RNA BIOLOGY
2017, VOL. 14, NO. 2, 137–145
http://dx.doi.org/10.1080/15476286.2016.1265197

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POINT OF VIEW

FXR1a-associated microRNP: A driver of specialized non-canonical translation in quiescent conditions

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ABSTRACT

Eukaryotic protein synthesis is a multifaceted process that requires coordination of a set of translation factors in a particular cellular state. During normal growth and proliferation, cells generally make their proteome via conventional translation that utilizes canonical translation factors. When faced with environmental stress such as growth factor deprivation, or in response to biological cues such as developmental signals, cells can reduce canonical translation. In this situation, cells adapt alternative modes of translation to make specific proteins necessary for required biological functions under these distinct conditions. To date, a number of alternative translation mechanisms have been reported, which include non-canonical, cap dependent translation and cap independent translation such as IRES mediated translation. Here, we discuss one of the alternative modes of translation mediated by a specialized microRNA complex, FXR1a-microRNP that promotes non-canonical, cap dependent translation in quiescent conditions, where canonical translation is reduced due to low mTOR activity.

ARTICLE HISTORY
Received 7 October 2016
Revised 19 November 2016
Accepted 21 November 2016

KEYWORDS
4EBP dephosphorylation; DAP5; FXR1a; low mTOR activity; microRNA; mRNA cap binding; non-canonical translation; PARN; poly(A) shortening; quiescence

Introduction

MicroRNAs are well recognized as one of the major regulatory small non-coding RNAs in eukaryotic cells. MicroRNAs generally repress gene expression by suppressing mRNA translation and by degradation of mRNA.[1] Specifically, microRNAs can regulate translation by binding to the 3′ untranslated regions (3′UTRs) of target mRNAs.[2-4] They can associate with members of the Argonaute (AGO) protein family to form microRNA-protein complexes (microRNPs).[5,6] The microRNP conventionally associates with an important co-factor, GW182, as well as other effector proteins.[1,7-9] Together, this canonical microRNP deadenylates or removes the poly(A) tails of mRNAs, as well as represses mRNA translation.[1,8,10-14] Importantly, microRNA-mediated repression and deadenylation involves the role of canonical translation factors like poly(A) binding protein (PABP) and helicases that are associated with conventional translation.[1,8,10,11,15] Besides repression, microRNAs can activate the translation of specific mRNAs in distinct cellular conditions.[16-26] In quiescent (G0) mammalian cells and immature *Xenopus laevis* oocytes, we previously uncovered that microRNAs can activate translation of specific mRNAs such as TNFα and MYT1 respectively.[16,25] The translation activation machinery includes a specific microRNP comprising an Argonaute family member protein AGO2, and a distinct spliced isoform of an RNA binding protein, Fragile-X-mental-retardation-syndrome-Related protein 1a (FXR1-iso-a)[27,28] that promotes translation,[16,17,29,30] instead of the repressive GW182 co-factor present in the conventional microRNP.[1] Additionally, microRNAs have been reported to activate translation in the absence of GW182 in Drosophila embryo extracts[21] and in other cellular conditions.[26]

Until recently, the detailed mechanism of microRNA mediated translation upregulation in these cellular states remained elusive. Our recent study delineated the mechanism of microRNA mediated translation upregulation in quiescent mammalian cells and *Xenopus laevis* immature oocytes, where canonical (cap and poly(A) dependent) translation is reduced.[31] Under these cellular conditions, FXR1a-associated microRNP (FXR1a-microRNP) interacts with PARN and DAP5/p97 that serve as alternate, non-canonical translation factors[31] to mediate specialized translation of specific poly(A) shortened target mRNAs associated with this complex (Fig. 1). Importantly, microRNAs have been reported to activate translation in a 5′ cap and poly(A) independent manner in other specific cellular conditions[21,26] with absence of GW182—consistent with our findings in quiescent cells and early oocytes.

