




REVIEW

Translational regulation of cell invasion through extracellular matrix—an emerging role for ribosomes [version 1; peer review: 1 approved, 2 approved with reservations]

David R. Sherwood , Isabel W. Kenny-Ganzert, Siddharthan Balachandar Thendral

Biology, Duke University, Durham, North Carolina, 27708, USA

V1 First published: 29 Nov 2023, 12:1528
<https://doi.org/10.12688/f1000research.143519.1>

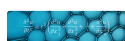
Latest published: 29 Nov 2023, 12:1528
<https://doi.org/10.12688/f1000research.143519.1>

Abstract

Many developmental and physiological processes require cells to invade and migrate through extracellular matrix barriers. This specialized cellular behavior is also misregulated in many diseases, such as immune disorders and cancer. Cell invasive activity is driven by pro-invasive transcriptional networks that activate the expression of genes encoding numerous different proteins that expand and regulate the cytoskeleton, endomembrane system, cell adhesion, signaling pathways, and metabolic networks. While detailed mechanistic studies have uncovered crucial insights into pro-invasive transcriptional networks and the distinct cell biological attributes of invasive cells, less is known about how invasive cells modulate mRNA translation to meet the robust, dynamic, and unique protein production needs of cell invasion. In this review we outline known modes of translation regulation promoting cell invasion and focus on recent studies revealing elegant mechanisms that expand ribosome biogenesis within invasive cells to meet the increased protein production requirements to invade and migrate through extracellular matrix barriers.

Keywords

cell invasion, cell migration, translational regulation, translation initiation, ribosomes, ribosome biogenesis, ribosome localization



This article is included in the [Cell Migration](#) collection.

Open Peer Review

Approval Status ? ✓ ?

	1	2	3
version 1 29 Nov 2023	? view	✓ view	? view

1. **Congying Wu**, Peking University, Beijing, China
2. **Julie Plastino**, Ecole Normale Supérieure, Paris, France
3. **frederic saltel**, INSERM, Rue Léo Saignat, Bordeaux, France

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: David R. Sherwood (david.sherwood@duke.edu)

Author roles: **Sherwood DR:** Conceptualization, Funding Acquisition, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Kenny-Ganzert IW:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Balachandar Thendral S:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: DRS, IWK, and SBT were supported by the National Institutes of Health (R35GM118049 and R21OD032430). *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

Copyright: © 2023 Sherwood DR *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Sherwood DR, Kenny-Ganzert IW and Balachandar Thendral S. **Translational regulation of cell invasion through extracellular matrix—an emerging role for ribosomes [version 1; peer review: 1 approved, 2 approved with reservations]** F1000Research 2023, 12:1528 <https://doi.org/10.12688/f1000research.143519.1>

First published: 29 Nov 2023, 12:1528 <https://doi.org/10.12688/f1000research.143519.1>

Abbreviations

aa-tRNA: Aminoacyl-tRNA
 ECM: Extracellular matrix
 EMT: Epithelial-mesenchymal transition
 ER: Endoplasmic reticulum
 IRES: Internal ribosome entry site
 Met-tRNA: Methionyl-tRNA
 PABP: Poly(A)-binding protein
 PIC: 43S pre-initiation complex
 rRNAs: Ribosome RNAs

Introduction

During development many animal cells migrate to form tissues and organs. For example, muscle precursor cells in vertebrates undergo an epithelial-mesenchymal transition (EMT) to delaminate from the somatic dermomyotome and then migrate long distances to construct muscles of the limbs, the diaphragm, and the tongue (Talbot *et al.*, 2019; Vasyutina and Birchmeier, 2006). Neural crest cells also undergo an EMT to detach from the neural tube and travel throughout the embryo to form connective tissue, bones, neurons, and epidermis (Szabo and Mayor, 2018). During their migrations cells encounter and must invade through extracellular matrices (ECMs) to reach their destinations (McLennan *et al.*, 2020). Cells confront the two main forms of ECM—thin dense laminin and type IV collagen rich basement membranes that surround most tissues and type I and type III collagen rich interstitial matrices that rest between tissues (Duband and Thiery, 1987; Gros and Tabin, 2014; Pompili *et al.*, 2021). In fact, during EMT, cells must immediately breach the underlying epithelial basement membrane to delaminate from the epithelial tissue, and invasive behavior is thought to be a core component of the EMT program (McClay, 2021). Cell migration and invasion through ECM also plays important roles during immune cell trafficking to sites of infection and injury (DeDreu *et al.*, 2022). Misregulation of invasion underlies many human diseases, such as multiple sclerosis, rheumatoid arthritis, the pregnancy disorder pre-eclampsia, and most notably cancer (Greter *et al.*, 2005; Padmanaban *et al.*, 2019; Stanford *et al.*, 2016; Zou *et al.*, 2019). Understanding how cells migrate and invade through ECM is thus of crucial importance to human development and health.

Invasive cells use specialized F-actin-based plasma membrane protrusions to degrade and breach ECM barriers. These protrusions have been termed podosomes in normal cells and invadopodia in cancer cells (Cambi and Chavrier, 2021). Collectively these invasive protrusions are referred to as invadosomes, which are likely a related group of membrane-associated protrusive structures that alter their arrangements, dynamics, and composition in response to the environment (Cambi and Chavrier, 2021; Di Martino *et al.*, 2016; Paterson and Courtneidge, 2018). Invadosomes are highly complex and harbor numerous proteins, such as actin regulatory proteins, adhesion proteins, proteases, and signaling molecules that regulate the formation and function of invadosomes in breaking down ECM (Cambi and Chavrier, 2021; Ezzoukhry *et al.*, 2018). Invadosomes are also sites of dynamic vesicle trafficking for protease secretion and membrane addition to support protrusion extension and thus require an expanded membrane trafficking system (Costa *et al.*, 2023; Feng *et al.*, 2014; Hastie and Sherwood, 2016; Naegeli *et al.*, 2017). To construct and sustain invasive F-actin polymerization, protein secretion, and membrane trafficking, invasive cells also have robust energy acquisition and delivery networks that facilitate dynamic glucose import, glucose processing, mitochondria localization, and oxidative phosphorylation-mediated production of high ATP levels (Garde *et al.*, 2022; Garde and Sherwood, 2021). The building of this complex invasive apparatus requires numerous and diverse genes whose expression is controlled by pro-invasive transcriptional networks (Medwig-Kinney *et al.*, 2020; Pastushenko and Blanpain, 2019). Evidence indicates the translation of the mRNA encoding proteins of the invasive machinery is also regulated to promote cell invasion.

Here, we provide an overview of translation, note aspects of translation that are modulated during invasion, and focus on new studies revealing the roles of ribosome regulation in cell invasion and migration through ECM. Because of the importance of invasion to metastasis, most studies on translation and invasion have been conducted in cancer cell lines and primary tumors *in vitro*. As cancerous cells are thought to hijack normal invasion mechanisms used in development and homeostasis (Paterson and Courtneidge, 2018), many of the mechanisms uncovered in tumors will likely apply broadly to other invasive cells.

Overview of protein translation

Translation is the process by which the information in the unique nucleotide sequence of an mRNA is used to synthesize a distinct protein composed of a chain of amino acids. The information in mRNA is in the form of triplet codes of nucleotides, termed codons, which specifies either a specific amino acid (of a possible 20) or a stop to translation.

mRNA is read by ribosomes using aminoacyl-tRNAs (aa-tRNAs) containing anticodons that match with each codon to select and then join specific amino acids together by forming peptide bonds to construct a protein. Translation is terminated by stop codons, which are recognized by release factors (see below). The untranslated sequence at the 5' end of an mRNA contains a 5' 7-methylguanosine cap that precedes the start codon, which is the first codon translated. There is also untranslated RNA at the 3' end of the mRNA that has a 3' poly(A) tail following the stop codon. Translation is complex and highly regulated and can be separated into three primary phases--initiation, elongation, and termination. Each step is assisted by translation associated factors, and these steps are briefly summarized below (Figure 1, for a more complete description, see [Blanchet and Ranjan \(2022\)](#) and [Hershey et al. \(2012\)](#)).

