We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Targeting of Post-Transcriptional Regulation as Treatment Strategy in Acute Leukemia

Paulina Podszywalow-Bartnicka, Magdalena Wolczyk and Katarzyna Piwocka

Abstract

Post-transcriptional regulation is an important step of gene expression that allows to fine-tune the cellular protein profile (so called proteome) according to the current demands. That mechanism has been developed to aid survival under stress conditions, however it occurs to be hijacked by cancer cells. Adjustment of the protein profile remodels signaling in cancer cells to adapt to therapeutic treatment, thereby enabling persistence despite unfavorable environment or accumulating mutations. The proteome is shaped at the post-transcriptional level by numerous mechanisms such as alternative splicing, mRNA modifications and triage by RNA binding proteins, change of ribosome composition or signaling, which altogether regulate the translation process. This chapter is an overview of the translation disturbances found in leukemia and their role in development of the disease, with special focus on the possible therapeutic strategies tested in acute leukemia which target elements of those regulatory mechanisms.

Keywords: leukemia treatment, therapy resistance, mRNA translation, RNA binding proteins, ribosomal proteins

1. Introduction

Translation is one of the regulatory levels that allows cells to adapt the profile of proteins (the proteome) to the current demand of cellular processes like cell division or environmental signals such as hypoxia. Generally, protein synthesis requires activation of the complex mechanisms that are tightly regulated [1]. Since the protein synthesis is related to cell growth and cell cycle, any disturbances of this process can be a mechanism underlying unregulated cell growth, neoplastic transformation and tumor development.

For the great majority of cellular mRNAs, the 5′ cap-dependent translation is the most efficient mechanism of protein synthesis [2]. An alternative mechanism of translation initiation is engaged during cell cycle progression [3], cell differentiation and apoptosis, as well as during cellular stress response [4]. Global regulation of translation is often based on the activation or inhibition of one or more components of the translational machinery (eukaryotic initiation factors, ribosomal proteins, ribosomal RNA), whereas the specific regulation often occurs through the action of two groups of factors: *cis*-acting elements found in mRNA molecule

(specific mRNA sequences such as internal ribosome entry sites IRES, mRNA posttranscriptional modifications) and *trans*-acting factors (such as RNA-binding proteins, microRNAs) that bind to mRNA [5]. Furthermore, changes in the cellular signaling can also trigger translational reprogramming. Based on the significant role that all steps of the translation regulation play in development of cancers, including hematological malignancies, and their pro-survival and adaptive function, therapeutic targeting of those mechanisms has been proposed and studied.

2. Modifications of RNA

Posttranscriptional modifications have been found in non-coding RNAs such as ribosomal RNAs (rRNA) and transfer RNAs (tRNA) as well as in messenger RNAs (mRNA). There are about 150 modifications discovered by far. They include pseudouridylation (ψ), methylation or deamination of adenosine to inosine (A-to-I editing). Such modifications have impact on the splicing and translation of mRNA and contribute to epitranscriptional regulation of gene expression. Some modifications exist only in the coding sequence (like A-to-I editing), whilst others are deposited only in a 5′-untranslated regions (5'UTR) such as 5-methylcytosine (m5C) and 7-methylguanosine (m7G). The N6-methyladenosine (m6A) modification is ubiquitously present and deposited in along the mRNA coding sequence and 5′/3′UTRs.

The m6A modification is added to the mRNA in the nucleus by so called 'writers' or removed by 'erasers' and is recognized by proteins which bind to m6A methylated mRNA (so called 'readers'). It has impact on the mRNA stability, export from the nucleus, decay and translation (for recent review on the role of RNA modifications in cancer, including acute myelogenous leukemia (AML) see: [6–8]). The m6A modification has been found to play a critical role in AML development and progression (for review see: [9, 10]).

The m6A writer proteins - methyltransferase-like protein (METTL) 3 and 14 are overexpressed in AML. It was reported that their deletion limits the cancerogenic cellular potential [11, 12]. On the other hand, METTL3 overexpression stimulated the translation of Myc, Bcl-2 and PTEN what contributed to increased proliferation and survival of AML cells [13]. Controversially, increased expression of fat mass and obesity-associated demethylase (FTO), which acts as a m6A eraser, also led to higher level of oncogene expression. Moreover, its inhibition reduced growth of AML cancer cells [14]. Activity of FTO has been found to be directly inhibited by R-2-hydroxyglutarate (R-2HG) leading to loss of stability of Myc mRNA and decreased proliferation rate of leukemic cells [15]. This effect is postulated to result from discrepancy of mRNA triage for translation or decay of pro- and anti-oncogenic proteins in respect to the presence of m6A deposition in mRNA [8].

Though YTHDF2, the m6A reader, appears not to be required for normal hematopoietic stem cells, it occurs to be essential for AML cells similarly to METTL3 and FTO. Its overexpression facilitates AML cells propagation, whereas its silencing disables proliferative and clonogenic potential of leukemia cells. Thus, YTHDF2 seems to be a good therapeutic target in AML, which would enable the selective eradication of cancer cells whilst spearing healthy hematopoietic stem cells [16].

Another m6A reader proteins might also play a key role in the regulation of cancer development. The insulin-like growth factor 2 mRNA-binding protein (IF2BP1–3) stabilizes m6A-modified mRNAs such as *MYC* oncogene, thus enhancing its translation and contributing to oncogenesis [17].

Apart from modification of mRNA, also pseudouridylation of tRNA contributes to AML progression. The tRNAs that contain 5′ terminal oligoguanine (TOG)

are the source of 18 nucleotide regulatory sequences (mTOGs), which stimulate differentiation and limit proliferation of hematopoietic stem cells (HSC) by inhibiting translation initiation in HSC. This effect depends on the presence of ψ on the mTOGs. It has been found that development of AML is accompanied by decreased level of pseudouridine synthase 7 (PUS7). Downregulation of PUS7 abolished healthy stem cells differentiation and increased translation demonstrating significance of ψ modification in the development of AML [18]. The oncogenic mTOGs, if attenuated by specific inhibitors, could constitute an effective therapeutic target.

The above examples show that the post-transcriptional regulation of gene expression at the step of RNA modifications constitutes a potent target to disable expression of some oncogenes that should allow to switch the cell fate back towards appropriate hematopoietic differentiation.

3. RNA binding proteins

Activation of RNA binding proteins (RBPs) constitutes an additional layer of posttranscriptional regulation, which has a great impact on the final protein level in the cell. The main function of RNA binding proteins is to recognize the primary transcript (pre-mRNA) and assemble ribonucleoprotein complexes, what governs processes of pre-mRNA maturation i.e. splicing, polyadenylation, attachment of a guanyl cap at the 5′ end of pre-mRNA and RNA modifications. Moreover, RBPs binding to the target mRNA is required for proper mRNA transportation from the nucleus to the cytoplasm and distribution into various cellular compartments. Additionally, *trans*-acting regulatory RNA binding proteins have the ability to affect translation of the specific mRNA, mainly through the interaction with untranslated regions (3′UTR and 5′UTR) and coding region of mature mRNA, what results in changes in ribosome recruitment.

Considering the multifunctional properties of RNA binding proteins, any alterations in those proteins' activity are associated with multiple cancers (reviewed in [19]), including leukemias (reviewed in [20]), and provide a substantial therapeutic opportunity.