Canonical translation mechanism

In proliferating cells in eukaryotes, most mRNAs are generally translated via the canonical translation mechanism. Canonical translation, often called cap dependent translation, depends on the recognition of mRNA 5′ caps by the canonical cap binding protein, eukaryotic translation initiation factor 4E (eIF4E), and its association with eIF4F complex and the 43S pre-initiation complex (PIC).[32-34] EIF4F consists of a scaffolding protein, eukaryotic translation initiation factor 4G (eIF4G), and a DEAD box RNA helicase, eIF4A. 43S PIC

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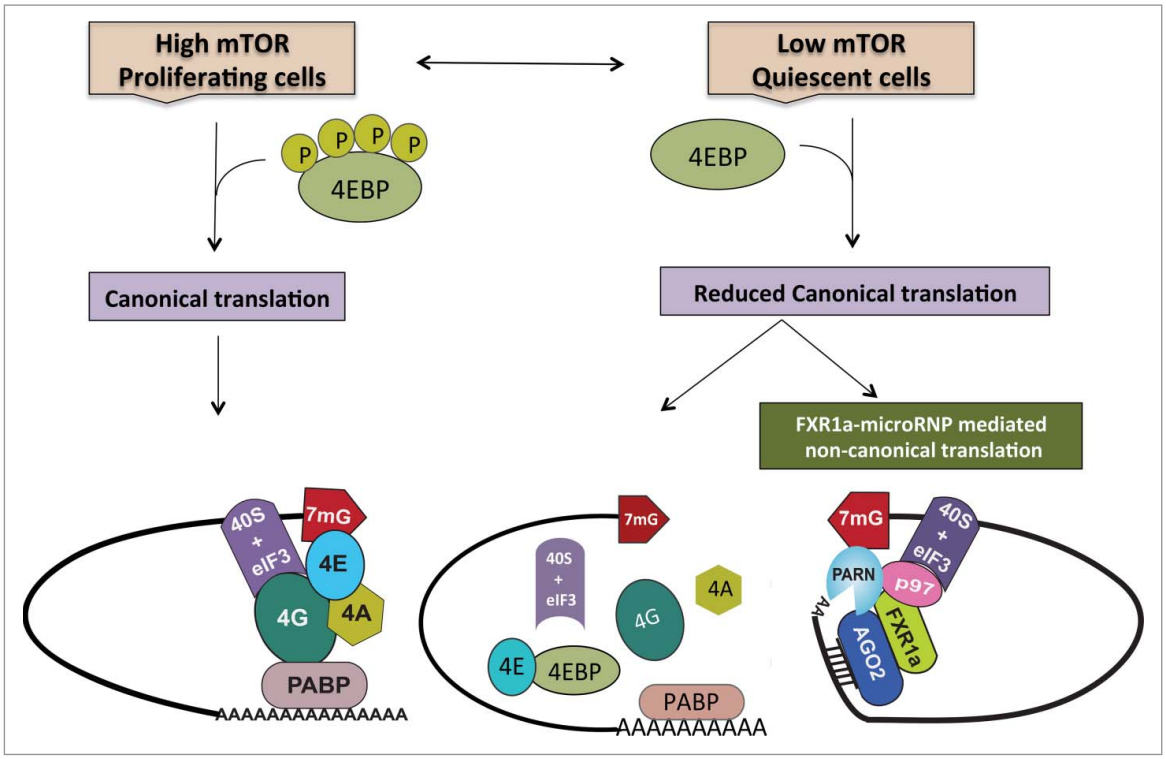

