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RNA-binding proteins in mouse male germline stem cells: a mammalian perspective

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Abstract

Adult stem cells that reside in particular types of tissues are responsible for tissue homeostasis and regeneration. Cellular functions of adult stem cells are intricately related to the gene expression programs in those cells. Past research has demonstrated that regulation of gene expression at the transcriptional level can decisively alter cell fate of stem cells. However, cellular contents of mRNAs are sometimes not equivalent to proteins, the functional units of cells. It is increasingly realized that post-transcriptional and translational regulation of gene expression are also fundamental for stem cell functions. Compared to differentiated somatic cells, effects on cellular status manifested by varied expression of RNA-binding proteins and global protein synthesis have been demonstrated in several stem cell systems. Through the cooperation of both cis-elements of mRNAs and trans-acting RNA-binding proteins that are intimately associated with them, regulation of localization, stability, and translational status of mRNAs directly influences the self-renewal and differentiation of stem cells. Previous studies have uncovered some of the molecular mechanisms that underlie the functions of RNA-binding proteins in stem cells in invertebrate species. However, their roles in adult stem cells in mammals are just beginning to be unveiled. This review highlights some of the RNA-binding proteins that play important functions during the maintenance and differentiation of mouse male germline stem cells, the adult stem cells in the male reproductive organ.

Keywords: Adult stem cells, RNA-binding proteins, Post-transcriptional regulation, Translational regulation, Protein synthesis

Introduction

Tissue homeostasis and regeneration require balanced regulation of self-renewal and differentiation of adult stem cells (ASCs) that reside in particular tissues. Like any other cell type, cellular functions of ASCs depend on specific gene expression programs that are subject to precise control in order to produce necessary and sufficient proteins, the functional units within cells. In response to environmental stimuli, genetic information is transferred to proteins through messenger RNA (mRNA) production (transcription) and protein synthesis (translation) under the regulation of cell-autonomous and non-autonomous factors in order for cells to elicit proper functions. Intensive investigations over past decades have uncovered key factors and molecular mechanisms that govern the regulation of gene expression during self-renewal and differentiation of ASCs, of which transcription factors and transcriptional regulation have been at the center stage. However, abundance of mRNAs in a cell is not necessarily equivalent to the abundance of functional proteins that cells produce. From the birth of mRNAs to their translation and eventual degradation, mRNAs undergo extensive modifications and regulation, mainly through the action of RNA-binding proteins (RBPs) (Fig. 1). Since cells often dedicate ~20 % of their cellular energy to the process of protein synthesis, regulation of gene expression at the post-transcriptional and translational levels are thus of great importance. It has been increasingly realized that post-transcriptional and translational regulation hold fundamental roles in

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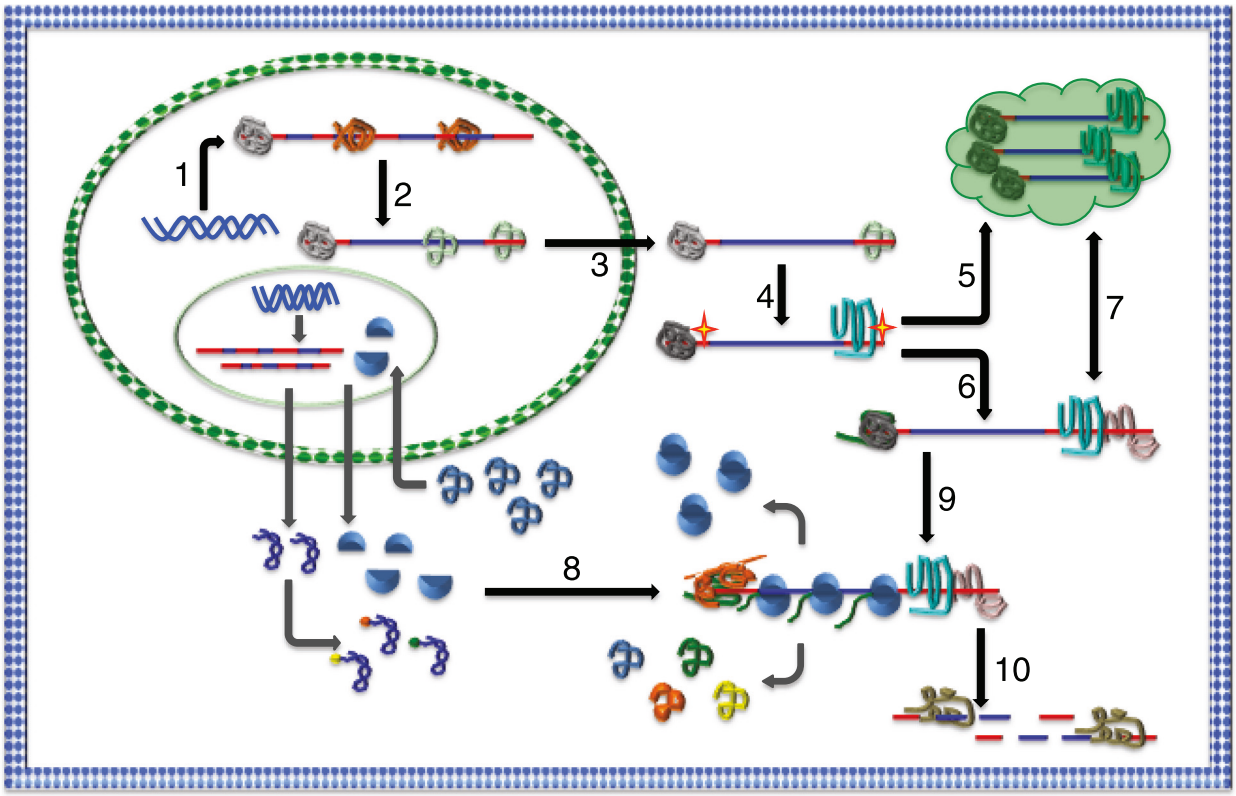