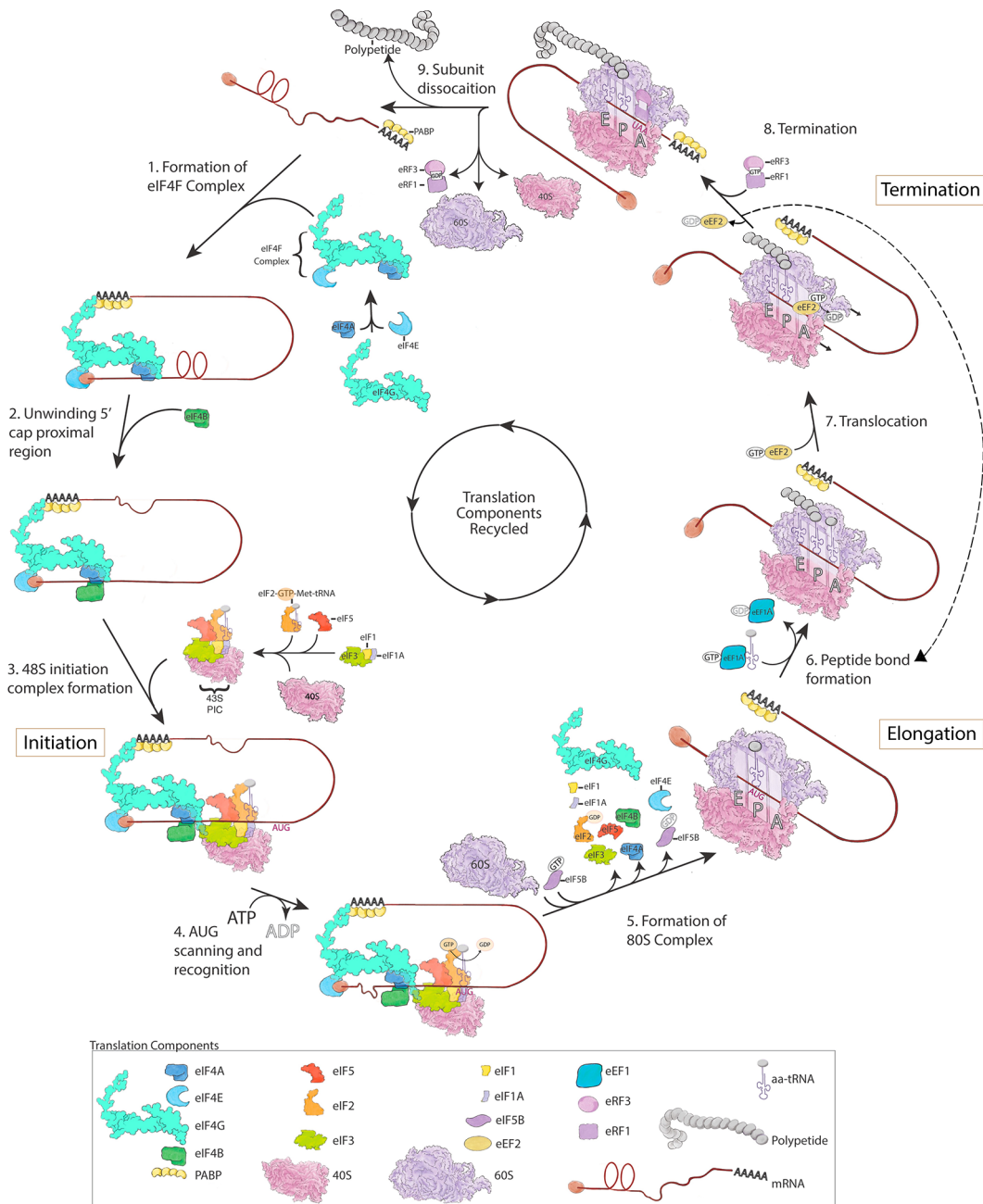


Figure 1. Overview of mRNA Translation. mRNA translation is divided into three steps: (1-5) initiation, (6-7) elongation, and (8-9) termination. For detailed descriptions of these distinct steps that match the figure depiction please see the text. This figure is an original figure produced by the authors for this review article.

Cap-dependent translation initiation in eukaryotes occurs when the translation initiation complex (eIF4F), composed of eIF4A, eIF4E and eIF4G, is formed and binds to the 7-methylguanosine cap at the 5' end of mRNAs (Smith *et al.*, 2021). eIF4E is a cap-binding protein, eIF4G is a scaffolding protein that interacts with poly(A)-binding protein (PABP) at the 3' end of mRNAs, and eIF4A is a helicase that unwinds secondary structure of mRNA into a single strand in conjunction with the RNA-binding protein eIF4B (or eIF4H, not shown in Figure 1) (Smith *et al.*, 2021). After the eIF4F complex is assembled on an mRNA, it recruits the 43S pre-initiation complex (PIC) through an interaction between eIF4G in the eIF4F complex and eIF3 in the 43S PIC (Villa *et al.*, 2013). The 43S PIC is composed of eIF3, a multiprotein factor comprised of 13 proteins in mammals, and the 40S ribosomal subunit bound to the initiation factors eIF1, eIF1A, eIF5 and the ternary complex (eIF2-GTP-Met-tRNA). The ternary complex harbors the initiator methionyl-tRNA (Met-tRNA) (Hinnebusch, 2017). The assembly of these components forms the 48S initiation complex (Figure 1), which scans the mRNA in a 5' to 3' direction to locate the start codon (AUG). In addition to cap dependent initiation, in ~10% of mammalian mRNAs, the 40S ribosomal subunit binds directly to an internal region of the mRNA, called the internal ribosome entry site (IRES), which then may proceed to scan the mRNA for the start codon (Weingarten-Gabbay *et al.*, 2016). The recognition of a start AUG codon by the anti-codon of Met-tRNA triggers the hydrolysis of GTP by eIF2 in the ternary complex and allows the 60S ribosomal subunit to join the 48S initiation complex (Llacer *et al.*, 2018; Majumdar and Maitra, 2005; Smith *et al.*, 2021). Hydrolysis of GTP by the GTPase eIF2, releases eIF2-GDP from the 48S complex and is thought to lead to the disassembly of many initiation factors (Blanchet and Ranjan, 2022; Smith *et al.*, 2021), although eIF4F might remain at the 5' cap and allow for recruitment of the next 43S PIC (Bohlen *et al.*, 2020). The assembly of the 60S onto the 48S initiation complex to form the 80S complex is facilitated by GTP-bound eIF5B along with eIF1A. Hydrolysis of GTP by eIF5B and displacement of eIF5B-GDP and eIF1A allows the 80s ribosome to enter the elongation phase of translation (Pestova *et al.*, 2000).

Ribosomes contain three sites where tRNA binds—A (aminoacyl) site that binds newly arriving tRNAs carrying amino acids, P (peptidyl) site where tRNA with the growing polypeptide chain resides, and an E (exit) site, where the tRNA leaves the ribosome after transferring its amino acid. The initiator Met-tRNA, however, functions differently from other tRNAs and is the only tRNA that binds directly to the P site of the ribosome during the translational cycle (Kolitz and Lorsch, 2010). Subsequent aa-tRNAs are then delivered through GTP-bound eEF1A in a process that involves complementary base pairing between the mRNA codon and the anticodon of the aa-tRNA in the A site of the ribosome (Figure 1 dashed arrow) (Knight *et al.*, 2020). Codon recognition triggers GTP hydrolysis in eEF1A and eviction of eEF1A-GDP from the A site. In parallel, the ribosome undergoes a conformational change that promotes movement of the aa-tRNA in the A site to contact the tRNA bound to the polypeptide chain in the P site. The movement of the tRNAs from the A to P and P to E sites stimulates ribosome catalyzed peptide bond formation and transfer of the growing polypeptide to the aa-tRNA entering the P site. GTP bound eEF2 then enters the empty A site and through hydrolysis of GTP induces a ribosome conformational change that facilitates movement of the ribosome along the mRNA. The eviction of eEF2-GDP then allows the next aa-tRNA to enter the A site and repeat the elongation cycle (Knight *et al.*, 2020; Taylor *et al.*, 2007). Most mRNAs are translated by many ribosomes simultaneously, each following another along the mRNA and forming a polysome.

Upon encountering a stop codon (UAA, UAG or UGA), translation is terminated by two release factors—eRF1, which recognizes stop codons, and eRF3, a GTPase that promotes the activity of eRF1 (Alkalaeva *et al.*, 2006; Zhouravleva *et al.*, 1995). In addition to recognizing stop codons, eRF1 also catalyzes peptidyl-tRNA hydrolysis and the release of the newly made protein. Following translation termination, the deacylated tRNA is released and ribosomal subunits disassociate into 40S and 60S subunits (for ribosome disassociation mechanisms see (Blanchet and Ranjan, 2022)), which are then recycled for use in the translation of other mRNAs (Shoemaker and Green, 2011).

Translation regulation and cell invasion

Translation regulators often modulate translation of specific mRNA transcripts by interacting with the unique structural and sequence-specific elements within distinct 5' or 3' UTRs of mRNAs (de la Parra *et al.*, 2018; Falletta *et al.*, 2017; Ho *et al.*, 2021; Smith *et al.*, 2021; Song *et al.*, 2021; Truitt and Ruggero, 2016). A crucial node for pro-invasive protein regulation is translation initiation (Verma *et al.*, 2019). Alterations in expression of many translation initiation factors and the activity of signaling pathways that act on translation initiation factors are associated with fostering invasion and metastasis in numerous human cancers and in developmental processes (Chen *et al.*, 2019; Esteves *et al.*, 2020; Falletta *et al.*, 2017; Fan and Guo, 2015; Furic *et al.*, 2010; Hao *et al.*, 2020; Jaiswal *et al.*, 2019; Joyce *et al.*, 2017; Martineau *et al.*, 2013; Nasr *et al.*, 2013; Pinzaglia *et al.*, 2015; Ruan *et al.*, 2020; Vaysse *et al.*, 2015; Wan *et al.*, 2015; Wang *et al.*, 2016). For example, eIF4G and eIF4E proteins have increased expression across a variety of human cancers and inhibition of eIF4G in prostate cancer cells and eIF4E in ovarian cancer, breast cancer, and melanoma cell lines inhibits invasive activity (Jaiswal *et al.*, 2019; Joyce *et al.*, 2017; Nasr *et al.*, 2013; Wan *et al.*, 2015). Further, experimentally increasing expression of eIF4E in a weakly invasive breast cancer cell line strongly enhances invasive ability (Nasr *et al.*, 2013). Polysome profiling, a method that determines the mRNAs being translated in the cell and the degree of translation

of particular mRNAs (Chasse *et al.*, 2017), revealed that translation of MMP9, a metalloproteinase associated with cell invasion, was selectively diminished after reduction of eIF4E (Nasr *et al.*, 2013). Phosphorylation of eIF4E is also elevated in many cancers as a result of RAS/RAF/ERK and PI3K/AKT/mTOR signaling (Martineau *et al.*, 2013) and leads to the preferential increase in translation of mRNAs encoding the pro-invasive matrix metalloproteinase MMP3 and the chemokine CCL2 in prostate cancer cells (Furic *et al.*, 2010).