Figure 1. During normal proliferation, when mTOR kinase activity is high, cells depend on canonical cap dependent translation for global protein synthesis. However, under specific conditions such as quiescence, canonical protein synthesis is reduced due to low mTOR activity that causes dephosphorylation and thereby, activation of 4EBPs. Activated 4EBPs inhibit canonical cap dependent translation by binding eIF4E (the canonical cap binding protein) and preventing its interactions with eIF4G. In order to maintain the cellular state, cells operate alternative translation mechanisms to express specific genes. In quiescence, apart from low mTOR activity and 4EBP dephosphorylation—in certain cell lines and in immature oocytes where FXR1 levels are increased—a specialized FXR1a-microRNP complex mediates one such alternative mechanism. Similar to the conventional repressive microRNP, FXR1a-microRNP contains AGO2 and microRNAs but lacks the canonical microRNP repression effector, GW182. Instead, in FXR1a-microRNP, AGO2 interacts with a specific spliced isoform of the RNA binding protein FXR1a that does not participate in microRNA mediated repression[142,143] and promotes specific mRNA translation.[17,29,30] MicroRNA bound AGO2 directs recruitment of the complex to 3′UTRs. Poly (A) tails are decreased in these low mTOR conditions to avoid binding PABP that can recruit GW182 and promote microRNA-mediated deadenylation and repression. Increased deadenylation is brought about by PARN deadenylase in G0 cells, which is attributed to increased cap binding by PARN in G0.[65] FXR1a-microRNP interacts with p97/DAP5, a non-canonical translation factor that brings in eIF3–40S ribosome subunit in place of eIF4G.[103-113] FXR1a-microRNP also interacts with PARN that binds mRNA 5′ caps in G0 in place of eIF4E, thus connecting p97-FXR1a-microRNP that is recruited to the 3′ UTR, with the 5′cap to replace the canonical 5′-3′ eIF4E-eIF4G-PABP link.[31] These alternate cap binding and ribosome recruitment factors promote specialized translation of specific poly(A) shortened mRNAs associated with FXR1a-microRNP in quiescent conditions, where canonical translation is reduced.

consists of the 40S small ribosomal subunit, the eukaryotic translation initiation factors (eIFs) eIF1, eIF1A, eIF3, eIF5 and the ternary complex comprising initiator methionyl-tRNA (Met-tRNA), eIF2 and GTP.[32,35,36] The 43S PIC complex is recruited to the 5′ cap of the mRNA and connected to the cap through eIF4G in the eIF4F complex.[34] EIF4G not only connects with eIF3 and recruits the 43S PIC but also enhances the binding of eIF4E to the cap, thus facilitating cap dependent translation.[32,34,36-39] EIF4G also connects with PABP at the 3′ end of the mRNA, thereby connecting the 5′ and 3′ ends of the mRNA, which is thought to enhance translation.[40-43] Therefore, canonical translation can be regulated via interference with eIF4E and eIF4G interactions.

Cap binding by eIF4F complex is a key regulatory event in canonical translation initiation, which is controlled by important pathways, including mechanistic/mammalian target of rapamycin (mTOR) kinase activity.[44-47] mTOR complex 1 (mTORC1) kinase activity phosphorylates eIF4E-binding proteins (eIF4EBPs or 4EBPs).[44,48] Phosphorylated 4EBP dissociates from eIF4E, allowing eIF4E-eIF4G interaction and eIF4F complex formation.[36,49,50] Reduced mTOR activity leads to hypo-phosphorylation of 4EBPs. Hypo-phosphorylated 4EBP binds to eIF4E with high affinity, blocking the interaction of eIF4G with eIF4E, and thus inhibits canonical translation through: disruption of recruitment of eIF3 and PIC by eIF4G, decreased cap binding affinity of eIF4E without eIF4G, and decreased synergy with PABP at the 3′ mRNA end. Canonical translation is reduced when the cells are under distinct cellular stresses—like growth factor depletion, nutrient deficiency and hypoxia—primarily due to low mTOR activity in these conditions.[48,51-58]

MicroRNA mediated translation requires decrease of mTOR activity

G0 is a reversible state of cell cycle arrest that cells enter in response to environmental stress or developmental cues.[59-62] mTOR activity, which is known to play an important role in cell proliferation, is reduced in G0.[54,55,63] In serum starved G0 mammalian cells and immature *Xenopus laevis* oocytes, canonical cap and poly(A) dependent translation is compromised due to shortened poly(A) tails on mRNAs and low mTOR activity that leads to 4EBP mediated inhibition of eIF4E-eIF4G interaction.[31] Poly(A) tails of mRNAs are shortened due to

