Animal Reproduction Science 134 (2012) 2–8

Contents lists available at SciVerse ScienceDirect

Animal Reproduction Science

journal homepage: www.elsevier.com/locate/anireprosci

The "closed loop model" in controlling mRNA translation during development☆

Wolfgang Tomek*, Karin Wollenhaupt

Leibniz Institute for Farm Animal Biology, Dep. of Reproductive Biology, Wilhelm-Stahl-Allee 2, 18196 Dummerstorf, Germany

ARTICLE INFO

Article history:
Available online 11 August 2012

Keywords:
Translation initiation factors
eIF4E
4E-BP1
Translational regulation
Tarm animals

ABSTRACT

Translational control is particularly important in situations where the correlation of a distinct mRNA and the abundance of the corresponding protein might be low. This is the case for instance during oocyte maturation, shortly before the GVBD when the chromatin is condensed, until the embryonic genome is activated. In these situations, gene expression relies on the activation of maternal mRNAs which were stored stably in a dormant form. The most sophisticated model for translational initiation at present is the so-called "closed loop" model, where a circularization of the mRNA is mediated by associated 5′-cap- and 3′-poly(A) binding proteins. Depending on differential interactions, this event can result in translational stimulation or repression. Several studies describe correlated regulation mechanisms in model organisms like mouse or Xenopus, but data addressing translational regulation in farm animals are rare. Cytoplasmic mRNA activating or repressing factors, however, might contribute to achieve developmental competence in bovine or porcine oocytes. Recently we showed that, in the pig, embryonic signals can modify essential components of the mRNA-5′-translation initiation complex in the uterine luminal epithelium at the time of implantation. In accordance with the closed loop model of translational initiation, this review focuses on the regulatory impact of 5′-mRNA end associated proteins (components of the mRNA-cap binding complex) and 3′-end associated proteins (components of the poly(A) binding complex) during *in vitro* maturation of cattle and pig oocytes, early embryonic development and in the pig uterine epithelia.

1. Introduction

Translational control by using pre-existing mRNAs allows rapid response to changes in different circumstances. For instance, during final maturation, when the chromatin is condensed, oocytes are practically disabled for transcription and gene expression is mainly regulated at the translational level until the embryonic genome is activated (Bonnet et al., 2008). There is a growing body of evidence that, during oocyte growth in mice, the mRNA is stabilized by the germ-cell specific RNA-binding protein MSY2 (Medvedev et al., 2011). The mRNA concerned is accumulated in a translationally dormant state and can be used later to sustain meiotic maturation and early embryonic development. Although there is no direct evidence, a similar function of MSY2 is believed to exist in oocytes and early developmental embryos of cattle (Vigneault et al., 2004).

The translation of mRNA is mainly regulated at the initiation step, which is suggested to be rate-limiting for overall protein synthesis, whereby the mRNA-cap binding protein eIF4E (see below) might be the limiting factor in somatic cells (Gingras et al., 1999; Sonenberg, 2008). In the first step, the mRNA activating process, different translational initiation factors (eIFs) act in concert to direct the mRNA to the ribosome. The most sophisticated model for the

☆ This paper is part of the special issue entitled: 3rd Embryo Genomics, Guest Edited by D. Tesfaye and K. Schellander.

* Corresponding author. Tel.: +49 3820868779; fax: +49 3820868752.
E-mail address: tomek@fbn-dummerstorf.de (W. Tomek).

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http://dx.doi.org/10.1016/j.anireprosci.2012.08.005

