C/EBPβ, Runx2, MyoD or Myogenin interact with rRNA genes during mitosis when the nucleolar structures are dissolved to repress rRNA synthesis.[4,5] We now have discovered that Extended-C/EBPα, a specific translational isoform of the transcription factor C/EBPα, is retained in the nucleoli and stimulates Pol I-mediated transcription.[6]

The intron-less C/EBPα mRNA is translated into three protein isoforms with different biological functions due to different length of their N-termini (**Fig. 1**). The full-length (p42) isoform is a transcriptional activator and tumor suppressor. In contrast, the truncated isoform (p30) that virtually only contains the C-terminal DNA binding domain competes with the full-length isoform for DNA binding and hence its function. Previously, we have shown that translation of the truncated isoform is regulated through a small upstream open reading frame (uORF) in the C/EBPα mRNA that serves as cis-regulatory element and allows ribosome scanning and re-initiation at a downstream initiation site.[7] Aberrant expression of Truncated-C/EBPα is oncogenic at least in the hematopietic system.[8] The extended isoform is translated from an upstream unconventional CUG initiation-codon and uniquely contains a nucleolar localization signal (NoLS). Our results suggest that once in the nucleolus Extended-C/EBPα interacts with its cognate recognition sequences in the rDNA promoter and facilitates recruitment of the crucial RNA-polymerase I transcription factor UBF-1 and the SL1/TF-IB complex to stimulate rRNA synthesis.[6] Moreover, we observed an increase in the cell volume in response to Extended-C/EBPα overexpression that has also been observed in response to c-Myc expression in certain systems.[9]

While our studies revealed a new role of C/EBPα in the nucleolus it also raised a number of interesting questions. Although it has been proposed that translation initiation at a CUG-codon is independent of the translation initiation factor eIF2, which normally delivers the initiator Met-tRNA^{iMet} to the ribosome, the involved regulators and pathways are completely unknown.[10] It is intriguing that the translation of several mRNAs coding for regulators of cell proliferation begins with non-AUG codons. Thus, elucidating the mechanism of CUG initiation-codon usage will be an important step in the understanding of proliferation specific translation control. In addition, we identified a serine residue in the C-terminus of the extended isoform that once mutated into a phosphorylation-mimicking aspartate strongly stimulated nucleolar retention.[6] Hence, our data support the idea that upstream signal transduction pathways, which are currently unknown, tightly control nucleolar retention of Extended-C/EBPα.

Does the nucleolar function of C/EBPα have implications for development of human diseases, in particular of cancer? We observed a translational upregulation and nucleolar retention of Extended-C/EBPα simultaneously with the proto-oncogenic Truncated-C/EBPα in proliferating HL60 promyelocytic leukemia cells.[6] The simultaneous regulation suggests a dual role of the extended- and truncated isoforms in promoting cell growth and proliferation, respectively (**Fig. 1**). Extended-C/EBPα exclusively binds to nucleophosmin (NPM1), which is found mutated or rearranged in several hematologic malignancies.[11] Therefore, it would be interesting to examine whether cancerous mutations of NPM1 have an effect on functions of C/EBPα in the control of cell proliferation and growth.

With the discovery of the function of the extended C/EBPα isoform a fascinating new aspect of C/EBPα biology emerges. This new finding strongly emphasizes the importance of translational control of C/EBPα expression, which allows an elegant and rapid adjustment of C/EBPα activity in response to changes to growth/proliferation conditions.

*Correspondence to: Cornelis F. Calkhoven; Email: calkhoven@fli-leibniz.de
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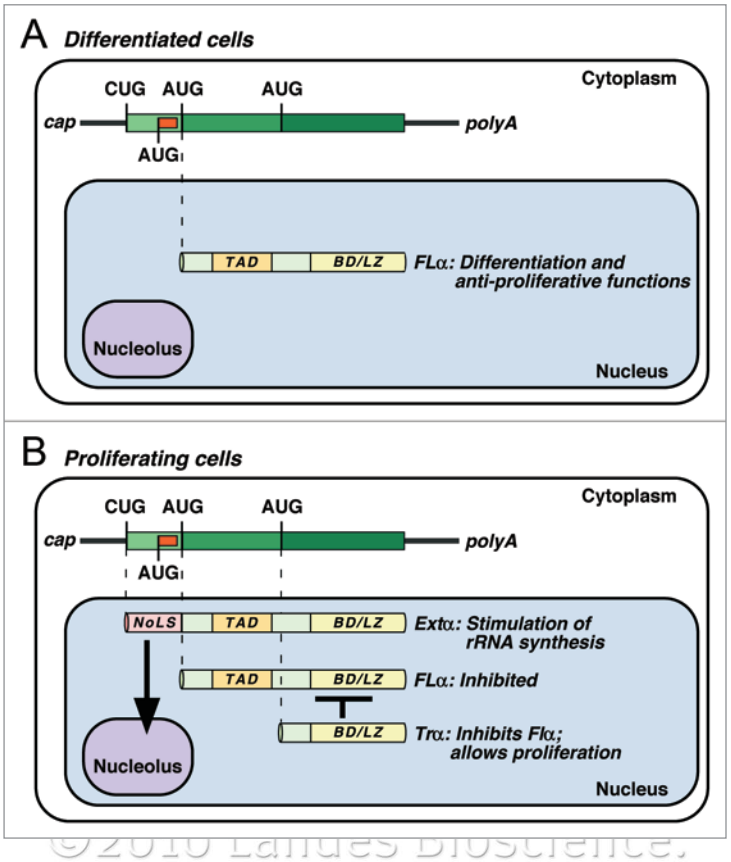

Figure 1. Hypothetical model of a translational C/EBPα isoform switch. (A) In differentiated cells the full-length C/EBPα (Flα) isoform is predominantly expressed and maintains the differentiated state by transcriptionally regulating differentiation specific target genes and by inhibiting cell cycle progression. (B) In proliferating cells translation of the extended (Extα) and the truncated C/EBPα (Trα) isoforms is induced which contribute to cell growth and proliferation in two ways: the truncated isoform blocks the anti-proliferative activity of the full-length isoform; the extended isoform escapes from this inhibition by relocating to the nucleolus where it stimulates rRNA synthesis. The uORF in the C/EBPα mRNA that is required for translation into Truncated-C/EBPα isoform is depicted in orange. NoLS, nucleolar localization signal; TAD, transactivation domain; BD/LZ, basic region/leucine zipper DNA binding domain.

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