increased activity of Poly(A) ribonuclease (PARN),[31,64-66] blocking the role of poly(A) and PABP in canonical translation. Our laboratory and other groups have shown that translation of certain mRNAs occurs in these conditions, despite reduced canonical translation, suggestive of alternative modes of translation.[25,31,67,68] Several alternative translation mechanisms have been reported under different cellular states such as cap independent internal ribosome entry site (IRES) mediated translation.[53,67-74] In G0, a specialized FXR1a-microRNP mediates alternative translation of specific mRNAs (Fig. 1).[31] FXR1a-microRNP recruits targets for translation activation in the nucleus exclusively, which enables selection of specific mRNAs for translation activation.[75] FXR1a-microRNP activates translation of reporter mRNAs bearing microRNA target sites in the 3′UTR, and of specific endogenous mRNAs like TNFα and MYT1 in G0 mammalian cells and *Xenopus* immature oocytes respectively.[17,25,31] Proliferating THP1 cells, treated with mTOR inhibitor Torin1 that blocks 4EBP phosphorylation and thereby, canonical translation—recreating conditions similar to G0 cells—show microRNA mediated translation activation of reporter mRNAs.[31] Similarly, overexpression in proliferating cells of phosphorylation defective 4EBP mutant (eIF4EBP-T37A) that cannot dissociate from eIF4E, led to increase in microRNA mediated reporter translation.[31] These data indicate the requirement for active, dephosphorylated 4EBP to inhibit canonical cap dependent translation and enable this alternative mechanism.

Poly(A) tail shortened/unadenylated mRNAs are targets of microRNA-mediated translation

The poly(A) tail is not required for microRNA mediated repression but is known to enhance microRNA mediated deadenylation and repression through PABP, which interacts with and enhances recruitment of the repressive GW182 factor of canonical microRNPs.[1,11,76,77] Only unadenylated or poly(A) shortened (shorter than a PABP site) reporter mRNAs were translationally upregulated in the presence of the microRNA in G0 THP1 cells and in immature oocytes.[31] Measurement of poly(A) tail length of the validated endogenous targets of activation, using poly(A) tail assay, showed shortened poly(A) tails of these targets.[31] Poly(A) tails, under normal proliferating conditions, enhance canonical translation by recruiting PABP, which interacts with the canonical translation initiation complex via eIF4G,[40,42] as well as promotes recruitment of the repressive microRNP.[11,78,79] Polyadenylated reporter mRNAs did not show microRNA mediated activation; however, polyadenylated reporter mRNAs could function in translation activation upon expression of Poly(A) binding protein interacting protein 2 (PAIP2),[31] which can inhibit PABP associations with the poly(A) tail and with eIF4G.[80,81] Therefore, shortened poly(A) tails may allow these targets to avoid repression by preventing PABP interactions in canonical translation that is reduced in these conditions, as well as by precluding PABP-GW182 interaction to favor recruitment of the FXR1a-microRNP—which promotes non-canonical translation.

PARN is essential for FXR1a-microRNP mediated translation as a cap binding protein and an active deadenylase

Poly(A) ribonuclease (PARN) is a 3′ exonuclease of the DEDD class, which acts as a dimer to mediate degradation of poly (A) tails.[82] PARN is an unusual deadenylase with mRNA cap binding activity.[83-85] Biochemical and structural studies revealed that PARN binds to the 7-methylguanosine cap (m^7G) of mRNAs via specific tryptophan residues.[86-89] Cap binding enhances the deadenylation activity of PARN.[83,89] PARN is localized to both the nucleus and cytoplasm and is known to play a role in gene expression regulation.[64,90-92] PARN plays an important role during oocyte development by regulating poly (A) tail length and thereby, translation.[64,93] Besides its role in early development, PARN has been implicated in certain cancers, in Dyskeratosis congenita, and in pulmonary fibrosis.[94-97] PARN is phosphorylated and its levels are increased in acute lymphocytic leukemia (ALL), and acute myeloid leukemia (AML).[98] Similarly, PARN levels are altered in lung cancers,[95] suggesting a clinical significance of PARN in cancer apart from development.