Other aspects of translational regulation also promote invasion and metastasis in cancer. These include the misexpression of translation elongation factors (Li *et al.*, 2017; Mathews and Hershey, 2015; Xie *et al.*, 2018; Zhu *et al.*, 2009) and changes in expression and modification of tRNAs that likely favor translation of mRNAs enriched with their cognate codons encoding pro-invasive proteins (Birch *et al.*, 2016; Goodarzi *et al.*, 2016; Knight *et al.*, 2020; Wan Makhtar *et al.*, 2017). Additional translation regulators driving invasion include expression of lncRNAs (Karakas and Ozpolat, 2021), microRNAs (Ma *et al.*, 2007), N6-methyladenosine (m⁶A) modification of mRNA transcripts (Lin *et al.*, 2019; Zhao *et al.*, 2022), and increased expression of RNA binding proteins that modulate translation (Evdokimova *et al.*, 2009; Wurth *et al.*, 2016).

The numerous identified mechanisms regulating mRNA translation that support and drive invasion and migration highlight the importance of modulating translation. Interestingly, recent findings indicate that the ribosome supramolecular complex itself—the molecular machine through which mRNA is turned into proteins—is also regulated to favor invasive behavior.

Ribosome regulation during cell invasion and migration

Ribosome biogenesis promotes invasion and migration by expanding translation capacity

Eukaryotic ribosomes are composed of two dissociable subunits called the large and small, referred to as the 60S (47 proteins and the 28S, 5.8S and 5S rRNA molecules) and 40S (33 proteins and 18S rRNA molecule) subunits, which come together on mRNAs to form the 80S ribosome as outlined above (Ni and Buszczak, 2023a). Ribosome biogenesis involves ribosome assembly within the nucleolus, a nuclear subcompartment, and requires the coordinated production of ribosome RNAs (rRNAs) and ribosomal proteins (Ni and Buszczak, 2023a). There is now strong evidence indicating that ribosome biogenesis is required within invasive cells to expand translation capacity to produce the numerous cytoskeletal proteins, matrix degrading enzymes, adhesion and signaling proteins, and metabolic enzymes required for invasion and migration.

Studies in PC3 human prostate cancer cells were among the first to implicate ribosome biogenesis in cell invasive behavior. Upregulation of mTOR is strongly associated as a driver of prostate cancer metastasis (Murugan, 2019). Using polysome profiling in prostate cancer cells, the translation of 144 mRNAs were identified as dependent on mTOR activity (Hsieh *et al.*, 2012). These included 70 mRNAs encoding ribosomal proteins, consistent with the role of mTOR in controlling ribosome biogenesis (Iadevaia *et al.*, 2014), as well as pro-invasive protein encoding mRNAs, such as vimentin, MTA1 (metastasis associated 1), and CD44 (Hsieh *et al.*, 2012). The increased translation of ribosomal proteins alongside pro-invasive proteins suggested a possible role for ribosome biogenesis in cell invasiveness, however, the functional relevance of new ribosome construction in promoting invasion was not examined.

Further support for ribosome biogenesis as a key element in cell invasion was provided by a study investigating EMT. Examination of several mammalian epithelial cell lines and in vivo analysis of neural crest EMT in mice and chick, revealed an upregulation of ribosome biosynthesis during EMT. Evidence included an increase in nascent rRNA synthesis and processing, which initiates ribosome biogenesis (Gentilella *et al.*, 2015), an increase in size of the nucleolus, and increased expression of many proteins that direct ribosome biogenesis (Prakash *et al.*, 2019). Supporting a key role for ribosome biogenesis in cell invasion during EMT, pharmacological inhibition of rRNA synthesis in a mouse epithelial cell line, reduced TGFβ-induced EMT invasion and migration (Prakash *et al.*, 2019). In addition, high levels of RNA Polymerase I, which generates the 5.8S, 18S and 28S rRNAs of the ribosome, are present in invasive breast tumor tissue and pharmacological inhibition of rRNA synthesis in mouse models of breast cancer metastasis (MMTV-PyMT and EO771) reduced metastatic seeding (Prakash *et al.*, 2019).

Recent studies examining *C. elegans* anchor cell invasion have further established a crucial role for ribosome biogenesis in promoting cell invasion and helped clarify a key function for biogenesis in expanding translation capacity to produce the numerous proteins that execute invasion. The anchor cell is a specialized uterine cell that invades through basement membrane separating the uterine and vulval tissues to initiate the uterine-vulval connection during *C. elegans* development (Kenny-Ganzert and Sherwood, 2023). The anchor cell is born eight hours prior to invasion, grows, and then invades through the basement membrane during a specific 90-minute period using invadosomes armed with protrusive F-actin, microtubules, MMPs, and cell adhesion receptors. By using genome editing to endogenously tag proteins that are required for invasion with genetically encoded fluorophores, it was shown that the levels of these pro-invasive proteins,

such as the actin nucleator Arp2/3, microtubule end binding protein EBP-2, integrin adhesion receptor INA-1, glucose importer FGT-1, and small Ras-like GTPase RAP-1, ramp up dramatically approximately two hours prior to invasion and peak in levels at the time of basement membrane breaching (Costa *et al.*, 2023). A recently generated anchor cell transcriptome revealed that mRNAs encoding many ribosomal proteins are enriched in the anchor cell during invasion (Costa *et al.*, 2023). Analysis of ribosomes and ribosome biogenesis markers indicated that a burst of ribosome biogenesis occurs approximately four hours prior to invasion and before the ramp up of pro-invasive protein levels (Costa *et al.*, 2023). Using RNAi at different time points prior to invasion to deplete ribosomal proteins, revealed that only a modest decrease in ribosomal protein levels blocks anchor cell invasion and reduces the translation of many pro-invasive proteins. These results support the notion that early ribosome biogenesis is required to expand translation capacity to produce the many pro-invasive proteins that mediate basement membrane breaching (Costa *et al.*, 2023). Importantly, these observations do not rule out other roles for ribosome biogenesis in supporting invasion, including constructing specialized ribosomes tuned for translating invasive transcripts (see below), as well as ribosomes serving as scaffolds on which signaling components, such as mTOR, can be activated to promote pro-invasive protein production (Zinzalla *et al.*, 2011).

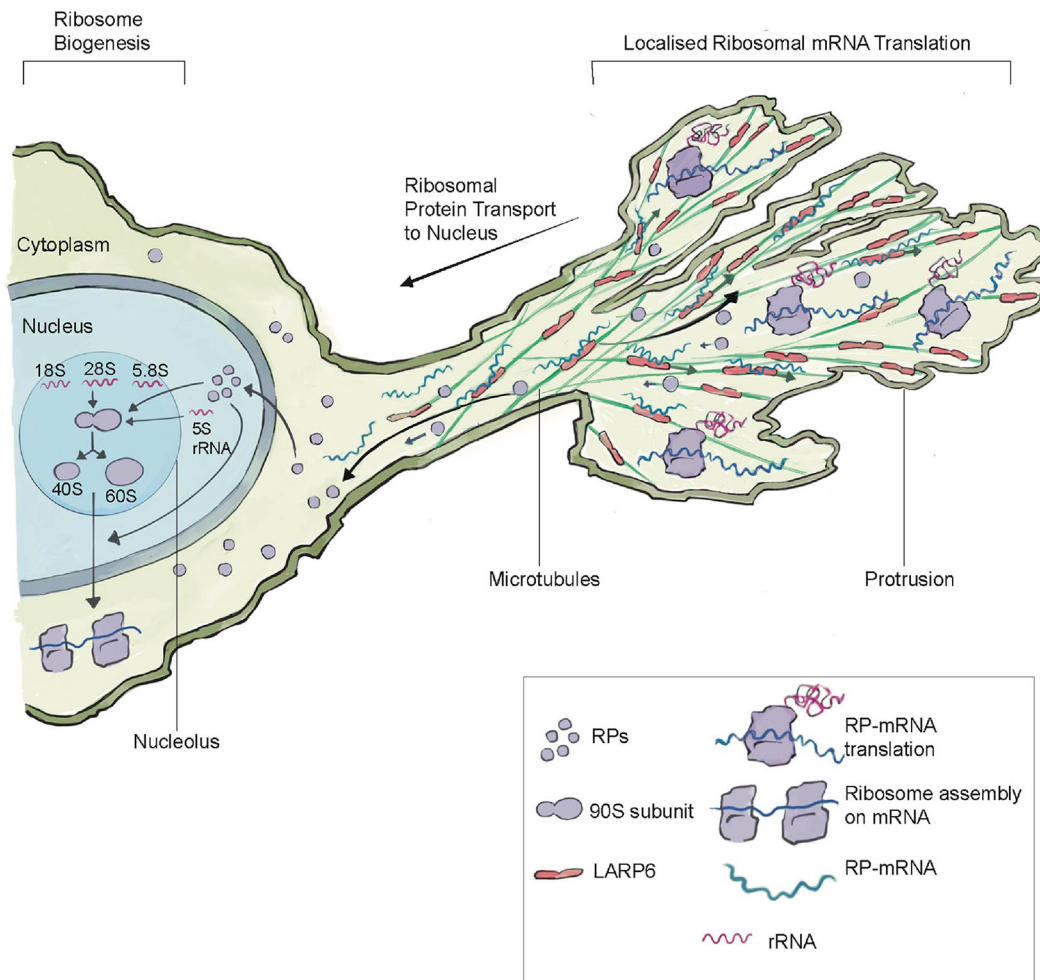


Figure 2. LARP6-mediated Ribosome Biogenesis Regulation in Protrusions. The microtubule binding protein LARP6 enriches in protrusions, where it binds to mRNAs encoding ribosomal protein mRNAs (RP-mRNAs). There is also enrichment of the translation machinery within protrusion, which leads to the translation of ribosomal proteins within protrusions. After translation, ribosomal proteins move back and enter the nucleus, where they are assembled into ribosomes in the nucleolus by combining 5.8S, 5S rRNA, and 46 ribosomal proteins to make the large 60S subunit and the 18S rRNA and 33 ribosomal proteins to make the small 40S subunit. Protrusion formation and LARP6-mediated ribosomal protein translation leads to an increase in ribosome levels. LARP6-mediated ribosome biogenesis may be a form of feed-forward regulation, where migratory and invasive protrusions lead to the production of more translation machinery to support cell invasive and migratory behavior. This figure was adapted from Dermit *et al.* (2020) with permission from Elsevier.