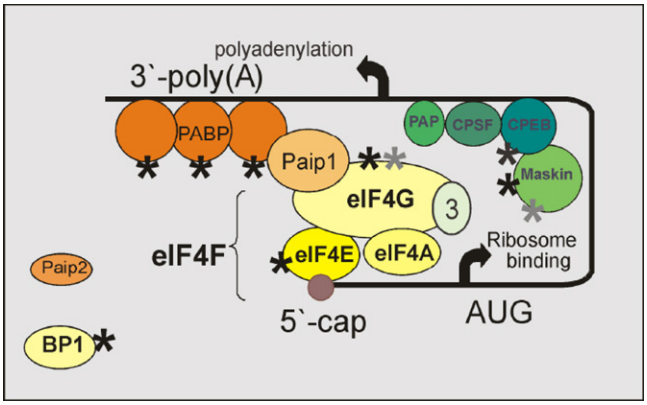

Fig. 1. Highly schematic "closed loop" model for mRNA activation during translational initiation (according to Wells et al., 1998; Mangus et al., 2003; Sonenberg and Hinnebusch, 2009; Jackson et al., 2010). The physical bridging of 5′- and 3′-ends of the mRNA is mediated by protein factors which sustain the cap and poly(A) function of the mRNA. Proteins with stimulating phosphorylation sites are marked with black stars, repressing phospo-sites are marked in grey. Hypophosphorylated 4E-BP1 (BP1) binds to eIF4E and impairs eIF4F formation. Paip2 can bind to Paip1 and destabilizes eIF4G/PABP interaction. Dependent on the phosphorylation state Maskin can bind to CPEB and eIF4E and in such a way prevents eIF4F formation and cytoplasmic polyadenylation of the mRNA. All these processes impair the interaction of the 5′- and 3′-ends of the mRNA and, therefore, repress translational initiation. For details see text. eIF4E, G, A: eukaryotic initiation factor 4E, 4G, 4A; BP1, 4E-BP1, eIF4E binding protein 1; PABP: poly(A) binding protein; Paip1, 2: PABP interacting protein 1, 2; CPEB: cytoplasmytic polyadenylation element binding protein; CPSF: cleavage polyadenylation stimulating factor; PAP: Poly(A) polymerase; 3: eIF3.

onset of translational initiation at present is the so-called closed loop model (Wells et al., 1998; Mangus et al., 2003; Sonenberg and Hinnebusch, 2009; Jackson et al., 2010), where the physical bridging of 5′- and 3′-ends of the mRNA is mediated by protein factors (Fig. 1). In such a way, mRNA secondary structures are resolved and ribosome entry is facilitated. The mRNA circularization may also enhance re-initiation and ensure that only intact mRNA is translated (Gingras et al., 1999).

The 5′-acting factors mediate the function of the mRNA-cap, a guanine nucleotide methylated on the 7 position (abbreviated m^7G) and connected to the mRNA *via* an unusual 5′ to 5′ triphosphate linkage. The cap binding protein eIF4E directly binds to m^7G and recruits other factors of the cap-binding complex eIF4F. These are eIF4G, a scaffold protein and eIF4A which act as an RNA helicase. eIF4G in turn provides additional binding sites for the poly(A) binding protein (PABP), thereby bridging the 3′-poly(A) tail to the 5′-cap and promoting mRNA circularization. The initiation factor eIF3, the largest scaffolding initiation factor, composed of 13 subunits links the eIF4F complex *via* eIF4G binding to the small ribosomal subunit. Additionally, eIF4G binds to MNK, the MAPK interacting kinase, which directly phosphorylates eIF4E (Pyronnet et al., 1999). eIF4G can also interact directly with RNA and the binding of PABP to eIF4G can be stabilized by the interacting protein Paip1 or impaired by Paip2 (Craig et al., 1998; Khaleghpour et al., 2001).

Beside the 5′-cap, and the 3′-poly(A) tail, there are specific sequences in the 3′-untranslated region (3′-UTR) with potential regulatory impact. They direct proteins, which for instance modulate the cytoplasmic polyadenylation of mRNAs. At least three motifs are involved: first the hexanucleotide AAUAAA which is bound by the cleavage polyadenylation stimulating factor (CPSF) and functions as a nuclear polyadenylation element; second the cytoplasmatic polyadenylation element (CPE) with the consensus sequence UUUUUAU which is bound by the CPEB and located upstream to AAUAAA; and third PBE, a sequence that is bound by the Pumilio RNA-binding protein which is believed to stabilize the binding of CPEB to CPE. Moreover, investigation in Xenopus revealed that the number of CPEs and the distance between the different motifs is critical to the occurrence of effective cytoplasmic polyadenylation (Piqué et al., 2008). Together with CPSF, CPEB can activate a poly(A) polymerase which in turn prolongs the poly(A) tail and stimulates translational initiation by PABP/eIF4G/eIF4E mediated mRNA circularization, as described above.

Investigations in Xenopus oocytes also revealed a repressive function of the CPEB (Barnard et al., 2005). In this case, a protein called Maskin is involved. It acts as a CPEB and eIF4E binding protein and by interacting with both factors, the eIF4F complex formation and cytoplasmic polyadenylation is impaired and translation is held in a repressed state.

Moreover, a subset of ubiquitous eIF4E binding proteins exist, called 4E-BP1, 2 and 3 which compete for eIF4G binding and prevent eIF4F formation. However, the binding of eIF4E to the cap is not impaired by the 4E-BPs, but rather the binding is stabilized (von der Haar et al., 2004; Tomoo et al., 2005) and the repressed mRNA is probably protected against decapping and ribonuclease attack.

The canonical model for translational initiation describes the interaction of the different factors as being regulated by phosphorylation. In somatic cells, a variety of stimuli like growth factors, cytokines and amino acids yield eIF4E phosphorylation at Ser 209 by the MAPK signalling cascade involving MNK which directly phosphorylates the factor. A similar mechanism was also described in cattle (Tomek et al., 2002a) and pig oocytes (Ellederova et al., 2008). Ser 209 is located near the cap-binding pocket, however, the effect of this phosphorylation on cap binding and on translation rates has been the topic of controversial discussion (reviewed in Topisirovic et al.,