In G0, PARN cap binding and deadenylase activity increases, which causes deadenylation of mRNAs.[65] This was attributed to the decreased phosphorylation of 4EBP, which allows dephosphorylated 4EBP to disrupt the eIF4E-eIF4G interaction that binds the cap much more strongly than eIF4E alone (nanomolar range compared with low micromolar range).[65,89,99] PARN interacts with FXR1a-microRNP in G0 and in immature oocytes, indicating a role in microRNA-mediated translation activation (Fig. 1).[31] This interaction with the 3′UTR bound FXR1a-microRNP likely enables increased cap binding on these target mRNAs by PARN, facilitating PARN further to compete for cap binding on these target mRNAs. PARN has been recently observed to interact with AGO2[100] and can trim and process non-coding RNAs.[101,102] PARN depletion leads to increased lengths of poly(A) tails of reporters and endogenous target mRNAs, resulting in loss of activation of reporters as well as decreased levels of endogenous target proteins.[31] Re-establishing PARN expression rescues microRNA-mediated activation of reporters and protein levels of endogenous targets.

Interestingly, un-adenylated reporters that should not need the deadenylase function of PARN do not show activation in cells depleted of PARN. Therefore, in addition to its deadenylase activity, PARN is required for an additional role in microRNA dependent translation upregulation in quiescent conditions.[31] PARN binding to m^7G caps is increased (~2.5-fold) in G0 THP1 cells while binding of the canonical cap binding protein, eIF4E, is reduced (~25%).[31,65] Point mutations in PARN that inactivate either cap binding or deadenylase activity prevent microRNA mediated activation, which revealed that both cap binding and deadenylase activities of PARN are required for microRNA mediated activation in these conditions.[31] Together, these data indicate that in G0, PARN functions to not only shorten poly(A) tails of target mRNAs but also as an alternate cap binding protein that connects the 3′ UTR bound FXR1a-microRNP with 5′ caps. These interactions replace the canonical eIF4E-eIF4G-PABP 5′-3′

link—that is disrupted by active 4EBP and poly(A) shortening—to mediate non-canonical translation of associated, specific mRNAs.[31]

DAP5/p97 is essential for FXR1a-microRNP mediated non-canonical translation

Death-associated protein 5 (DAP5, p97 or NAT1) is an EIF4G homolog that mediates non-canonical translation.[103-106] P97 lacks eIF4E and PABP binding sites, but possesses a similar eIF3 binding site to that of canonical translation factor eIF4G, which can recruit eIF3 and thereby, 40S ribosome subunits to initiate translation.[105,107] P97 has been shown to mediate cap independent, IRES driven translation during cellular stress and specific conditions[107-113] where p97 is recruited via mRNA interactions. P97 mediates cap dependent alternative translation in quiescent conditions, where canonical translation factor eIF4G—that brings in the 40S ribosome subunit to initiate translation—cannot be recruited due to interference with the cap complex by active 4EBPs.[31] P97 interacts with FXR1a-microRNP and PARN in G0 to mediate non-canonical translation of specific mRNAs associated with FXR1a-microRNP (Fig. 1).[31] Depletion of p97 results in loss of FXR1a-microRNP mediated activation of reporters as well as of endogenous targets in G0 cells and in immature oocytes. Loss of p97 also affects oocyte development due to decreased translation of the microRNA target MYT1 that is required to maintain the immature state. Consequently, p97 depletion results in loss of the immature state and premature maturation of oocytes.[31] Restoring p97 rescues reporter and endogenous target mRNA translation, including the endogenous target MYT1 protein levels and thereby, the immature oocyte state.[31] These data suggest a role for p97 and this specialized translation mechanism in oocyte development.

Critical features of FXR1a-microRNP mediated translation

Certain mechanistic features are critical for microRNA mediated translation activation in quiescent conditions. These features include: FXR1a-microRNP recruitment of poly(A) shortened target mRNAs, avoidance of repressive microRNP factors, and reduction of canonical translation to enable this alternative translation mechanism.[31]