Recent studies have also revealed that many invasive and migratory cells have an elegant system for regulating ribosome biogenesis (Figure 2). A study examining a diverse group of normal and malignant migratory human cell lines discovered that mRNAs encoding ribosomal proteins are localized to protrusive fronts (Dermitt *et al.*, 2020). Localization to protrusions is mediated by LARP6, a microtubule-associated protein that binds to ribosomal protein mRNAs. Protrusive fronts also harbor enrichment of translation initiation and elongation factors (Figure 2). RiboPuromylation analysis, an immunofluorescence method to visualize translation sites at the sub-cellular resolution (Bastide *et al.*, 2018), indicated strong colocalization of ribosomal protein-mRNAs and sites of active translation in protrusions (Dermitt *et al.*, 2020). Formation of protrusions promoted ribosomal protein translation, enhanced ribosome biogenesis, and boosted the overall protein synthesis of cells. It has been proposed that protrusion regulated ribosome biogenesis might be a form of feedforward control, where the size and stability of protrusions regulates ribosome biogenesis, which further supports migratory and invasive abilities of cells. Notably, the EMT driving transcription factor Snail1, induces both rRNA synthesis to initiate ribosome biogenesis (Prakash *et al.*, 2019) and triggers expression of LARP6 (Dermitt *et al.*, 2020), indicating that ribosome biogenesis and its regulation is a critical component the EMT invasion and migratory program.

Together, these studies spanning diverse invasive and migratory cells highlight the importance of ribosome biogenesis in expanding translation capacity to promote invasive activity and cell movement. Further, they have revealed an elegant mechanism of modulating ribosome production involving the mRNA binding protein LARP6, which is a promising therapeutic target to specifically inhibit invasive cells in cancer (Dermitt *et al.*, 2020).

Ribosomes enrich at invadosomes and the endoplasmic reticulum (ER) within invasive cells

Recent advances in ribosome tagging and subcellular biochemical analysis have discovered enrichment of ribosomes and translation at several locations within invasive cells where localized translation mediates important functions (Figure 3). Using laser capture microdissection, mass spectrometry, immunolocalization, and correlative light and electron microscopy (CLEM) analysis of invadosomes formed in NIH-3T3-Src cells, pioneering studies revealed that ribosomes and translation regulators are highly enriched at these invasive structures (Ezzoukhry *et al.*, 2018). Further, RiboPuromylation analysis confirmed active translation around F-actin rich invadosomes. Consistent with a potential reliance on

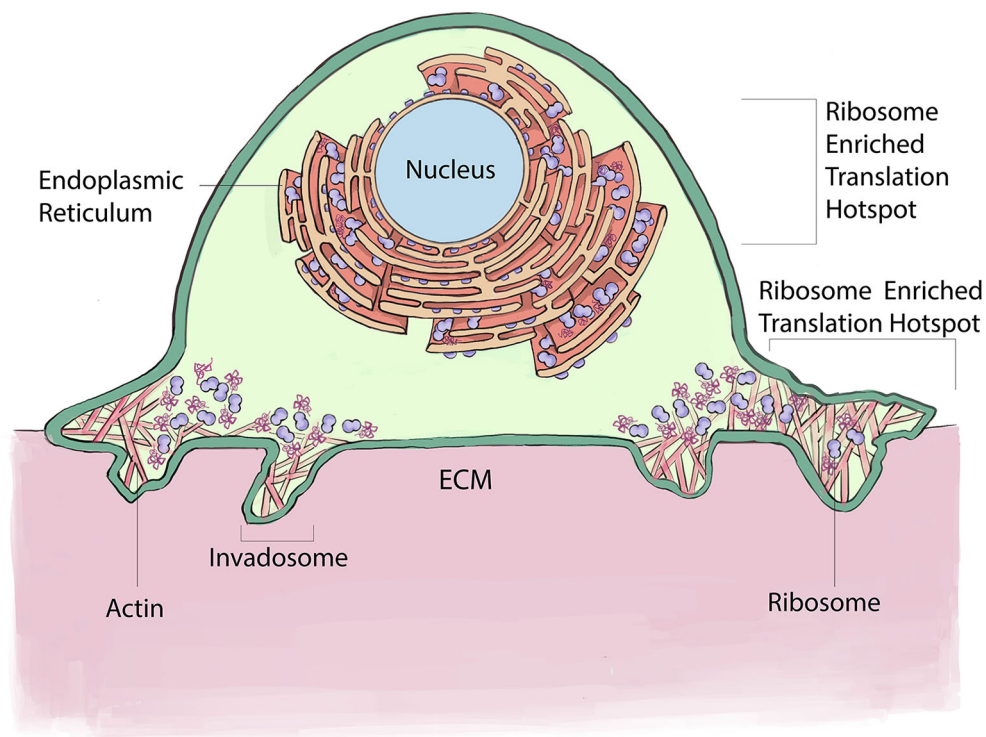


Figure 3. Ribosomes Enrich at the ER and around Invadosomes within invasive cells. Ribosomes enrich at the ER within invasive cells where they support the translation of secretory and transmembrane proteins. In addition, ribosomes localize around ECM degrading invadosomes, where they mediate localized translation necessary for invadosome formation and function. This figure is an original figure produced by the authors for this review article.

this enrichment, targeting of translation regulators with siRNA or treatment with the translation inhibitor anisomycin, inhibited the ability to form invadosomes and limited invadosome degradation of ECM (Ezzoukhry *et al.*, 2018).

Examining ribosomes in living animals has been challenging because large fluorophores on ribosomal proteins appear to interfere with the complex assembly and tightly packed ribosome structure (Noma *et al.*, 2017). Recently, a split-GFP strategy was developed to label ribosomal proteins endogenously in *C. elegans* (Costa *et al.*, 2023; Noma *et al.*, 2017). Examination of endogenous localization of the large ribosomal proteins RPL4 and RPL31 using the split-GFP approach in the invasive anchor cell in *C. elegans*, revealed that approximately three hours prior to invasion, ribosomes co-localize with the endoplasmic reticulum (ER) and Sec61 translocon (Costa *et al.*, 2023). Enrichment at the ER/Sec61 translocon is likely required to translate the many secreted and transmembrane proteins that must enter the endomembrane system to promote invasion. Consistent with high levels of new protein production within the ER, the transcription factor XBP1, the effector of the ER stress sensor IRE1 (Limia *et al.*, 2019), is present at high levels in the nucleus of the anchor cell prior to invasion (Costa *et al.*, 2023). Activated IRE1 directs the splicing of an intron from XBP1 mRNA, which is translated in the cytosol and then trafficked to the nucleus to regulate the expression of genes that counter ER stress (Cox and Walter, 1996). Interestingly, cytosolic XBP1 localizes to the anchor cell invasive front, suggesting that higher levels of translation are occurring near the site of basement membrane breaching—perhaps to facilitate rapid trafficking through the endomembrane system to the invasive front. Sensitivity to ER stress has been linked to EMT events in vertebrate neural crest cells and several cancers (Feng *et al.*, 2014; Limia *et al.*, 2019). Thus, localization of ribosomes to the ER to increase secretory and transmembrane protein production might be a common feature of invasive cells that allows increased translation of proteins that are needed at the cell surface to mediate invasion through ECM.

How ribosomes become enriched in different regions of the cell to support localized translation is unclear. Interestingly, approximately 400 ribosome-associated proteins have been identified in embryonic stem cells from mice (Simsek *et al.*, 2017). Although the functional significance of most of these interactions remain unknown, one of these, pyruvate kinase muscle (PKM), attaches to ER associated ribosomes and appears to bind to, localize, and help translate ER-destined mRNAs (Simsek *et al.*, 2017). It will be important in future studies to determine if PKM or other ribosome-associated proteins help direct ribosomes to the ER and possibly other regions such as invadosomes within invasive cells.

Ribosomal protein misexpression can drive or inhibit cell invasion in cancer cells

Misexpression of several ribosomal proteins has also been associated with regulating cell invasive activity in cancer. For example, RPL34 is overexpressed in pancreatic cancer and glioma and in vitro cell culture studies have implicated RPL34 in promoting cell invasion through activation of MAPK, p53, and the JAK/STAT3 signaling pathways (Ji *et al.*, 2019; Wei *et al.*, 2016). The small ribosomal protein RPS6 and phosphorylated-RPS6 also have increased abundance in many cancers, such as ovarian cancer, esophageal squamous cell carcinoma, and non-small cell lung cancer and promotes invasive activity (Kim *et al.*, 2013; Yang *et al.*, 2020). While overexpression of these two ribosomal proteins is strongly associated with cancer progression and cell invasion, it is unclear whether they function within ribosomes to enhance cell invasion or alternatively have pro-invasive activity outside of their roles as components of the ribosome (extra-ribosomal functions).