The Musashi (MSI) RNA binding proteins (MSI1 and MSI2) contribute to development of various types of cancer. Their elevated expression has been demonstrated in acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia blastic phase (CML-BP) [21–23]. MSI proteins regulate translation of mRNAs encoding proteins involved in several oncogenic signaling pathways, such as MYC [24], TGFβ/SMAD3 [25] and PTEN/mTOR [26]. Thus, inhibition of MSI RNA-binding activity could demonstrate a novel therapeutic strategy, probably not only in solid tumors but in hematological malignancies as well. A small molecule Ro 08–2750 (Ro) has been shown recently to bind selectively to MSI2 and interfere with its mRNA binding activity, thus triggering increased apoptosis and inhibition of known MSI targets in myeloid leukemia cells [27]. Other agents with presumptive MSI1 inhibitory activity have also been tested and they include (−)-gossypol (natural phenol extracted from cottonseed) [28] and ω − 9 monounsaturated fatty acids (e.g. oleic acid) [29]. Although those agents display inhibitory effects on MSI1 activity, the specificity of both should be further confirmed.

Another RNA binding protein involved in mRNA translation and deregulated in leukemia is DDX3. Mutations in DDX3 gene display oncogenic potential in T-cell lymphoma [30] and lymphocytic leukemia [31]. A small molecule inhibitor (RK-33) targeting DDX3, which has been tested so far, demonstrates the pro-apoptotic activity. Its administration promoted higher sensitivity to radiation in lung cancer

DDX3-overexpressing cells [32, 33], thus providing an argument to develop and improve DDX3 inhibitors, which can target cancer cells, including leukemia.

The activity of HuR RNA binding protein is also deregulated in some types of leukemia [34–37]. Elevated HuR level promotes tumorigenesis, thus targeting HuR could be a promising anti-cancer therapy. A few chemical compounds against HuR activity have been tested so far. MS-444 small molecule inhibitor interfered with HuR binding to target ARE-mRNAs and showed anti-tumor properties in various types of cancers [38–40]. Quercetin and b-40 have been found to inhibit HuR binding to TNFα mRNA, what resulted in TNFα destabilization and decreased TNFα secretion [41]. A coumarin-derived and HuR-targeted small molecule inhibitor CMLD-2, exhibited cytotoxicity towards human lung cancer cells [42], proving that HuR is a good candidate for cancer treatment strategy.

Aberrations of other RNA binding proteins have been linked to the activity of BCR-ABL1, an oncoprotein responsible for chronic myeloid leukemia (CML) development. BCR-ABL1-dependent decrease of CUGBP1 level resulted in repression of the C/EBPβ mRNA translation [43]. As C/EBPβ transcriptional activity controls the maturation of hematopoietic cells in the myeloid lineage, its deficiency contributes to differentiation arrest of CML cells and CML progression to the blast crisis [44]. An increased level and activity of RNA binding proteins: hnRNP K [45], hnRNP A1 [46], hnRNP E2 [46], TLS/FUS [47] and La/SSB [48] have also been observed. These proteins regulate translation of important cancer-related factors: the hnRNP K protein positively regulates c-MYC mRNA translation, protein La/SSB promotes MDM2 mRNA translation, and increased hnRNP E2 activity leads to inhibition of the C/EBP1α protein synthesis.

Activities of RNA binding proteins described above result in the differentiation arrest of CML cell, but also their increased proliferation and survival. Considering the mentioned features, RNA binding proteins provide a significant therapeutic possibility to treat acute leukemia patients.

A single RBP interacts with a number of different mRNAs, and prerequisite for this is a presence of the RBP's binding sequence. The recognition motif for a given protein is often present in mRNAs encoding proteins needed in a certain process. For instance, mRNAs of cell cycle regulating proteins are bound by HuR. Thus, targeting activity of the specific RBP, interfering with its binding ability or masking the targeted sequence would impact the fate of a group of mRNAs. Therefore, this constitutes an opportunity to modulate synthesis of functionally related proteins.

4. Alternative splicing

This post-transcriptional process is one of the key steps of messenger RNA maturation (mRNA) but apart from that, it allows to elevate complexity of the cellular proteome. A core complex called spliceosome is responsible for excision of introns from pre-mRNA in the nucleus. It consists of five small nuclear ribonucleoproteins (snRNPs) – U1, U2, U5, U4/U6 – and small nuclear RNA (snRNA). Splicing is regulated by *cis*-acting elements, which are the nucleotide sequences of primary transcript, *trans*-acting elements, which are the splicing factors or other RNA binding proteins regulating splicing: heterogenous nuclear ribonucleoproteins (hnRNPs) and serine/arginine-rich (SR) proteins. The nucleotide sequence of the transcript promotes or represses splicing at the certain sites. The *trans*-acting elements can antagonize the activity of splicing factors leading to change in splice site selection, known as alternative splicing event. For an overview of the splicing process or interactions of RNA binding proteins with regulators of alternative splicing see: [49–51]. Furthermore, modification of RNA within the *cis*-acting region (like m6A) is one

of the major factors that has impact on the binding of *trans*-acting elements (as described above). It has been found that the m6A modification enhances binding by RBPs such as hnRNP A2B1 [52] or SRSF3, whilst respells SRSF10 from transcript [53], exerting the effect on splicing of mRNA. This demonstrates how two distinct post-transcriptional events, RNA methylation and splicing, can cross-talk to tightly control the transcript fate and expression of a particular protein.

Extracellular signals lead to modification of operation of *trans*-acting proteins, affecting or enhancing their action. Therefore, activity of regulatory elements involved in this process is sensitive to environmental signals such as cytokines or hypoxia. Through modulation of alternative splicing, the level of proteins' isoforms can be adjusted according to the circumstances. Additionally to selective intron skipping/excision, alternative splicing can affect length of poly(A) region. As a result, this influence stability of the mRNA, causing its enhanced decay or translation. Apart from that, mutation of the gene sequence modifies binding of RBPs what has impact on the ultimate expression level. Some of the splicing regulators were reported to play an oncogenic role, whilst others act as tumor suppressors.

Apoptosis-stimulating Protein of TP53–2 (ASPP2) is a tumor suppressor enhancing TP53-mediated apoptosis. It has been found that a splice variant ASPP2κ is overexpressed in AML and displays anti-apoptotic function, therefore supporting proliferation of the cells [54].

Analysis of the transcriptome profile revealed that progression of CML from chronic phase (CML-CP) towards acute blastic phase (CML-BP) is accompanied by changes in splicing pattern of genes, thus affecting spliceosome. The exon skipping event in hnRNP A1 led to accumulation of bigger isoform in the CML-BP, though the biological significance of this has not been studied [55].

Altogether, it makes the alternative splicing machinery a powerful tool for cancer cells to support their survival. On the other hand, the necessity to achieve certain modifications through splicing makes cancer cells dependent on this process. Such regulation creates an opportunity for therapeutic targeting.

Activity of SR proteins can be modulated by modifications: phosphorylation of SR proteins can affect activity and switch general splicing repressor to selective activator [56], methylation of SRSF1 by the protein arginine methyltransferase 5 (PRMT5) modulates splicing of many proteins involved in proliferation, therefore supports leukemia development [57]. Its overexpression exerts oncogenic effect increasing aggressiveness of leukemia cells [58]. Specific inhibitors of PRMT5 have been clinically tested for potential treatment of blood and solid cancers [59]. As transcription of PRMT5 it directly stimulated by MYC transcription factor [60], thus leukemia cells overexpressing MYC could be selected for treatment with PRMT5 inhibitors.