Fig. 1 The life cycle of mRNAs. mRNAs undergo a series of modification events since they are transcribed from the genome. These processes are facilitated by the action of numerous RNA-binding proteins (RBPs) (shown as *molten globules* in the diagram), which interact with mRNAs at various regions through conserved RNA-binding domains. Interactions with RBPs and associated proteins render status of mRNAs as either repressive or active for protein synthesis in the cytoplasm of a cell. mRNAs can be stored in large RNA-protein complexes (RNA granules, *cloud in green*) in the cytoplasm when translation is not permitted. The dynamic exchange of mRNAs between cytoplasm and RNA granules is mediated by RBPs that are not fully characterized. Translational machinery, including tRNAs, ribosomal RNAs, and subunits are synthesized in the nucleolus and exported to cytoplasm in order for protein synthesis to occur. Following translation, tRNAs and ribosomal subunits can be recycled for additional rounds of translation. Major processes of mRNAs' life cycle are indicated in *numbers* (*black arrows*). (*1*) Transcription; (*2*) splicing; (*3*) nuclear export; (*4*) post-transcriptional modification of mRNAs; (*5*) cytoplasmic ribonucleoprotein complex (RNA granule) formation; (*6*) cytoplasmic alternative polyadenylation (APA); (*7*) exchange of mRNAs between RNA granule and cytoplasm; (*8*) complex formation at the 5′- and 3′-UTRs of mRNAs, translation initiation; (*9*) translation; and (*10*) degradation. *Blue rod*: exons; *red rod*: untranslated regions of mRNA

stem cells [1, 2]. Global effects of protein synthesis on stem cell behavior manifested by RBPs and translational regulation have been demonstrated in several stem cell systems [3–5]. However, how RBPs participate in various steps of RNA metabolism during self-renewal and differentiation of ASCs and how ASCs are regulated at the post-transcriptional and translational levels in order to accommodate tissue homeostasis and regeneration remain largely unexplored.

Germline stem cells in adult animals are ASCs in reproductive organs and have been one of the widely utilized systems for stem cell research. In mouse embryos, primordial germ cells (PGCs) are formed around E6.25 from proximal posterior epiblast. They then proliferate and migrate into embryonic gonad to form either prospermatogonia or oogonia in male and female animals, respectively. In males, prospermatogonia (also called gonocytes) are the precursor of future spermatogonial stem cells (SSCs) in adult animals. Quiescent gonocytes in the embryo (arrested at prophase of mitotic cell cycle) only resume cell division following birth of the animal. During the first 3 days of post-natal development (1–3 dpp (days post-partum)), gonocytes proliferate and migrate from the center of developing seminiferous tubule to the basement membrane. Colonies of SSCs composed of type A undifferentiated stem cell populations are established around 7 dpp. These cells exist as single cells (A_{single} or A_s) or cohorts (A_{paired} or A_{pr} and $A_{aligned}$ or A_{align}, due to incomplete cytokinesis). Although poorly defined, niche environment consisting of surrounding somatic Sertoli cells, Leydig cells and interstitial Myoid cells provide essential stimuli, such as hormones and