There is emerging evidence for extra-ribosomal functions of the small ribosomal protein RPS3 and the large ribosome protein RPL3 in regulating cell invasion in cancer cells. RPS3 is misexpressed in multiple cancers (El Khoury and Nasr, 2021), and overexpression of RPS3 reduces invasiveness of fibrosarcoma cells in vitro (Kim and Kim, 2006). RPS3 binds to the nucleoside diphosphate kinase A (nm23-H1) (Kim and Kim, 2006), which acts as a suppressor of metastasis in some tumors (Yu *et al.*, 2021). Binding of RPS3 to nm23-H1 might thus reduce invasiveness by enhancing nm23-H1 function. The large ribosomal protein, RPL3, is also misregulated in cancer and low expression is associated with invasion (Pecoraro *et al.*, 2019). Studies of RPL3 in a human colon cancer cell line indicate that RPL3 binds to the nuclear DNA binding protein poly ADP-ribose polymerase 1 (PARP-1) and represses the transcription of pro-invasive genes (Pecoraro *et al.*, 2019).

The misregulation of several other ribosomal proteins has also been implicated in invasive cancers, such as decreased levels of RPL5 in invasive breast carcinoma (Fancello *et al.*, 2017) and increased expression of RPL19 and RPL31 in malignant prostate cancer and colorectal cancer, respectively (Bee *et al.*, 2006; Sharen *et al.*, 2022). Unraveling how misregulated expression of ribosomal proteins alters invasive and migratory activity is challenging as these proteins might have functions within the ribosome, have extra-ribosomal functions, or might activate ribosomal stress pathways (Kang *et al.*, 2021). It is also currently unclear if these identified altered ribosomal protein levels is a normal physiological program that regulates cell invasion or rather an aspect of ribosomal protein misregulation that is only found in certain cancers. Interestingly, RPL31 is upregulated in the anchor cell of *C. elegans* during invasion (see below) (Costa *et al.*, 2023), suggesting that altered expression of ribosomal proteins could be an element of normal cell invasion programs.

Ribosome heterogeneity and cell invasion and migration

There is abundant evidence that ribosomes can be heterogenous from the assembly of different ribosomal proteins, ribosomal protein paralogs, ribosome-associated factors, post-translational modifications, rRNA variations, and rRNA modifications (Norris *et al.*, 2021). This heterogeneity could provide a cell a remarkable toolkit to create specialized ribosomes to fine tune translation of groups of mRNAs for distinct cell biological functions, including cell migration and invasion. Yet, the functional significance of heterogenous ribosomes remains largely unclear because of the technical challenges of identifying and assessing the function of distinct ribosome populations (Ni and Buszczak, 2023b).

Two observations are often cited to support the possibility of specialized ribosomes—tissue specific expression of ribosomal proteins and tissue specific phenotypes when different ribosomal protein encoding genes are disrupted (Norris *et al.*, 2021). Importantly, reduced production of ribosomal proteins can lead to a decrease in overall ribosome levels (Mills and Green, 2017) and translation efficiency of different mRNAs can depend on ribosome levels (Hu *et al.*, 2022; Khajuria *et al.*, 2018; Mills and Green, 2017). Thus, tissue specific phenotypes caused by alterations in ribosomal proteins, could simply be caused by tissue specific differences in levels of ribosomes (Mills and Green, 2017). Further, it is often difficult to rule out extra-ribosomal protein functions, as well as ribosome stress responses caused by ribosome dysfunction (Mills and Green, 2017). The critical test for specialized ribosomes requires evidence showing that different mRNAs are bound and translated by distinct ribosomes (via ribosome profiling using Ribo-Seq or ART-Seq) and determining if this translation is functionally significant (Barna *et al.*, 2022; Kondrashov *et al.*, 2011; Shi *et al.*, 2017). While there is emerging support for specialized ribosomes in yeast (Ferretti *et al.*, 2017; Gilbert, 2011; Hu *et al.*, 2022), there is only limited evidence in animals (Ni and Buszczak, 2023b).

The requirement for ribosome biogenesis prior to cell invasive activity and migration provides a potential mechanism for the generation of specialized ribosomes to promote invasion (see above). A transcriptome captured from the *C. elegans* anchor cell at the time of basement membrane invasion revealed upregulation of 13 large ribosomal subunit proteins (Costa *et al.*, 2023). Detailed examination of one of these, RPL31, which might be a regulatory ribosomal protein (Pech *et al.*, 2010), was suggestive of ribosome specialization. First, split-GFP labeling confirmed that RPL31 increased in levels more dramatically leading up to invasion than the core ribosomal protein RPL4 (Costa *et al.*, 2023; Shi *et al.*, 2017), which was not significantly upregulated in the transcriptome. Furthermore, RNAi mediated reduction of RPL31 and RPL4 had different effects on translation. Notably, reduction of RLP31 did not decrease translation of the actin regulator Ena/Vasp (*C. elegans* UNC-34), whereas reduction of RPL4 dramatically decreased Ena/Vasp translation. Further, reduction of RPL31 more severely decreased the translation of the integrin activation GTPase RAP-1 compared to reduction of RPL4 (Costa *et al.*, 2023). This observation supports the idea that RPL31 might be a component of specialized ribosomes that could enhance translation of a group of pro-invasive mRNAs, but not regulate the translation of other proteins. However, these observations do not rule out the possibility that some mRNAs have distinct translation sensitivities to ribosome concentrations that might be differentially affected by RNAi mediated reduction of RPL4 and RPL31 (Mills and Green, 2017).

It will be important in future studies to perform ribosome profiling in the anchor cell and other invasive cells to examine individual ribosome compositions and the mRNAs ribosomes are actively translating (Reynoso *et al.*, 2015). It will also be crucial to combine this analysis with targeted single cell protein degradation systems such as AID and ZF1 (Armenti *et al.*, 2014; Xiao *et al.*, 2023) and overexpression of ribosomal proteins to clarify the possible roles of specialized ribosomes in tuning translation for invasion.

Outlook

The ability of cells to invade and migrate through tissue and ECM barriers requires the production of many different proteins involved with membrane trafficking, ECM modification, energy production, and the cytoskeleton. Compared with transcription, translational control provides a more direct, rapid, and robust means to adjust protein levels (Hao *et al.*, 2020), which is well suited to meet the dynamic needs of invasive cells to rapidly alter protein levels to overcome and migrate through matrix and tissue barriers. The studies reviewed here highlight the importance and breadth of translational regulation in cell invasion, the challenge of studying translational control, and key gaps in our understanding as well as new opportunities to further our knowledge of how translation regulates cell invasion.

One gap in the field is that it has been dominated by investigation of translation regulation in human cancers and cancer cell lines in vitro. More studies in normal developmental and native physiological settings will help clarify core mechanisms of translational regulation and how these mechanisms are subverted in disease states. An additional challenge is that many aspects of translational regulation are subtle and difficult to disentangle experimentally from critical functions of translation to cellular viability. It will be important in the future to further develop methodologies that separate out core functions of translation from regulatory functions, such as experimental reduction of regulatory

components rather than complete loss (Costa *et al.*, 2023; Shi *et al.*, 2017), as well as temporal and cell specific removal of translation regulatory components (Costa *et al.*, 2023).

Significant advances have been made in visualizing active translation in cells, imaging ribosomes and translation regulatory components, biochemically isolating ribosomes actively translating mRNA, and revealing the association of ribosomes with many other proteins (Costa *et al.*, 2023; Dermitt *et al.*, 2020; Shi *et al.*, 2017; Simsek *et al.*, 2017). It will be vital to build on these techniques and findings to further our understanding of translation in cell invasion and migration. For example, it will be informative to characterize the ~400 protein-ribosome interactions, as they will likely reveal fascinating and unexpected regulation of ribosomes and translation. Furthermore, it will be crucial to expand on the limited number of ribosome composition and profiling studies to perform ribosome profiling in migratory and invasive cells to directly address the functional significance of ribosome heterogeneity in cell invasion. Finally, pushing the frontiers of technological approaches will continue to be important, as super-resolution imaging and expansion microscopy offer the ability to resolve the subcellular localization of individual mRNAs and ribosomes in cells (Cho and Chang, 2022; Ruland *et al.*, 2021), which should lead to deeper insights into ribosome localization and translation. In addition, CRISPR/Cas9 genome engineering is allowing unprecedented manipulation of genomes to probe translation mechanisms, such as the combined genetic removal of all 24 genes encoding paralogs of small ribosomal proteins in a yeast strain (Hu *et al.*, 2022).

Future mechanistic studies on translational regulation in invasive and migratory cells will be critical as they offer to deepen our understanding of the fascinating mechanisms that guide this fundamental cell biological behavior. Studying translation regulation also holds the promise of uncovering new potent therapeutic strategies, such as with the ribosome biogenesis regulator LARP6 (Dermitt *et al.*, 2020), to target cell invasive activity more specifically in cancer and immune system disorders.

Acknowledgements

The authors thank Dan Costa for helpful comments on the manuscript and figures.