A screen of RBPs playing role in AML revealed that RNA binding motif protein 39 (RBM39) plays a significant role in RNA splicing and stimulates proliferation of leukemia cells [61]. A sulfonamid drugs (indisulam, tasisulam, E7820 and CQS,), which are an example of proteolysis-targeting chimeras (PROTACs) compounds, led to polyubiquitination and proteasomal degradation of RBM39, what exerts anticancer activity [62]. The effect depended on the CUL4-DCAF15 E3 ubiquitin ligase, therefore the level of expression of this enzyme could be used as indicative marker in therapy involving sulfonamid drugs [62, 63].

Leukemia development and progression can be triggered by occurrence of point mutations in splicing factors such as SF3B. Activity of spliceosomal complex containing the mutated protein, but not wild type SF3B, can be blocked by a specific small molecule inhibitor H3B-8800 [64]. It has been shown that AML cells with mutated U2 Small Nuclear RNA Auxiliary Factor 1 (U2AF1), a component of spliceosome, display increased sensitivity to sudemycin – a drug targeting SF3BP1, both

in vitro and *in vivo*. Transcripts altered by sudemycin treatment encoded proteins involved in receptor and signal transduction activities [65]. Noteworthy, SF3B1 has distinct effect on the transcript splicing than SRSF2. Mutation in any of them led to hyperactivation of NF-κB signaling, whilst simultaneous mutation of both SF3B1 and SRSF2 displayed synthetically lethal effect [66].

The splicing regulatory network is complex and full of various cross-talk regulations and interactions. Due to interactive nature of regulatory factors, which influence each other's activity, lowering the level of one factor activates a compensatory mechanism that is mediated by another factor. This refers to both SR [67] as well as hnRNP proteins [68]. Thus, the results should be interpreted cautiously, because the observed effect resulting from a loss of one splicing factor may in fact be the secondary effect of a change in the network. Nevertheless, targeting of the *cis*- or *trans*-regulating elements gives possibility to hit precisely the source of oncogenic transformation.

5. Translation initiation

Previously we described the processes, which regulate translation of the specific RNA in a controlled manner. The initiation of translation is another step on the way of protein synthesis, which is tightly controlled. The process can be remodeled by multiple cellular intrinsic signaling pathways that can be active in malignant cells.

Constitutive activation of the PI3K/Akt/mTOR signaling pathway [69, 70] has been observed in various types of leukemia, including acute lymphoblastic leukemia (ALL), Philadelphia (Ph) chromosome positive and Ph-like acute lymphoblastic leukemia (BCR-ABL1-like ALL) or AML. Continuous activity of the PI3K/Akt/mTOR pathway contributes to unregulated proliferation and leads to resistance to therapy with tyrosine kinase inhibitors (TKI) [71]. Activation of mTOR results in phosphorylation of S6K kinase and eukaryotic translation initiation factor 4E binding protein (4E-BP1), promoting cap-dependent mRNA initiation of translation and increased protein synthesis in leukemia cells [72]. On the other hand, mTOR pathway stimulates cap-independent translation mediated by internal ribosome entry sites IRES, mainly by activation of eIF4A helicase [73]. Another signaling pathway that regulates initiation of translation is the Ras/MAPK/ERK pathway. Its activity has also been found in leukemia cells [71, 74]. Activation of that pathway resulted in phosphorylation of the translation initiation factor eIF4E by MNK1/2 kinases. This contributed to increased β-catenin mRNA translation efficiency and activation of the Wnt/β-catenin signaling pathway, which plays an important role in differentiation and proliferation of leukemia cells [71, 75]. Microenvironmental signals, such as acute hypoxia or nutrient deprivation, trigger so called Integrated Stress Response (ISR) pathway, which shapes the mRNA translation. There are four protein kinases activated dependently on the stressor type: GCN – amino acid deprivation, PKR – appearance of viral RNA, PERK – accumulation of unfolded/misfolded proteins in the ER and HRI – oxidative stress, heme deficiency, osmotic shock and heat shock. Activation of these kinases in response to stress leads to phosphorylation of eukaryotic initiation factor 2 subunit alpha (eIF2α) and 4E-BP, which orchestrate number of downstream events regulating translation. ISR has been shown to be active in leukemia cells and displayed pro-survival properties of those cells [76].

Changes in cellular signaling provide a great opportunity for the anti-leukemia treatment strategy. One is based on the inhibition of PI3K/Akt/mTOR [77] and Ras/MAPK/ERK [78] signaling pathways. Rapamycin, an inhibitor of the mTOR signaling pathway, has been tested in the context of leukemia treatment [79].

Moreover, PP242 and hippuristanol, inhibitors of mTOR-eIF4A pathways, also have the potential to overcome TKI resistance [73]. Recent reports have shown that ribavirin, which is used as an antiviral drug, inhibits the mTOR/eIF4E and ERK/Mnk1/eIF4E pathways in leukemia cells expressing BCR-ABL1 oncogene and ultimately leads to reduction of anti-apoptotic proteins, inhibition of proliferation and consequently apoptosis of leukemia cells [80]. Salubrinal, guanabenz and Sephin1 are known agents inhibiting activity of phosphatase, which dephosphorylates eIF2α. Their effectiveness has been studied mainly in the context of neurological disorders, but leukemia should also be included into this research. Inactivation of ISR pathway can constitute a significant treatment strategy. The best described group of molecules targeting ISR are inhibitors of the kinases phosphorylating eIF2α, i.e. PERK kinase. The compounds GSK2606414 and GSK2656157 were designed to bind selectively to the ATP binding pocket of the PERK kinase and to inhibit PERK activity. Their potency has been studied in a vast number of cancers. Unfortunately, the use of those inhibitors caused serious side effects [81] and recently not specific effects have been reported [82]. Alternatively, a small molecule ISRIB (ISR inhibitor) is another example of the drug that inhibits general translation. It acts downstream of the eIF2α factor in the ISR signaling pathway and through direct interaction with eIF2B abolishes the phosphorylation effect of eIF2α [83].

Initiation of the translation process can be altered by aberrant cell signaling leading to enhanced expression of proteins, which play a pro-survival role and support cell proliferation. Therefore, interference with elements enabling the stimulated translation, could be one of the strategies that, by targeting general protein synthesis, restrict propagation potential of acute leukemia cells. The broad spectrum of proteins which synthesis might be disturbed by such treatment, has both advantages and disadvantages. On one hand such treatment will affect most of actively translating cells in the body. On the other hand however, this attitude represents a powerful tool to block highly proliferative acute leukemia cells by limiting their ability to propagate. Moreover, taking into account the heterogeneity of cancer, it might be effective towards broader spectrum of leukemia cell clones and push the clonal selection towards less proliferative, so less aggressive form of cancer. This in turn enables other drugs, which can be then used in combinatory treatment to exert the beneficial effect.

6. Ribosomal proteins

Machinery that physically executes the protein synthesis on the matrices of mRNA is based on ribosomes. This complex entities are formulated of rRNA core and ribosomal proteins (RPs) of small (RPS) or large (RPL) subunit. Recent evidence demonstrated that ribosomes can contain different RPL/RPS, thus indicating a heterogeneity among ribosomes. Additionally, different expression of some RPL and RPS in the tissues has been observed. There are RPs, such as RPL38, which regulate translation of the Homeobox genes during embryo development [84], showing involvement of RPs in directing tissue organization. This heterogeneity of the translational machinery is further amplified by proteins associating/interacting with ribosomes [85, 86] (reviewed in more detail here [87]).

