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Small activating mRNA (*samRNA*): A hypothesis for a specific positive feedback regulation of gene expression

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Abstract Small interference RNAs (siRNAs) target their corresponding mRNAs or homologous genomic DNA sequences to induce gene silencing for down-regulation of gene expressions. In contrast, how the cells can sense the requirement for a gene expression and specifically activate its expression remains a puzzle. We hypothesize that an mRNA fragment-regulated process is a common mechanism for a specific positive feedback regulation of gene expression. We rationalize that a gene's own mRNA degradative product can positively regulate its expression through sequence specific interaction with the genomic DNA at the transcription initiation site. When an mRNA translates to a protein, it degrades into small fragments. These mRNA fragments, especially the 5′ capped RNA fragments, are subjected to cytoplasm–nucleus shuttling, providing a spatial and temporal regulation of a gene. These mRNA fragments are defined as a ''***s***mall ***a***ctivating ***mRNA*** (***samRNA***).'' The *samRNA* acts as a sensor and a stimulator for its own gene expression, which play an active role in the specific positive feedback regulation of the gene expression. As such, *siRNA* and *samRNA* provide a ''yin'' (negative regulation) and ''yang'' (positive regulation) regulation for gene expression. Establishment of the novel technology platform built upon the *samRNA*-mediated positive regulation mechanism will enable therapeutic induction of the gene expression in gene therapy, aging prevention, guided stem cell differentiation, and reprogramming of the human mature cells into induced pluripotent cells.

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Background

Transcription factors play important roles in the activation of gene expression associated with cell signaling pathways. The assembly of transcription factors and RNA polymerase II into a pre-initiation complex with the TATA binding protein (TBP) at the promoter is believed to be a key event in gene regulation. However, current findings seriously challenge this concept. The expression of a gene can be activated by using two pieces of double-stranded RNA that is complementary to a DNA control sequence promoter of the gene. These RNAs, if they exist in the cell, work in a rather random process than in a common mechanism in the cell for gene expression.

Gene regulation occurs in response to the diversity of stimuli that induce a different hierarchies of regulatory mechanisms including transcriptional, translational, post-translational and epigenetic level [1,2]. Craig Mello has demonstrated that double-stranded RNA triggers suppression of gene activity in a homology-dependent manner, a process named RNA interference (RNAi) [3,4]. Small RNA molecules, namely microRNAs (miRNAs), regulate about 30% of all genes in the genome [5]. This siRNA family plays a negative regulatory function in gene regulation. However, little is known about the possible positive regulation of the mRNA fragments.

It is known that mRNA degradation is an important step in regulation of gene expression [6,7]. The level of each mRNA in the cell is coupled together and tightly regulated by its rate of transcription, processing, translation, and degradation [8]. During embryogenesis in vertebrates, maternal gene products and trace levels of zygotic gene activity direct the early steps of embryo development. Degradation of maternal mRNAs during the midblastula transition is concomitant with the major activation of zygotic transcription [9], suggesting that accumulated mRNA fragments play a positive regulatory and guiding role in the gene expression in development. When a protein is consistently demanded for the cellular function, the translation process is facilitated by a positive feedback mechanism to monitor the usage and degradation of the protein.

Translation is inevitably coupled with mRNA degradation, however; highly expressed proteins (haemoglobin, actins, tubulin, etc.) are believed to be expressed from stable and long-lived mRNAs. Little is known about mechanism by which the translation process triggers the degradation of the mRNA or vice versa. Ribosome-bound tubulin mRNA destabilization pathway requires ongoing ribosome translocation and this transient change in the stability is what readjusts the steady state levels of the mRNA [10,11]. Although this ''autoregulation'' of tubulin expression is thus obligatorily linked to the translation process, the mechanism by which the translation process triggers RNA degradation is largely unknown. An extensive destabilization of yeast mRNA is intimately coupled with its increased translation, suggesting the potential link between translation and stability of the yeast GCN4 mRNA whose translational rates change with respect to amino acid availability [12].

How does the cell sense the shortage of the mRNA and activate the gene's expression? This link is missing in our current understanding of the gene regulation. The following hypothesis provides a link to the regulatory process.

Presentation of the hypothesis

As shown in Fig. 1, we hypothesize that there is a common mechanism in the cell for a specific feedback regulation of gene expression. We propose that the cell links a particular gene expression level and its production process by its own mRNA degradative products, namely ''*s*mall *a*ctivating *mRNA* fragments (***samRNA***).'' When an mRNA is translated to a protein, the mRNA template is gradually degradated into small fragments. These small mRNA fragments, especially the 5′ end capped mRNA fragments, are the most likely the functional *samRNA*.

We rationalize that in the living cell an mRNA is transcribed from its DNA template by RNA polymerases and transported into the cytoplasm for translation through a nucleus-cytoplasmic shuttling. The degradative mRNA fragments, i.e., *samRNA*, after translation, are transported into the nucleus via a cytoplasm—nucleus shuttling. Within the nucleus, *samRNA* initiates the displacement of the roadblock proteins from the DNA by a complementary mechanism to target the transcription initial site. As such, *samRNA* acts as a sensor for the shortage of a specific protein to activate its own gene expression. Nevertheless, our hypothesis is further supported by the following evidence.

Testing the hypothesis

The *samRNA* can activate the transcriptional initiation both in viral and eukaryotic gene expression. For example, the

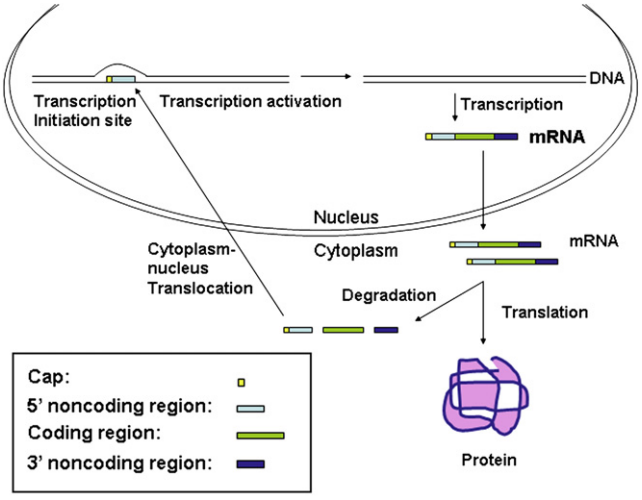

Figure 1 Gene activation by its own degraded transcript, small activating mRNA fragments (*samRNA*). After an mRNA translates into a protein, the mRNA is degraded into mRNA fragments. The 5′ capped fragments, which act as a sensor for shortage of a specific gene product mRNA, are subjected to the cytoplasm—nucleus translocation into the nucleus. Inside the nucleus, these mRNA fragments activate the transcription of the corresponding gene by targeting the transcription initiation site. These positive regulatory mRNA fragments are defined as *s*mall *a*ctivating *mRNA* fragments (***samRNA***).