References

- Alkalaeva EZ, Pisarev AV, Frolova LY, *et al.*: **In vitro reconstitution of eukaryotic translation reveals cooperativity between release factors eRF1 and eRF3.** *Cell.* 2006; **125**: 1125–1136.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Armenti ST, Lohmer LL, Sherwood DR, *et al.*: **Repurposing an endogenous degradation system for rapid and targeted depletion of *C. elegans* proteins.** *Development.* 2014; **141**: 4640–4647.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Barna M, Karbstein K, Tollervey D, *et al.*: **The promises and pitfalls of specialized ribosomes.** *Mol. Cell.* 2022; **82**: 2179–2184.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bastide A, Yewdell JW, David A: **The RiboPuromylation Method (RPM): an Immunofluorescence Technique to Map Translation Sites at the Sub-cellular Level.** *Bio Protoc.* 2018; **8**.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bee A, Ke Y, Forootan S, *et al.*: **Ribosomal protein I19 is a prognostic marker for human prostate cancer.** *Clin. Cancer Res.* 2006; **12**: 2061–2065.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Birch J, Clarke CJ, Campbell AD, *et al.*: **The initiator methionine tRNA drives cell migration and invasion leading to increased metastatic potential in melanoma.** *Biol. Open.* 2016; **5**: 1371–1379.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Blanchet S, Ranjan N: **Translation Phases in Eukaryotes.** *Methods Mol. Biol.* 2022; **2533**: 217–228.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bohlen J, Fenzl K, Kramer G, *et al.*: **Selective 40S Footprinting Reveals Cap-Tethered Ribosome Scanning in Human Cells.** *Mol. Cell.* 2020; **79**: 561–574.e5.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Cambi A, Chavrier P: **Tissue remodeling by invadosomes.** *Fac. Rev.* 2021; **10**: 39.
[Publisher Full Text](#)
- Chasse H, Boulben S, Costache V, *et al.*: **Analysis of translation using polysome profiling.** *Nucleic Acids Res.* 2017; **45**: gkw907.
[Publisher Full Text](#)
- Chen ZH, Qi JJ, Wu QN, *et al.*: **Eukaryotic initiation factor 4A2 promotes experimental metastasis and oxaliplatin resistance in colorectal cancer.** *J. Exp. Clin. Cancer Res.* 2019; **38**: 196.
[Publisher Full Text](#)
- Cho I, Chang JB: **Simultaneous expansion microscopy imaging of proteins and mRNAs via dual-ExM.** *Sci. Rep.* 2022; **12**: 3360.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Costa DS, Kenny-Ganzert IW, Chi Q, *et al.*: **The *Caenorhabditis elegans* anchor cell transcriptome: ribosome biogenesis drives cell invasion through basement membrane.** *Development.* 2023; **150**.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Cox JS, Walter P: **A novel mechanism for regulating activity of a transcription factor that controls the unfolded protein response.** *Cell.* 1996; **87**: 391–404.
[Publisher Full Text](#)
- de la Parra C, Walters BA, Geter P, *et al.*: **Translation initiation factors and their relevance in cancer.** *Curr. Opin. Genet. Dev.* 2018; **48**: 82–88.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- DeDreu J, Pal-Ghosh S, Mattapallil MJ, *et al.*: **Uveitis-mediated immune cell invasion through the extracellular matrix of the lens capsule.** *FASEB J.* 2022; **36**: e21995.
[Publisher Full Text](#)
- Dermitt M, Dodel M, Lee FCY, *et al.*: **Subcellular mRNA Localization Regulates Ribosome Biogenesis in Migrating Cells.** *Dev. Cell.* 2020; **55**: 298–313.e10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Di Martino J, Henriette E, Ezzoukhy Z, *et al.*: **The microenvironment controls invadosome plasticity.** *J. Cell Sci.* 2016; **129**: 1759–1768.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Duband JL, Thiery JP: **Distribution of laminin and collagens during avian neural crest development.** *Development.* 1987; **101**: 461–478.
[PubMed Abstract](#) | [Publisher Full Text](#)
- El Khoury W, Nasr Z: **Deregulation of ribosomal proteins in human cancers.** *Biosci. Rep.* 2021; **41**.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

- Esteves P, Dard L, Brillac A, et al.: **Nuclear control of lung cancer cells migration, invasion and bioenergetics by eukaryotic translation initiation factor 3F.** *Oncogene.* 2020; **39**: 617–636.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Evdokimova V, Tognon C, Ng T, et al.: **Translational activation of snail1 and other developmentally regulated transcription factors by YB-1 promotes an epithelial-mesenchymal transition.** *Cancer Cell.* 2009; **15**: 402–415.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ezzoukhry Z, Henriot E, Cordelieres FP, et al.: **Combining laser capture microdissection and proteomics reveals an active translation machinery controlling invadosome formation.** *Nat. Commun.* 2018; **9**: 2031.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Falletta P, Sanchez-Del-Campo L, Chauhan J, et al.: **Translation reprogramming is an evolutionarily conserved driver of phenotypic plasticity and therapeutic resistance in melanoma.** *Genes Dev.* 2017; **31**: 18–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Fan Y, Guo Y: **Knockdown of eIF3D inhibits breast cancer cell proliferation and invasion through suppressing the Wnt/beta-catenin signaling pathway.** *Int. J. Clin. Exp. Pathol.* 2015; **8**: 10420–10427.
[PubMed Abstract](#)
- Fancelli L, Kampen KR, Hofman JJ, et al.: **The ribosomal protein gene RPL5 is a haploinsufficient tumor suppressor in multiple cancer types.** *Oncotarget.* 2017; **8**: 14462–14478.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Feng YX, Sokol ES, Del Vecchio CA, et al.: **Epithelial-to-mesenchymal transition activates PERK-eIF2alpha and sensitizes cells to endoplasmic reticulum stress.** *Cancer Discov.* 2014; **4**: 702–715.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ferretti MB, Ghalei H, Ward EA, et al.: **Rps26 directs mRNA-specific translation by recognition of Kozak sequence elements.** *Nat. Struct. Mol. Biol.* 2017; **24**: 700–707.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Furic L, Rong L, Larsson O, et al.: **eIF4E phosphorylation promotes tumorigenesis and is associated with prostate cancer progression.** *Proc. Natl. Acad. Sci. U. S. A.* 2010; **107**: 14134–14139.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Garde A, Kenny IW, Kelley LC, et al.: **Localized glucose import, glycolytic processing, and mitochondria generate a focused ATP burst to power basement-membrane invasion.** *Dev. Cell.* 2022; **57**: 732–749.e7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Garde A, Sherwood DR: **Fueling Cell Invasion through Extracellular Matrix.** *Trends Cell Biol.* 2021; **31**: 445–456.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Gentilella A, Kozma SC, Thomas G: **A liaison between mTOR signaling, ribosome biogenesis and cancer.** *Biochim. Biophys. Acta.* 2015; **1849**: 812–820.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Gilbert WW: **Functional specialization of ribosomes?** *Trends Biochem. Sci.* 2011; **36**: 127–132.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Goodarzi H, Nguyen HCB, Zhang S, et al.: **Modulated Expression of Specific tRNAs Drives Gene Expression and Cancer Progression.** *Cell.* 2016; **165**: 1416–1427.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Greter M, Heppner FL, Lemos MP, et al.: **Dendritic cells permit immune invasion of the CNS in an animal model of multiple sclerosis.** *Nat. Med.* 2005; **11**: 328–334.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Gros J, Tabin CJ: **Vertebrate limb bud formation is initiated by localized epithelial-to-mesenchymal transition.** *Science.* 2014; **343**: 1253–1256.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hao P, Yu J, Ward R, et al.: **Eukaryotic translation initiation factors as promising targets in cancer therapy.** *Cell Commun. Signal.* 2020; **18**: 175.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hastie EL, Sherwood DR: **A new front in cell invasion: The invadopodial membrane.** *Eur. J. Cell Biol.* 2016; **95**: 441–448.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hershey JW, Sonenberg N, Mathews MB: **Principles of translational control: an overview.** *Cold Spring Harb. Perspect. Biol.* 2012; **4**.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hinnebusch AG: **Structural Insights into the Mechanism of Scanning and Start Codon Recognition in Eukaryotic Translation Initiation.** *Trends Biochem. Sci.* 2017; **42**: 589–611.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ho JJD, Man JHS, Schatz JH, et al.: **Translational remodeling by RNA-binding proteins and noncoding RNAs.** *Wiley Interdiscip. Rev. RNA.* 2021; **12**: e1647.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Hsieh AC, Liu Y, Edlind MP, et al.: **The translational landscape of mTOR signalling steers cancer initiation and metastasis.** *Nature.* 2012; **485**: 55–61.
[Publisher Full Text](#)
- Hu X, Jiang S, Xu F, et al.: **Engineering and functional analysis of yeast with a monotypic 40S ribosome subunit.** *Proc. Natl. Acad. Sci. U. S. A.* 2022; **119**.
[Publisher Full Text](#)
- Iadevaia V, Liu R, Proud CG: **mTORC1 signaling controls multiple steps in ribosome biogenesis.** *Semin. Cell Dev. Biol.* 2014; **36**: 113–120.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Jaiswal PK, Koul S, Palanisamy N, et al.: **Eukaryotic Translation Initiation Factor 4 Gamma 1 (EIF4G1): a target for cancer therapeutic intervention?** *Cancer Cell Int.* 2019; **19**: 224.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ji P, Wang L, Liu J, et al.: **Knockdown of RPL34 inhibits the proliferation and migration of glioma cells through the inactivation of JAK/STAT3 signaling pathway.** *J. Cell. Biochem.* 2019; **120**: 3259–3267.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Joyce CE, Yanez AG, Mori A, et al.: **Differential Regulation of the Melanoma Proteome by eIF4A1 and eIF4E.** *Cancer Res.* 2017; **77**: 613–622.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kang J, Brajanovski N, Chan KT, et al.: **Ribosomal proteins and human diseases: molecular mechanisms and targeted therapy.** *Signal Transduct. Target. Ther.* 2021; **6**: 323.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Karakas D, Ozpolat B: **The Role of LncRNAs in Translation.** *Noncoding RNA.* 2021; **7**.
[Publisher Full Text](#)
- Kenny-Ganzert IW, Sherwood DR: **The C. elegans anchor cell: A model to elucidate mechanisms underlying invasion through basement membrane.** *Semin. Cell Dev. Biol.* 2023; **154**: 23–34.
[Publisher Full Text](#)
- Khajuria RK, Munschauer M, Ulirsch JC, et al.: **Ribosome Levels Selectively Regulate Translation and Lineage Commitment in Human Hematopoiesis.** *Cell.* 2018; **173**: 90–103.e19.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kim SH, Jang YH, Chau GC, et al.: **Prognostic significance and function of phosphorylated ribosomal protein S6 in esophageal squamous cell carcinoma.** *Mod. Pathol.* 2013; **26**: 327–335.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Kim SH, Kim J: **Reduction of invasion in human fibrosarcoma cells by ribosomal protein S3 in conjunction with Nm23-H1 and ERK.** *Biochim. Biophys. Acta.* 2006; **1763**: 823–832.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Knight JRP, Garland G, Poyry T, et al.: **Control of translation elongation in health and disease.** *Dis. Model. Mech.* 2020; **13**.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kolitz SE, Lorsch JR: **Eukaryotic initiator tRNA: finely tuned and ready for action.** *FEBS Lett.* 2010; **584**: 396–404.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Kondrashov N, Pusic A, Stumpf CR, et al.: **Ribosome-mediated specificity in Hox mRNA translation and vertebrate tissue patterning.** *Cell.* 2011; **145**: 383–397.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Li X, Li J, Li F: **P21 activated kinase 4 binds translation elongation factor eEF1A1 to promote gastric cancer cell migration and invasion.** *Oncol. Rep.* 2017; **37**: 2857–2864.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Limia CM, Sauzay C, Urria H, et al.: **Emerging Roles of the Endoplasmic Reticulum Associated Unfolded Protein Response in Cancer Cell Migration and Invasion.** *Cancers (Basel).* 2019; **11**: 11.
[Publisher Full Text](#)
- Lin X, Chai G, Wu Y, et al.: **RNA m(6) A methylation regulates the epithelial mesenchymal transition of cancer cells and translation of Snail.** *Nat. Commun.* 2019; **10**: 2065.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Liacer JL, Hussain T, Saini AK, et al.: **Translational initiation factor eIF5 replaces eIF1 on the 40S ribosomal subunit to promote start-codon recognition.** *elife.* 2018; **7**.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ma L, Teruya-Feldstein J, Weinberg RA: **Tumour invasion and metastasis initiated by microRNA-10b in breast cancer.** *Nature.* 2007; **449**: 682–688.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Majumdar R, Maitra U: **Regulation of GTP hydrolysis prior to ribosomal AUG selection during eukaryotic translation initiation.** *EMBO J.* 2005; **24**: 3737–3746.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Martineau Y, Azar R, Bousquet C, et al.: **Anti-oncogenic potential of the eIF4E-binding proteins.** *Oncogene.* 2013; **32**: 671–677.
[PubMed Abstract](#) | [Publisher Full Text](#)