Existence of ribosomopathies demonstrates that RPs can play significant role in determining the cell fate. The first ribosomopathy which has been recognized was the Diamond-Blackfan anemia (DBA) caused by defect in RPS19 gene, what leads to the bone marrow failure [88]. Since then, more similar aberrations related to pathological state have been discovered. It has been observed that ribosomopathies are often related to cancers including leukemia, bone marrow failure and anemia.

Difference in expression of ribosomal proteins between normal and malignant tissues has been found [89] (for review see [90]). It has also been proposed that aberrant expression of ribosomal proteins might support cancer progression. Overexpression of RPL23 in CD34-positive myelodysplastic cells (MDS) had impact on therapy effectiveness and was associated with poor prognosis [91]. Moreover, CD34-positive cells refractory to azacitidine treatment, displayed upregulation of RPL15, RPL28, RPL31 and RPL32 ribosomal proteins [92]. Recent study of MDS revealed that progression to AML is accompanied by elevated expression of some ribosomal proteins in CD123-positive cells [93]. Contrary to this, some ribosomal proteins play a tumor suppressor role in development of leukemia. Loss of RPL11 promoted lymphomagenesis [94], deletion in RPL5 gene has been found in multiple myeloma [95] and mutations in RPL5 and RPL10 contribute to development of T-cell acute lymphoblastic leukemia [96]. Additionally, mutation in RPL10 caused upregulation of phosphoserine phosphatase, which stimulated proliferation of cancer cells [97], deletion of a fragment of chromosome 5 led to myelodysplastic syndrome, which may progress to AML caused by RPS14 haploinsufficiency [98], deletion of RPL22 led to T-cell ALL by inducing a stemness factor [99] and mutation of RPS15 has been discovered to drive chronic lymphoblastic leukemia (CLL) development [100] and to cause cancer relapse [101]. Altogether, these examples clearly show that abnormally expressed ribosomal proteins are strong candidates for leukemia drivers.

It has been shown that ribosomal proteins associated with the ribosome define pool of mRNA transcripts that are selectively translated by this ribosome [102]. There are RPs that facilitate translation upon stress by interacting with IRES or allowing for translation with the use of alternative upstream open reading frames [uORFs]. For instance, RPS5 regulates binding of transcripts with IRES-2 [103] and RPS25 regulates binding of IRES-1 in 40S subunit [104].

Phosphorylation or other modifications of ribosomal proteins might also have impact on the spectrum of translated proteins. However, even if the phosphorylation of RPS6 is well documented, its physiological role remains not clear (for review see [105]). More recently, a phosphorylation of RPL12 has been identified to facilitate translation of AU-rich mRNAs during mitosis [86].

Selectivity for mRNA binding by the particular RPs shows that besides being a part of the translational machinery, they might actually play an important regulatory role of this process. Furthermore, identification of numerous proteins that interact with ribosome, so called ribosome associated proteins, has revealed that its activity is shaped by the microenvironment [85]. Changes of mRNA translation upon RPL12 phosphorylation during cell cycle progression [86] represent an example of how cells could use the translational machinery itself, to adapt the proteome to the current demands. This creates possibility for cellular signals to have impact on the translation machinery, allowing adjustment of the profile of synthesized proteins and by that way contributing to leukemia progression.

Targeting of ribosome activity could be a strategy of leukemia treatment. Based on cryo-EM structure, an antibiotic called cycloheximide (CHX) has been designed, that stalls ribosomes on mRNA [106]. However, due to high toxicity level, CHX is mainly used in molecular biology assays nowadays. Homoharringtonine (omacetaxine, HHT) is now the only FDA approved drug to treat CML patients refractory to TKIs [107]. Its mechanism of action is based on prevention of binding of tRNA to the ribosome [108], while at the cellular level this compound reduces the level of anti-apoptotic proteins Bcl2 and MCL-1, thus guiding leukemic cells into the apoptotic pathway [109]. Targeting of monosome translation by HHT has been recently intensively tested. This drug is also examined in terms of AML treatment. Omacetaxine occurred to be highly potent in subpopulation of myelodysplastic

cells progressing towards AML [93]. Apart from that, usage of HHT has shown the synergistic effect in combinatory therapy (as reviewed in [110]).

Additionally, there are strategies to target ribosomal proteins biosynthesis at the step of transcription by using DNA intercalating agents such as: oxaliplatin, cisplatin or carboplatin [111] or by specific inhibition of ribosomal genes transcription by Polimerase I inhibitor CX-5461 [112]. This inhibitor showed the clinical potential in Myc expressing multiple myeloma [113, 114]. The Phase I clinical study in hematological malignancies has reported the increased patients survival/enhanced elimination of cancer cells [115].

The fact that the presence of ribosomal protein or its modification might be different in cancer versus healthy cells creates opportunity to target cancer cells in more precise way, limiting the damage of healthy tissue. Design of specific small molecule inhibitors or other drugs targeting precisely the deregulated ribosomes would allow effective elimination of leukemia cells 'hiding' quiescently in the niche.

7. Conclusions

Translation regulation is a key process, which enables cancer cells to adapt the proteome according to the cellular demands and therefore survive the therapeutic treatment. Moreover, it can contribute to oncogenic transformation, because deranged translation can be a source of enhanced expression of such oncogenes as Myc. This includes modification of activity of certain RNA binding proteins or stimulation of signaling, what leads to increase of global protein synthesis rate. Thus, targeting the translation regulatory mechanisms can be an effective way to eliminate the oncogene-driven malignant cells or just limit cancer cells potential for survival. In other words, therapeutic targeting of post-transcriptional regulation of gene expression gives possibility for both, precise medicine approach as well as blockade of cancer cells proliferation, irrespective of the evolving cancer clones or oncogene expression.

Acknowledgements

This work was supported by research grants from the National Science Centre UMO-2018/30/M/NZ3/00274 (PP-B) and UMO-2016/23/N/NZ3/02232 (MW).

Conflict of interest

The authors declare no competing interests.

IntechOpen

IntechOpen

Author details

Paulina Podszywalow-Bartnicka*, Magdalena Wolczyk and Katarzyna Piwocka
Nencki Institute of Experimental Biology, Polish Academy of Sciences, Warsaw, Poland

*Address all correspondence to: p.podszywalow@nencki.edu.pl

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Holcik M, Sonenberg N. Translational control in stress and apoptosis. Nature Reviews. Molecular Cell Biology. 2005 Apr;**6**(4):318-327. DOI: 10.1038/nrm1618

[2] Sonenberg N, Dever TE. Eukaryotic translation initiation factors and regulators. Current Opinion in Structural Biology. 2003 Feb;**13**(1):56-63. DOI: 10.1016/s0959-440x(03)00009-5

[3] Pyronnet S, Sonenberg N. Cell-cycle-dependent translational control. Current Opinion in Genetics & Development. 2001 Feb;**11**(1):13-18. DOI: 10.1016/s0959-437x(00)00150-7

[4] Clemens MJ. Translational regulation in cell stress and apoptosis. Roles of the eIF4E binding proteins. Journal of Cellular and Molecular Medicine. 2001 Sep;**5**(3):221-239. DOI: 10.1111/j.1582-4934.2001.tb00157.x