First, FXR1 levels are increased differentially in low mTOR activity conditions and in G0 in certain cell lines and in immature oocytes.[25,31] Second, FXR1a interacts with AGO2 forming an altered microRNP that causes activation of specific mRNAs.[16,17,114] FXR1 is a translation activator and is known to interact with the 60S ribosomal subunit.[29] In proliferating cells, FXR1a overexpression leads to microRNA mediated translation activation.[75] Consistently, proteomic studies in FXR1 depleted cells revealed decrease in protein levels of certain mRNAs that are targets of activation and require FXR1 for their polysome association.[31] Third, FXR1 does not interact with GW182 and does not lead to repression but instead promotes activation of translation.[29,31] In G0 and distinct oocyte stages,[115,116] the association of repressor GW182 protein with AGO2 may be reduced,[114,117-119] which may permit activation of specific mRNAs. Fourth, in order to get translation activation, target mRNAs and the microRNAs in quiescent conditions have to be recruited in the nucleus[75] by AGO2 and FXR1. mRNAs not associated in the nucleus with the FXR1a-microRNP are not translationally upregulated, and could be subject to repression by the canonical microRNP. Consistently, we find that Cyclin E mRNA that is not recruited by FXR1a-microRNP in the nucleus, is repressed in G0.[31,75,120] How specific microRNAs are recruited to this complex remain to be ascertained. Fifth, mRNAs recruited by the FXR1a-microRNP need to have short poly(A) tails to avoid PABP and thereby, avoid repression by GW182 and canonical translation that is inhibited in these conditions. Sixth, FXR1a-microRNP mediated translation requires low mTOR activity/4EBP active conditions, where canonical translation is decreased to permit this non-canonical translation mechanism. In such conditions, PARN, which also interacts with FXR1a-microRNP, shows increased binding to mRNA caps of such targets. The cap binding activity of PARN is required for activation, providing an alternative to the canonical cap binding eIF4E-eIF4G interaction that is inhibited by 4EBP in these conditions. Seventh, in low mTOR conditions, FXR1a-microRNP associates with specific target mRNAs via their 3′UTRs and interacts with p97—that brings in the 40S ribosomal subunit through interactions with eIF3—as well as connects to the 5′ cap through PARN interaction.[16,31] These features are essential to establish this specialized, non-canonical mechanism of translation (Fig. 1). Whether these features are sufficient in other cells and systems remain to be tested. These data suggest that translation activation of specific, poly(A) shortened mRNAs is mediated by FXR1a-microRNP that lacks GW182, and interacts with non-canonical cap binding and translation factors to promote translation in these distinct, quiescent conditions with reduced canonical translation.

Importantly, microRNA mediated translation activation has been previously observed in a Drosophila embryo extract system, and in mammalian cells,[17,21-23,26] where these features of requirement for shortened poly(A) tails, altered cap complex, and lack of GW182 have also been observed.[17,21,26,31,114] Together, these studies suggest a common alternative translation mechanism that is mediated by microRNAs in association with a distinct complex that lacks microRNP repressors, and involves avoidance of canonical translation to enable translation of specific mRNAs.

FXR1a-microRNP mediates translation of important genes

MicroRNA mediated translation of specific mRNAs plays an important role in maintaining the quiescent state. In immature oocytes, FXR1a-microRNP mediates translation of MYT1 kinase, a cell state regulator required for maintaining the immature oocyte state by phosphorylating CDC2 that inactivates maturation promoting factor.[25] Loss of microRNA mediated translation in oocytes therefore, leads to loss of the immature state, implicating this mechanism in development.

Quiescence is a hallmark of cancer stem cells that can give rise to cancer recurrences.[121-124] In G0 THP1 cells, FXR1a-microRNP mediates translation of immune genes like TNFα and CD209, and cell state regulator HES1.[31] TNFα and CD209

are known immune modulators that are implicated in tumors.[125-128] Hes1, a downstream effector of Notch signaling, is important for stem cell maintenance, prevents quiescent cells from differentiation and apoptosis, and is implicated in cancer progression.[59,121,129-133] Consistently, components of the FXR1a-microRNP are implicated in cancer progression: FXR1 is known to promote tumor invasion and progression,[30] while its interacting partners, PARN and p97, are increased in activity or levels in many cancers.[98,134] Targeting components of the FXR1a-microRNP mechanism or associated microRNAs may help block translation of critical genes required for maintaining dormant cancer cells, and might be a promising approach against cancer recurrence.