- Mathews MB, Hershey JW: **The translation factor eIF5A and human cancer.** *Biochim. Biophys. Acta.* 2015; **1849**: 836–844.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- McClay DR: **Perspective on Epithelial-Mesenchymal Transitions in Embryos.** *Methods Mol. Biol.* 2021; **2179**: 7–12.
[Publisher Full Text](#)
- McLennan R, McKinney MC, Teddy JM, *et al.*: **Neural crest cells bulldoze through the microenvironment using Aquaporin 1 to stabilize filopodia.** *Development.* 2020; **147**.
- Medwig-Kinney TN, Smith JJ, Palmisano NJ, *et al.*: **A developmental gene regulatory network for *C. elegans* anchor cell invasion.** *Development.* 2020; **147**.
[Publisher Full Text](#)
- Mills EW, Green R: **Ribosomopathies: There's strength in numbers.** *Science.* 2017; **358**: eaan2755.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Murugan AK: **mTOR: Role in cancer, metastasis and drug resistance.** *Semin. Cancer Biol.* 2019; **59**: 92–111.
[Publisher Full Text](#)
- Naegeli KM, Hastie E, Garde A, *et al.*: **Cell Invasion in vivo via Rapid Exocytosis of a Transient Lysosome-Derived Membrane Domain.** *Dev. Cell.* 2017; **43**: 403–417.e10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Nasr Z, Robert F, Porco JA Jr, *et al.*: **eIF4F suppression in breast cancer affects maintenance and progression.** *Oncogene.* 2013; **32**: 861–871.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ni C, Buszczak M: **The homeostatic regulation of ribosome biogenesis.** *Semin. Cell Dev. Biol.* 2023a; **136**: 13–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ni C, Buszczak M: **Ribosome biogenesis and function in development and disease.** *Development.* 2023b; **150**.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Noma K, Goncharov A, Ellisman MH, *et al.*: **Microtubule-dependent ribosome localization in *C. elegans* neurons.** *elife.* 2017; **6**.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Norris K, Hopes T, Aspden JL: **Ribosome heterogeneity and specialization in development.** *Wiley Interdiscip. Rev. RNA.* 2021; **12**: e1644.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Padmanaban V, Krol I, Suhail Y, *et al.*: **E-cadherin is required for metastasis in multiple models of breast cancer.** *Nature.* 2019; **573**: 439–444.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Pastushenko I, Blanpain C: **EMT Transition States during Tumor Progression and Metastasis.** *Trends Cell Biol.* 2019; **29**: 212–226.
[Publisher Full Text](#)
- Paterson EK, Courtneidge SA: **Invadosomes are coming: new insights into function and disease relevance.** *FEBS J.* 2018; **285**: 8–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Pech M, Spreter T, Beckmann R, *et al.*: **Dual binding mode of the nascent polypeptide-associated complex reveals a novel universal adapter site on the ribosome.** *J. Biol. Chem.* 2010; **285**: 19679–19687.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Pecoraro A, Carotenuto P, Russo G, *et al.*: **Ribosomal protein uL3 targets E2F1 and Cyclin D1 in cancer cell response to nucleolar stress.** *Sci. Rep.* 2019; **9**: 15431.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Pestova TV, Lomakin IB, Lee JH, *et al.*: **The joining of ribosomal subunits in eukaryotes requires eIF5B.** *Nature.* 2000; **403**: 332–335.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Pinzaglia M, Montaldo C, Polinari D, *et al.*: **EIF6 over-expression increases the motility and invasiveness of cancer cells by modulating the expression of a critical subset of membrane-bound proteins.** *BMC Cancer.* 2015; **15**: 131.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Pompili S, Latella G, Gaudio E, *et al.*: **The Charming World of the Extracellular Matrix: A Dynamic and Protective Network of the Intestinal Wall.** *Front. Med (Lausanne).* 2021; **8**: 610189.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Prakash V, Carson BB, Feenstra JM, *et al.*: **Ribosome biogenesis during cell cycle arrest fuels EMT in development and disease.** *Nat. Commun.* 2019; **10**: 2110.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Reynoso MA, Juntawong P, Lancia M, *et al.*: **Translating Ribosome Affinity Purification (TRAP) followed by RNA sequencing technology (TRAP-SEQ) for quantitative assessment of plant translatoemes.** *Methods Mol. Biol.* 2015; **1284**: 185–207.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ruan H, Li X, Xu X, *et al.*: **eIF4E S209 phosphorylation licenses myc- and stress-driven oncogenesis.** *elife.* 2020; **9**.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ruland JA, Kruger AM, Dorner K, *et al.*: **Nuclear export of the pre-60S ribosomal subunit through single nuclear pores observed in real time.** *Nat. Commun.* 2021; **12**: 6211.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Sharen G, Li X, Sun J, *et al.*: **Silencing eL31 suppresses the progression of colorectal cancer via targeting DEPDC1.** *J. Transl. Med.* 2022; **20**: 493.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Shi Z, Fujii K, Kovary KM, *et al.*: **Heterogeneous Ribosomes Preferentially Translate Distinct Subpools of mRNAs Genome-wide.** *Mol. Cell.* 2017; **67**: 71–83.e7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Shoemaker CJ, Green R: **Kinetic analysis reveals the ordered coupling of translation termination and ribosome recycling in yeast.** *Proc. Natl. Acad. Sci. U. S. A.* 2011; **108**: E1392–E1398.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Simsek D, Tiu GC, Flynn RA, *et al.*: **The Mammalian Ribo-interactome Reveals Ribosome Functional Diversity and Heterogeneity.** *Cell.* 2017; **169**: 1051–1065.e18.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Smith RCL, Kanellos G, Vlahov N, *et al.*: **Translation initiation in cancer at a glance.** *J. Cell Sci.* 2021; **134**.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Song P, Yang F, Jin H, *et al.*: **The regulation of protein translation and its implications for cancer.** *Signal Transduct. Target. Ther.* 2021; **6**: 68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Stanford SM, Aleman Muench GR, Bartok B, *et al.*: **TGFbeta responsive tyrosine phosphatase promotes rheumatoid synovial fibroblast invasiveness.** *Ann. Rheum. Dis.* 2016; **75**: 295–302.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Szabo A, Mayor R: **Mechanisms of Neural Crest Migration.** *Annu. Rev. Genet.* 2018; **52**: 43–63.
[Publisher Full Text](#)
- Talbot JC, Teets EM, Ratnayake D, *et al.*: **Muscle precursor cell movements in zebrafish are dynamic and require Six family genes.** *Development.* 2019; **146**.
- Taylor DJ, Nilsson J, Merrill AR, *et al.*: **Structures of modified eEF2 80S ribosome complexes reveal the role of GTP hydrolysis in translocation.** *EMBO J.* 2007; **26**: 2421–2431.
[Publisher Full Text](#)
- Truitt ML, Ruggero D: **New frontiers in translational control of the cancer genome.** *Nat. Rev. Cancer.* 2016; **16**: 288–304.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Vasyutina E, Birchmeier C: **The development of migrating muscle precursor cells.** *Anat. Embryol (Berl).* 2006; **211**: 37–41.
[Publisher Full Text](#)
- Vaysse C, Philippe C, Martineau Y, *et al.*: **Key contribution of eIF4H-mediated translational control in tumor promotion.** *Oncotarget.* 2015; **6**: 39924–39940.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Verma M, Choi J, Cottrell KA, *et al.*: **A short translational ramp determines the efficiency of protein synthesis.** *Nat. Commun.* 2019; **10**: 5774.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Villa N, Do A, Hershey JW, *et al.*: **Human eukaryotic initiation factor 4G (eIF4G) protein binds to eIF3c, -d, and -e to promote mRNA recruitment to the ribosome.** *J. Biol. Chem.* 2013; **288**: 32932–32940.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Wan J, Shi F, Xu Z, *et al.*: **Knockdown of eIF4E suppresses cell proliferation, invasion and enhances cisplatin cytotoxicity in human ovarian cancer cells.** *Int. J. Oncol.* 2015; **47**: 2217–2225.
[Publisher Full Text](#)
- Wan Makhtar WR, Browne G, Karountzos A, *et al.*: **Short stretches of rare codons regulate translation of the transcription factor ZEB2 in cancer cells.** *Oncogene.* 2017; **36**: 6640–6648.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Wang ZG, Zheng H, Gao W, *et al.*: **eIF5B increases ASAP1 expression to promote HCC proliferation and invasion.** *Oncotarget.* 2016; **7**: 62327–62339.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Wei F, Ding L, Wei Z, *et al.*: **Ribosomal protein L34 promotes the proliferation, invasion and metastasis of pancreatic cancer cells.** *Oncotarget.* 2016; **7**: 85259–85272.
[Publisher Full Text](#)
- Weingarten-Gabbay S, Elias-Kirma S, Nir R, *et al.*: **Comparative genetics. Systematic discovery of cap-independent translation sequences in human and viral genomes.** *Science.* 2016; **351**.
[Publisher Full Text](#)
- Wurth L, Papasaikas P, Olmeda D, *et al.*: **UNR/CSDE1 Drives a Post-transcriptional Program to Promote Melanoma Invasion and Metastasis.** *Cancer Cell.* 2016; **30**: 694–707.
[Publisher Full Text](#)