[5] Gebauer F, Preiss T, Hentze MW. From cis-regulatory elements to complex RNPs and back. Cold Spring Harbor Perspectives in Biology. 2012 Jul 1;**4**(7):a012245. DOI: 10.1101/cshperspect.a012245

[6] Frye M, Harada BT, Behm M, He C. RNA modifications modulate gene expression during development. Science. 2018;**361**(6409):1346-1349. DOI: 10.1126/science.aau1646

[7] Delaunay S, Frye M. RNA modifications regulating cell fate in cancer. Nature Cell Biology. 2019;**21**(5):552-559. DOI: 10.1038/s41556-019-0319-0

[8] Barbieri I, Kouzarides T. Role of RNA modifications in cancer. Nature Reviews. Cancer. 2020 Jun;**20**(6):303-322. DOI: 10.1038/s41568-020-0253-2

[9] Ianniello Z, Fatica A. N6-Methyladenosine Role in Acute Myeloid Leukaemia. International Journal of Molecular Sciences. 2018 Aug 9;**19**(8). DOI: 10.3390/ijms19082345

[10] Rosselló-Tortella M, Ferrer G, Esteller M. Epitranscriptomics in Hematopoiesis and Hematologic Malignancies. Blood Cancer Discov [Internet]. 2020 Jul 1 [cited 2020 Aug 18];1(1):26-31. Available from: https://bloodcancerdiscov.aacrjournals.org/content/1/1/26. DOI: 10.1158/2643-3249.BCD-20-0032.

[11] Barbieri I, Tzelepis K, Pandolfini L, Shi J, Millán-Zambrano G, Robson SC, et al. Promoter-bound METTL3 maintains myeloid leukaemia by m6A-dependent translation control. Nature. 2017 07;552(7683):126-31. DOI: 10.1038/nature24678

[12] Weng H, Huang H, Wu H, Qin X, Zhao BS, Dong L, et al. METTL14 Inhibits Hematopoietic Stem/Progenitor Differentiation and Promotes Leukemogenesis via mRNA m6A Modification. Cell Stem Cell. 2018;22(2):191-205.e9. DOI: 10.1016/j.stem.2017.11.016

[13] Vu LP, Pickering BF, Cheng Y, Zaccara S, Nguyen D, Minuesa G, et al. The N6-methyladenosine (m6A)-forming enzyme METTL3 controls myeloid differentiation of normal hematopoietic and leukemia cells. Nature Medicine. 2017 Nov;**23**(11):1369-1376. DOI: 10.1038/nm.4416

[14] Li Z, Weng H, Su R, Weng X, Zuo Z, Li C, et al. FTO Plays an Oncogenic Role in Acute Myeloid Leukemia as a N6-Methyladenosine RNA Demethylase. Cancer Cell. 2017;31(1):127-41. DOI: 10.1016/j.ccell.2016.11.017

[15] Su R, Dong L, Li C, Nachtergaele S, Wunderlich M, Qing Y, et al. R-2HG Exhibits Anti-tumor Activity by Targeting FTO/m6A/MYC/CEBPA

Signaling. Cell. 2018 11;172(1-2):90-105. e23. DOI: 10.1016/j.cell.2017.11.031

[16] Paris J, Morgan M, Campos J, Spencer GJ, Shmakova A, Ivanova I, et al. Targeting the RNA m6A Reader YTHDF2 Selectively Compromises Cancer Stem Cells in Acute Myeloid Leukemia. Cell Stem Cell. 2019 03;25(1):137-148.e6. DOI: 10.1016/j.stem.2019.03.021

[17] Huang H, Weng H, Sun W, Qin X, Shi H, Wu H, et al. Recognition of RNA N6-methyladenosine by IGF2BP proteins enhances mRNA stability and translation. Nature Cell Biology. 2018;**20**(3):285-295. DOI: 10.1038/s41556-018-0045-z

[18] Guzzi N, Cieśla M, Ngoc PCT, Lang S, Arora S, Dimitriou M, et al. Pseudouridylation of tRNA-Derived Fragments Steers Translational Control in Stem Cells. Cell. 2018 17;173(5):1204-1216.e26. DOI: 10.1016/j.cell.2018.03.008

[19] Pereira B, Billaud M, Almeida R. RNA-Binding Proteins in Cancer: Old Players and New Actors. Trends Cancer. 2017;**3**(7):506-528. DOI: 10.1016/j.trecan.2017.05.003

[20] Hodson DJ, Screen M, Turner M. RNA-binding proteins in hematopoiesis and hematological malignancy. Blood. 2019;**133**(22):2365-2373. DOI: 10.1182/blood-2018-10-839985

[21] Griner LN, Reuther GW. Aggressive myeloid leukemia formation is directed by the Musashi 2/Numb pathway. Cancer Biology & Therapy. 2010 Nov 15;**10**(10):979-982. DOI: 10.4161/cbt.10.10.14010

[22] Ito T, Kwon HY, Zimdahl B, Congdon KL, Blum J, Lento WE, et al. Regulation of myeloid leukaemia by the cell-fate determinant Musashi. Nature. 2010 Aug 5;**466**(7307):765-768. DOI: 10.1038/nature09171

[23] Kharas MG, Lengner CJ, Al-Shahrour F, Bullinger L, Ball B, Zaidi S, et al. Musashi-2 regulates normal hematopoiesis and promotes aggressive myeloid leukemia. Nature Medicine. 2010 Aug;**16**(8):903-908. DOI: 10.1038/nm.2187

[24] Park S-M, Gönen M, Vu L, Minuesa G, Tivnan P, Barlowe TS, et al. Musashi2 sustains the mixed-lineage leukemia-driven stem cell regulatory program. The Journal of Clinical Investigation. 2015 Mar 2;**125**(3):1286-1298. DOI: 10.1172/JCI78440

[25] Park S-M, Deering RP, Lu Y, Tivnan P, Lianoglou S, Al-Shahrour F, et al. Musashi-2 controls cell fate, lineage bias, and TGF-β signaling in HSCs. The Journal of Experimental Medicine. 2014 Jan 13;**211**(1):71-87. DOI: 10.1084/jem.20130736

[26] Wang S, Li N, Yousefi M, Nakauka-Ddamba A, Li F, Parada K, et al. Transformation of the intestinal epithelium by the MSI2 RNA-binding protein. Nature Communications. 2015 Mar 16;**6**:6517. DOI: 10.1038/ncomms7517

[27] Minuesa G, Albanese SK, Xie W, Kazansky Y, Worroll D, Chow A, et al. Small-molecule targeting of MUSASHI RNA-binding activity in acute myeloid leukemia. Nature Communications. 2019;**10**(1):2691. DOI: 10.1038/s41467-019-10523-3

[28] Lan L, Appelman C, Smith AR, Yu J, Larsen S, Marquez RT, et al. Natural product (−)-gossypol inhibits colon cancer cell growth by targeting RNA-binding protein Musashi-1. Molecular Oncology. 2015 Aug;**9**(7):1406-1420. DOI: 10.1016/j.molonc.2015.03.014

[29] Clingman CC, Deveau LM, Hay SA, Genga RM, Shandilya SM, Massi F, et al. Allosteric inhibition of a stem cell RNA-binding protein by an intermediary metabolite. Black DL, editor. eLife