Future questions

Our studies delineated the mechanism of FXR1a-microRNP mediated translation in quiescent cells.[25,31,75] Several intriguing questions emerge from these studies and remain to be addressed. First, it is not known how FXR1a-microRNP selects its targets for activation in G0. To be a bona fide activation target of this mechanism, we showed that the mRNA has to be recruited by distinct FXR1a-microRNPs, and thus associated with FXR1 and AGO2.[31] We found that nuclear recruitment is required for target mRNAs to be selected by FXR1a-microRNP.[75] However, it is not known whether these target mRNAs use additional motifs, apart from the microRNA binding site, to help select these mRNAs for activation. While our data with luciferase reporters showed that a single microRNA binding site in the 3′ UTR is sufficient to mediate translation activation, it would be interesting to find out if multiple binding sites and additional motifs can enhance translation activation of target mRNAs. Cross-linking immunoprecipitation (CLIP)[6,135] and ribosome profiling[136-139] of FXR1a-microRNP bound target mRNAs, as well as mRNA target site analyses, will help understand target selection by FXR1a-microRNP. Second, it would be important to uncover how microRNAs are selected for involvement in translation activation. We found that microRNAs that are involved in activation are associated with FXR1 and AGO2, in FXR1a-microRNPs—complexes that are distinct from canonical, repressive microRNPs that involve GW182 and AGO2. MicroRNAs like miR16 that mediate repression in association with canonical GW182 and AGO2 complexes,[140,141] can also associate with FXR1 in these distinct FXR1a and AGO2 complexes (FXR1a-microRNPs) in G0 cells to promote specific mRNA translation.[17,31] However, it is not known how many microRNAs bind FXR1 and how abundant these microRNAs are in G0 cells. Interestingly, we found that specific microRNAs associate with FXR1 at different levels—which could dictate their potential for activation. For example, less miR16 was found associated with FXR1 compared with miR369–3p in G0 THP1 cells, and other microRNAs that do not show activation were consistently, not associated with FXR1.[31] Profiling of FXR1 and AGO2 bound microRNAs in G0 cells, compared to their levels, and to their association with canonical, repressive GW182 complexes, will address this question. Third, the exact sequence of events, in which FXR1a, AGO2 and microRNA interact with each other remains to be investigated. FXR1 interacts with AGO2 in the nucleus and target mRNAs have to be recruited to FXR1a-microRNPs in the nucleus in order to mediate translation activation.[31,75] However, it is not known whether FXR1a-microRNP recruits its microRNAs in the nucleus or cytoplasm. It is possible that microRNAs bind FXR1 in the cytoplasm and are then imported to the nucleus—where they then interact with AGO2—as FXR1 possesses a nuclear localization signal.[28] Alternatively, microRNAs are imported to the nucleus by different means or via AGO2, and then associate with FXR1a-microRNP in the nucleus. High-throughput sequencing of FXR1a-microRNP associated targets and microRNAs in fractionated nuclei and cytoplasm, as well as in-depth functional analyses in G0 cells, will help answer these questions.

Conclusions

The majority of proteins in proliferating cells are translated via canonical cap dependent translation, which is a highly energy-consuming process. Under conditions of cellular stress like growth factor deprivation, conventional protein synthesis is inhibited and is replaced by various alternative translation mechanisms that express specific genes that are important to maintain the cellular state. During quiescence, which plays a critical role in early development and in cancer dormancy, one of the alternative mechanisms utilized by such cells to translate specific mRNAs is via a specialized microRNP-mediated translation mechanism. This novel mode of protein synthesis in quiescence is directed by a specific microRNP that has a translation activator FXR1a instead of the microRNP repressor, and replaces canonical translation factors with an alternate cap binding protein, PARN, and a non-canonical factor to recruit the ribosome, p97/DAP5 (Fig. 1). Understanding the role played by these non-canonical factors and specialized mechanisms in mediating translation of specific mRNAs will further our understanding of how these cells maintain their dormant state, and may lead to new therapeutic strategies against cancer.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed

Funding

SV is funded by NIGMS grant GM100202.

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