Xiao Y, Yee C, Zhao CZ, *et al.*: **An expandable FLP-ON::TIR1 system for precise spatiotemporal protein degradation in *Caenorhabditis elegans*.** *Genetics*. 2023; **223**.

[PubMed Abstract](#) | [Publisher Full Text](#)

Xie J, Shen K, Lenchine RV, *et al.*: **Eukaryotic elongation factor 2 kinase upregulates the expression of proteins implicated in cell migration and cancer cell metastasis.** *Int. J. Cancer*. 2018; **142**: 1865–1877.

[PubMed Abstract](#) | [Publisher Full Text](#)

Yang X, Xu L, Yang YE, *et al.*: **Knockdown of ribosomal protein S6 suppresses proliferation, migration, and invasion in epithelial ovarian cancer.** *J Ovarian Res*. 2020; **13**: 100.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Yu L, Wang X, Zhang W, *et al.*: **The multiple regulation of metastasis suppressor NM23-H1 in cancer.** *Life Sci*. 2021; **268**: 118995.

[PubMed Abstract](#) | [Publisher Full Text](#)

Zhao X, Li X, Li X: **Multiple roles of m(6) A methylation in epithelial-mesenchymal transition.** *Mol. Biol. Rep.* 2022; **49**: 8895–8906.

[PubMed Abstract](#) | [Publisher Full Text](#)

Zhouravleva G, Frolova L, Le Goff X, *et al.*: **Termination of translation in eukaryotes is governed by two interacting polypeptide chain release factors, eRF1 and eRF3.** *EMBO J*. 1995; **14**: 4065–4072.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Zhu G, Yan W, He HC, *et al.*: **Inhibition of proliferation, invasion, and migration of prostate cancer cells by downregulating elongation factor-1alpha expression.** *Mol. Med.* 2009; **15**: 363–370.

[Publisher Full Text](#)

Zinzalla V, Stracka D, Oppliger W, *et al.*: **Activation of mTORC2 by association with the ribosome.** *Cell*. 2011; **144**: 757–768.

[Publisher Full Text](#)

Zou Y, Li S, Wu D, *et al.*: **Resveratrol promotes trophoblast invasion in pre-eclampsia by inducing epithelial-mesenchymal transition.** *J. Cell. Mol. Med.* 2019; **23**: 2702–2710.

[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status: ? ✓ ?

Version 1

Reviewer Report 15 April 2024

<https://doi.org/10.5256/f1000research.157192.r231614>

© 2024 saltel f. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



frederic saltel

BRIC BoRdeaux Institute of onCology U1312, INSERM, Rue Léo Saignat, Bordeaux, France

Comments on manuscript

Title: *"Translational regulation of cell invasion through extracellular matrix—an emerging role for ribosomes »*

To Authors,

This manuscript is very clear and very well written, and it has the advantage of highlighting a new field of investigation. This review perfectly integrates the current problem(s). It is clear that cell invasion through the extracellular matrix is controlled by the regulation of translation.

There are many examples of this, and it is now necessary to understand and decipher the associated molecular mechanisms, particularly in order to determine whether this pathway has therapeutic potential. In addition, the state of the art is very detailed, making this work accessible to non-specialists in translation and ribosomal proteins.

After a brief introduction, the authors develop the key elements of translation in a paragraph to make it easier to read and understand the concepts developed in this review. In the following paragraph, the authors cite numerous articles demonstrating that translation regulation regulates invasion, and this in numerous models, particularly in the case of cancers, by highlighting the role of proteins such as eIF4G and eIF4E. In particular, the link between eIF4E and MMP9 is a strong argument.

The rest of the review focuses on ribosomes, and more specifically on their role as regulators of invasion and migration.

However, figure 2 needs to be revisited, as the notion of protrusion is not clear and can be applied to many cellular structures, such as lamellipodia, filopodia, etc. In addition, focusing in on this section would make it easier to understand the role of LARP6. Next, the notion of deregulation of ribosomal proteins in this process is well described, as is the notion of heterogeneity of ribosomes formed and involved in the invasion process.

This concept opens up a very interesting field of research, with the aim of identifying the molecular players that control the interactions between translation and cell invasion. At the same time the second aim is to reveal new therapeutic avenues, given that these mechanisms control the formation of metastases, which remain the leading cause of cancer-related death.

Minor points :

A table summarizing the proteins, particularly ribosomal proteins, involved in this process would be an interesting tool for readers.

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: cell biology, invadosome, extracellular matrix, proteomic

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 19 March 2024

<https://doi.org/10.5256/f1000research.157192.r248979>

© 2024 Plastino J. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



Julie Plastino

Ecole Normale Supérieure, Paris, France

This is a nice review of a complex and somewhat understudied subject: how cell invasion is regulated by modifying protein translation. Much is known about how genes are up or down regulated in cell invasion and cancer, but much less is clear concerning the protein consequences of this regulation.

Overall, the review does a great job of making a complicated subject with a multitude of molecular players accessible to non-specialists of ribosome biology and protein translation machinery.

There is one small thing that I found confusing: the section "Ribosomal protein misexpression can drive or inhibit cell invasion in cancer cells" seems contradictory with the previous parts, where

ribosome enrichment was linked invariably with an increase in invasion presumably by increasing the production of proteins necessary for the increased activity and growth that cancer cells display. Would it be correct to say that ribosome decrease only drives cancer via activities that aren't directly connected to protein translation? Perhaps this can be stated as such, because as it is, this section puts some doubt on what was up until then a strong message that ribosomes and ribosomal function are upregulated for invasion.

A few "cosmetic" comments:

1. In Figure 1, it would be nice to have EPA defined next to its first appearance, so next to the 80S blob between steps 5 and 6.
2. Also in Figure 1, a bracket and label for "48S initiation complex" and "80S complex" would be nice (as done for "43S PIC").
3. I think the "the" can be removed from this sentence on page 8: RiboPuromylation analysis, an immunofluorescence method to visualize translation sites at the sub-cellular resolution (Bastide et al., 2018)...
4. In this sentence on page 8, wouldn't it be better to say "revealed" instead of "discovered": Recent advances in ribosome tagging and subcellular biochemical analysis have discovered enrichment of ribosomes and translation at several locations within invasive cells where localized translation mediates important functions (Figure 3).

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: actin cytoskeleton, cell motility, C. elegans

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 01 March 2024

<https://doi.org/10.5256/f1000research.157192.r244481>

© 2024 Wu C. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Congying Wu**

Peking University, Beijing, Beijing, China

The manuscript is constructed in a way that basics of cell translation is first introduced. However, this part reads rather lengthy and key points are buried in lines. I would suggest reorganize this part to provide better readability to the whole text.

I also suggest the authors to expand on the introduction of cell migration - from a more broad migration view down to the specific type of invading through extracellular migration. mTORC1 is activated at focal adhesions and localized mRNA translation has been suggested to occur at these sites ref [1]and [2]. The differences between matrix-degrading invasion and non-degrading confined migration can also be discussed and relate to ribosomal regulation.

As for the second half of the review, the authors focus on ribosomes - its biogenesis, dyregulation of ribosomal proteins and ribosomal heterogeneity. However, the part subtitled "Ribosomal protein misexpression can drive or inhibit cell invasion in cancer cells" is not as well organized as the rest. Logical presentation of evidences and clear enunciation of views are needed.

Overall, this review is informative and fills the gap between our understanding of the central dogma and cell migration. It will help researchers in cell biology and cancer biology to grasp new directions and will be of great interest to a broad audience.

References

1. Rabanal-Ruiz Y, Byron A, Wirth A, Madsen R, et al.: mTORC1 activity is supported by spatial association with focal adhesions.*J Cell Biol.* 2021; **220** (5). [PubMed Abstract](#) | [Publisher Full Text](#)
2. Zhang C, Wang Y, Zhen Z, Li J, et al.: mTORC1 Mediates Biphasic Mechano-Response to Orchestrate Adhesion-Dependent Cell Growth and Anoikis Resistance.*Adv Sci (Weinh).* 2024; **11** (6): e2307206 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cell Migration and Adhesion

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research