[Internet]. 2014 Jun 16;3:e02848. DOI: 10.7554/eLife.02848

[30] Jiang L, Gu Z-H, Yan Z-X, Zhao X, Xie Y-Y, Zhang Z-G, et al. Exome sequencing identifies somatic mutations of DDX3X in natural killer/T-cell lymphoma. Nature Genetics. 2015 Sep;**47**(9):1061-1066. DOI: 10.1038/ng.3358

[31] Wang L, Lawrence MS, Wan Y, Stojanov P, Sougnez C, Stevenson K, et al. SF3B1 and other novel cancer genes in chronic lymphocytic leukemia. The New England Journal of Medicine. 2011 Dec 29;**365**(26):2497-2506. DOI: 10.1056/NEJMoa1109016

[32] Bol GM, Vesuna F, Xie M, Zeng J, Aziz K, Gandhi N, et al. Targeting DDX3 with a small molecule inhibitor for lung cancer therapy. EMBO Molecular Medicine. 2015 May;**7**(5):648-669. DOI: 10.15252/emmm.201404368

[33] Heerma van Voss MR, Vesuna F, Bol GM, Afzal J, Tantravedi S, Bergman Y, et al. Targeting mitochondrial translation by inhibiting DDX3: a novel radiosensitization strategy for cancer treatment. Oncogene. 2018;**37**(1):63-74. DOI: 10.1038/onc.2017.308

[34] Annabi B, Currie J-C, Moghrabi A, Béliveau R. Inhibition of HuR and MMP-9 expression in macrophage-differentiated HL-60 myeloid leukemia cells by green tea polyphenol EGCg. Leukemia Research. 2007 Sep;**31**(9):1277-1284. DOI: 10.1016/j.leukres.2006.10.001

[35] Ishimaru D, Ramalingam S, Sengupta TK, Bandyopadhyay S, Dellis S, Tholanikunnel BG, et al. Regulation of Bcl-2 expression by HuR in HL60 leukemia cells and A431 carcinoma cells. Molecular Cancer Research. 2009 Aug;**7**(8):1354-1366. DOI: 10.1158/1541-7786.MCR-08-0476

[36] Ko C-Y, Wang W-L, Li C-F, Jeng Y-M, Chu Y-Y, Wang H-Y, et al. IL-18-induced interaction between IMP3 and HuR contributes to COX-2 mRNA stabilization in acute myeloid leukemia. Journal of Leukocyte Biology. 2016 Jan;**99**(1):131-141. DOI: 10.1189/jlb.2A0414-228RR

[37] Blackinton JG, Keene JD. Functional coordination and HuR-mediated regulation of mRNA stability during T cell activation. Nucleic Acids Research. 2016 Jan 8;**44**(1):426-436. DOI: 10.1093/nar/gkv1066

[38] Meisner N-C, Hintersteiner M, Mueller K, Bauer R, Seifert J-M, Naegeli H-U, et al. Identification and mechanistic characterization of low-molecular-weight inhibitors for HuR. Nature Chemical Biology. 2007 Aug;**3**(8):508-515. DOI: 10.1038/nchembio.2007.14

[39] Blanco FF, Preet R, Aguado A, Vishwakarma V, Stevens LE, Vyas A, et al. Impact of HuR inhibition by the small molecule MS-444 on colorectal cancer cell tumorigenesis. Oncotarget. 2016 Nov 8;**7**(45):74043-74058. DOI: 10.18632/oncotarget.12189

[40] Filippova N, Yang X, Ananthan S, Sorochinsky A, Hackney JR, Gentry Z, et al. Hu antigen R (HuR) multimerization contributes to glioma disease progression. The Journal of Biological Chemistry. 2017;**292**(41):16999-17010. DOI: 10.1074/jbc.M117.797878

[41] Chae M-J, Sung HY, Kim E-H, Lee M, Kwak H, Chae CH, et al. Chemical inhibitors destabilize HuR binding to the AU-rich element of TNF-alpha mRNA. Experimental & Molecular Medicine. 2009 Nov 30;**41**(11):824-831. DOI: 10.3858/emm.2009.41.11.088

[42] Muralidharan R, Mehta M, Ahmed R, Roy S, Xu L, Aubé J, et al.

HuR-targeted small molecule inhibitor exhibits cytotoxicity towards human lung cancer cells. Scientific Reports. 2017;**7**(1):9694. DOI: 10.1038/s41598-017-07787-4

[43] Timchenko NA, Welm AL, Lu X, Timchenko LT. CUG repeat binding protein (CUGBP1) interacts with the 5′ region of C/EBPbeta mRNA and regulates translation of C/EBPbeta isoforms. Nucleic Acids Research. 1999 Nov 15;**27**(22):4517-4525. DOI: 10.1093/nar/27.22.4517

[44] Guerzoni C, Bardini M, Mariani SA, Ferrari-Amorotti G, Neviani P, Panno ML, et al. Inducible activation of CEBPB, a gene negatively regulated by BCR/ABL, inhibits proliferation and promotes differentiation of BCR/ABL-expressing cells. Blood. 2006 May 15;**107**(10):4080-4089. DOI: 10.1182/blood-2005-08-3181

[45] Notari M, Neviani P, Santhanam R, Blaser BW, Chang J-S, Galietta A, et al. A MAPK/HNRPK pathway controls BCR/ABL oncogenic potential by regulating MYC mRNA translation. Blood. 2006 Mar 15;**107**(6):2507-2516. DOI: 10.1182/blood-2005-09-3732

[46] Iervolino A, Santilli G, Trotta R, Guerzoni C, Cesi V, Bergamaschi A, et al. hnRNP A1 nucleocytoplasmic shuttling activity is required for normal myelopoiesis and BCR/ABL leukemogenesis. Molecular and Cellular Biology. 2002 Apr;**22**(7):2255-2266. DOI: 10.1128/mcb.22.7.2255-2266.2002

[47] Perrotti D, Bonatti S, Trotta R, Martinez R, Skorski T, Salomoni P, et al. TLS/FUS, a pro-oncogene involved in multiple chromosomal translocations, is a novel regulator of BCR/ABL-mediated leukemogenesis. The EMBO Journal. 1998 Aug 3;**17**(15):4442-4455. DOI: 10.1093/emboj/17.15.4442

[48] Trotta R, Vignudelli T, Candini O, Intine RV, Pecorari L, Guerzoni C, et al. BCR/ABL activates mdm2 mRNA translation via the La antigen. Cancer Cell. 2003 Feb;**3**(2):145-160. DOI: 10.1016/s1535-6108(03)00020-5

[49] Fu X-D, Ares M. Context-dependent control of alternative splicing by RNA-binding proteins. Nature Reviews. Genetics. 2014 Oct;**15**(10):689-701. DOI: 10.1038/nrg3778

[50] da Silva MR, Moreira GA, Gonçalves da Silva RA, de Almeida Alves Barbosa É, Pais Siqueira R, Teixera RR, et al. Splicing Regulators and Their Roles in Cancer Biology and Therapy. BioMed Research International. 2015;2015:150514. DOI: 10.1155/2015/150514

[51] Wang E, Aifantis I. RNA Splicing and Cancer. Trends Cancer. 2020 Aug;**6**(8):631-644. DOI: 10.1016/j.trecan.2020.04.011

[52] Alarcón CR, Goodarzi H, Lee H, Liu X, Tavazoie S, Tavazoie SF. HNRNPA2B1 Is a Mediator of m(6)A-Dependent Nuclear RNA Processing Events. Cell. 2015 Sep 10;**162**(6):1299-1308. DOI: 10.1016/j.cell.2015.08.011

[53] Xiao W, Adhikari S, Dahal U, Chen Y-S, Hao Y-J, Sun B-F, et al. Nuclear m(6)A Reader YTHDC1 Regulates mRNA Splicing. Molecular Cell. 2016 Feb 18;**61**(4):507-519. DOI: 10.1016/j.molcel.2016.01.012

[54] Schittenhelm MM, Walter B, Tsintari V, Federmann B, Bajrami Saipi M, Akmut F, et al. Alternative splicing of the tumor suppressor ASPP2 results in a stress-inducible, oncogenic isoform prevalent in acute leukemia. eBioMedicine. 2019 Apr;**42**:340-351. DOI: 10.1016/j.ebiom.2019.03.028

[55] Li S-Q, Liu J, Zhang J, Wang X-L, Chen D, Wang Y, et al. Transcriptome profiling reveals the high incidence of hnRNPA1 exon 8 inclusion in chronic myeloid leukemia. Journal of Advanced

Research. 2020 Jul;**24**:301-310. DOI: 10.1016/j.jare.2020.04.016

[56] Feng Y, Chen M, Manley JL. Phosphorylation switches the general splicing repressor SRp38 to a sequence-specific activator. Nature Structural & Molecular Biology. 2008 Oct;**15**(10):1040-1048. DOI: 10.1038/nsmb.1485

[57] Radzisheuskaya A, Shliaha PV, Grinev V, Lorenzini E, Kovalchuk S, Shlyueva D, et al. PRMT5 methylome profiling uncovers a direct link to splicing regulation in acute myeloid leukemia. Nature Structural & Molecular Biology. 2019;**26**(11):999-1012. DOI: 10.1038/s41594-019-0313-z

[58] Shailesh H, Zakaria ZZ, Baiocchi R, Sif S. Protein arginine methyltransferase 5 (PRMT5) dysregulation in cancer. Oncotarget. 2018 Nov 30;**9**(94):36705-36718. DOI: 10.18632/oncotarget.26404

[59] Li X, Wang C, Jiang H, Luo C. A patent review of arginine methyltransferase inhibitors (2010-2018). Expert Opinion on Therapeutic Patents. 2019;**29**(2):97-114. DOI: 10.1080/13543776.2019.1567711

[60] Koh CM, Bezzi M, Low DHP, Ang WX, Teo SX, Gay FPH, et al. MYC regulates the core pre-mRNA splicing machinery as an essential step in lymphomagenesis. Nature. 2015 Jul 2;**523**(7558):96-100. DOI: 10.1038/nature14351

[61] Wang E, Lu SX, Pastore A, Chen X, Imig J, Chun-Wei Lee S, et al. Targeting an RNA-Binding Protein Network in Acute Myeloid Leukemia. Cancer Cell. 2019;**35**(3):369-384.e7. DOI: 10.1016/j.ccell.2019.01.010

[62] Han T, Goralski M, Gaskill N, Capota E, Kim J, Ting TC, et al. Anticancer sulfonamides target splicing by inducing RBM39 degradation via recruitment to DCAF15. Science. 2017;**356**(6336). DOI: 10.1126/science.aal3755

[63] Faust TB, Yoon H, Nowak RP, Donovan KA, Li Z, Cai Q, et al. Structural complementarity facilitates E7820-mediated degradation of RBM39 by DCAF15. Nature Chemical Biology. 2020;**16**(1):7-14. DOI: 10.1038/s41589-019-0378-3

[64] Seiler M, Yoshimi A, Darman R, Chan B, Keaney G, Thomas M, et al. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. Nature Medicine. 2018;**24**(4):497-504. DOI: 10.1038/nm.4493

[65] Shirai CL, White BS, Tripathi M, Tapia R, Ley JN, Ndonwi M, et al. Mutant U2AF1-expressing cells are sensitive to pharmacological modulation of the spliceosome. Nature Communications. 2017;8:14060. DOI: 10.1038/ncomms14060

[66] Lee SC-W, North K, Kim E, Jang E, Obeng E, Lu SX, et al. Synthetic Lethal and Convergent Biological Effects of Cancer-Associated Spliceosomal Gene Mutations. Cancer Cell. 2018 13;34(2):225-241.e8. DOI: 10.1016/j.ccell.2018.07.003

[67] Pandit S, Zhou Y, Shiue L, Coutinho-Mansfield G, Li H, Qiu J, et al. Genome-wide analysis reveals SR protein cooperation and competition in regulated splicing. Molecular Cell. 2013 Apr 25;**50**(2):223-235. DOI: 10.1016/j.molcel.2013.03.001

[68] Huelga SC, Vu AQ, Arnold JD, Liang TY, Liu PP, Yan BY, et al. Integrative genome-wide analysis reveals cooperative regulation of alternative splicing by hnRNP proteins. Cell Reports. 2012 Feb 23;**1**(2):167-178. DOI: 10.1016/j.celrep.2012.02.001

[69] Ly C, Arechiga AF, Melo JV, Walsh CM, Ong ST. Bcr-Abl kinase

modulates the translation regulators ribosomal protein S6 and 4E-BP1 in chronic myelogenous leukemia cells via the mammalian target of rapamycin. Cancer Research. 2003 Sep 15;**63**(18):5716-5722

[70] Mirabilii S, Ricciardi MR, Piedimonte M, Gianfelici V, Bianchi MP, Tafuri A. Biological Aspects of mTOR in Leukemia. International Journal of Molecular Sciences. 2018 Aug 14;**19**(8). DOI: 10.3390/ijms19082396

[71] Redig AJ, Vakana E, Platanias LC. Regulation of mammalian target of rapamycin and mitogen activated protein kinase pathways by BCR-ABL. Leukemia & Lymphoma. 2011 Feb;**52**(Suppl 1):45-53. DOI: 10.3109/10428194.2010.546919

[72] Hirao A, Hoshii T. Mechanistic / mammalian target protein of rapamycin signaling in hematopoietic stem cells and leukemia. Cancer Science. 2013 Aug;**104**(8):977-982. DOI: 10.1111/cas.12189

[73] Tsai BP, Jimenez J, Lim S, Fitzgerald KD, Zhang M, Chuah CTH, et al. A novel Bcr-Abl-mTOR-eIF4A axis regulates IRES-mediated translation of LEF-1. Open Biology. 2014 Nov;**4**(11):140180. DOI: 10.1098/rsob.140180

[74] Xian J, Shao H, Chen X, Zhang S, Quan J, Zou Q, et al. Nucleophosmin Mutants Promote Adhesion, Migration and Invasion of Human Leukemia THP-1 Cells through MMPs Up-regulation via Ras/ERK MAPK Signaling. International Journal of Biological Sciences. 2016;**12**(2):144-155. DOI: 10.7150/ijbs.13382

[75] Wang X, Pesakhov S, Weng A, Kafka M, Gocek E, Nguyen M, et al. ERK 5/MAPK pathway has a major role in 1α,25-(OH)2 vitamin D3-induced terminal differentiation of myeloid leukemia cells. J Steroid Biochem Mol Biol. 2014 Oct;144 Pt A:223-227. DOI: 10.1016/j.jsbmb.2013.10.002

[76] Kusio-Kobialka M, Podszywalow-Bartnicka P, Peidis P, Glodkowska-Mrowka E, Wolanin K, Leszak G, et al. The PERK-eIF2α phosphorylation arm is a pro-survival pathway of BCR-ABL signaling and confers resistance to imatinib treatment in chronic myeloid leukemia cells. Cell Cycle. 2012 Nov 1;**11**(21):4069-4078. DOI: 10.4161/cc.22387

[77] Dinner S, Platanias LC. Targeting the mTOR Pathway in Leukemia. Journal of Cellular Biochemistry. 2016;**117**(8):1745-1752. DOI: 10.1002/jcb.25559

[78] Dreas A, Mikulski M, Milik M, Fabritius C-H, Brzózka K, Rzymski T. Mitogen-activated Protein Kinase (MAPK) Interacting Kinases 1 and 2 (MNK1 and MNK2) as Targets for Cancer Therapy: Recent Progress in the Development of MNK Inhibitors. Current Medicinal Chemistry. 2017;**24**(28):3025-3053. DOI: 10.2174/0929867324666170203123427

[79] Truitt ML, Ruggero D. New frontiers in translational control of the cancer genome. Nature Reviews. Cancer. 2016;**16**(5):288-304. DOI: 10.1038/nrc.2016.27

[80] Shi F, Len Y, Gong Y, Shi R, Yang X, Naren D, et al. Ribavirin Inhibits the Activity of mTOR/eIF4E, ERK/Mnk1/eIF4E Signaling Pathway and Synergizes with Tyrosine Kinase Inhibitor Imatinib to Impair Bcr-Abl Mediated Proliferation and Apoptosis in Ph+ Leukemia. PLoS One. 2015;**10**(8):e0136746. DOI: 10.1371/journal.pone.0136746

[81] Axten JM, Romeril SP, Shu A, Ralph J, Medina JR, Feng Y, et al. Discovery of GSK2656157: An Optimized PERK Inhibitor Selected

for Preclinical Development. ACS Medicinal Chemistry Letters. 2013 Oct 10;**4**(10):964-968. DOI: 10.1021/ml400228e

[82] Rojas-Rivera D, Delvaeye T, Roelandt R, Nerinckx W, Augustyns K, Vandenabeele P, et al. When PERK inhibitors turn out to be new potent RIPK1 inhibitors: critical issues on the specificity and use of GSK2606414 and GSK2656157. Cell Death Differ. 2017;24(6):1100-10. DOI: 10.1038/cdd.2017.58

[83] Sidrauski C, McGeachy AM, Ingolia NT, Walter P. The small molecule ISRIB reverses the effects of eIF2α phosphorylation on translation and stress granule assembly. eLife. 2015 Feb 26;**4**. DOI: 10.7554/eLife.05033

[84] Kondrashov N, Pusic A, Stumpf CR, Shimizu K, Hsieh AC, Ishijima J, et al. Ribosome-mediated specificity in Hox mRNA translation and vertebrate tissue patterning. Cell. 2011 Apr 29;**145**(3):383-397. DOI: 10.1016/j.cell.2011.03.028

[85] Simsek D, Tiu GC, Flynn RA, Byeon GW, Leppek K, Xu AF, et al. The Mammalian Ribo-interactome Reveals Ribosome Functional Diversity and Heterogeneity. Cell. 2017 Jun 1;**169**(6):1051-1065.e18. DOI: 10.1016/j.cell.2017.05.022

[86] Imami K, Milek M, Bogdanow B, Yasuda T, Kastelic N, Zauber H, et al. Phosphorylation of the Ribosomal Protein RPL12/uL11 Affects Translation during Mitosis. Mol Cell. 2018 04;72(1):84-98.e9. DOI: 10.1016/j.molcel.2018.08.019

[87] Genuth NR, Barna M. The Discovery of Ribosome Heterogeneity and Its Implications for Gene Regulation and Organismal Life. Mol Cell. 2018 02;71(3):364-74. DOI: 10.1016/j.molcel.2018.07.018

[88] Gustavsson P, Willing TN, van Haeringen A, Tchernia G, Dianzani I, Donnér M, et al. Diamond-Blackfan anaemia: genetic homogeneity for a gene on chromosome 19q13 restricted to 1.8 Mb. Nature Genetics. 1997 Aug;**16**(4):368-371. DOI: 10.1038/ng0897-368

[89] Guimaraes JC, Zavolan M. Patterns of ribosomal protein expression specify normal and malignant human cells. Genome Biol. 2016 24;17(1):236. DOI: 10.1186/s13059-016-1104-z

[90] Bastide A, David A. The ribosome, (slow) beating heart of cancer (stem) cell. Oncogene. 2018 Apr 20;7(4):34. DOI: 10.1038/s41389-018-0044-8

[91] Wu L, Li X, Xu F, Chang C, He Q, Zhang Z, et al. Over-expression of RPL23 in myelodysplastic syndromes is associated with apoptosis resistance of CD34+ cells and predicts poor prognosis and distinct response to CHG chemotherapy or decitabine. Annals of Hematology. 2012 Oct;**91**(10):1547-1554. DOI: 10.1007/s00277-012-1486-2

[92] Monika Belickova M, Merkerova MD, Votavova H, Valka J, Vesela J, Pejsova B, et al. Up-regulation of ribosomal genes is associated with a poor response to azacitidine in myelodysplasia and related neoplasms. International Journal of Hematology. 2016 Nov;**104**(5):566-573. DOI: 10.1007/s12185-016-2058-3

[93] Stevens BM, Khan N, D'Alessandro A, Nemkov T, Winters A, Jones CL, et al. Characterization and targeting of malignant stem cells in patients with advanced myelodysplastic syndromes. Nat Commun. 2018 12;9(1):3694. DOI: 10.1038/s41467-018-05984-x

[94] Morgado-Palacin L, Varetti G, Llanos S, Gómez-López G, Martinez D, Serrano M. Partial Loss of Rpl11 in Adult Mice Recapitulates

Diamond-Blackfan Anemia and Promotes Lymphomagenesis. Cell Reports. 2015 Oct 27;**13**(4):712-722. DOI: 10.1016/j.celrep.2015.09.038

[95] Hofman IJF, van Duin M, De Bruyne E, Fancello L, Mulligan G, Geerdens E, et al. RPL5 on 1p22.1 is recurrently deleted in multiple myeloma and its expression is linked to bortezomib response. Leukemia. 2017;**31**(8):1706-1714. DOI: 10.1038/leu.2016.370

[96] De Keersmaecker K, Atak ZK, Li N, Vicente C, Patchett S, Girardi T, et al. Exome sequencing identifies mutation in CNOT3 and ribosomal genes RPL5 and RPL10 in T-cell acute lymphoblastic leukemia. Nature Genetics. 2013 Feb;**45**(2):186-190. DOI: 10.1038/ng.2508

[97] Kampen KR, Fancello L, Girardi T, Rinaldi G, Planque M, Sulima SO, et al. Translatome analysis reveals altered serine and glycine metabolism in T-cell acute lymphoblastic leukemia cells. Nat Commun. 2019, 2542;**10**(1). DOI: 10.1038/s41467-019-10508-2

[98] Ebert BL, Pretz J, Bosco J, Chang CY, Tamayo P, Galili N, et al. Identification of RPS14 as a 5q- syndrome gene by RNA interference screen. Nature. 2008 Jan 17;**451**(7176):335-339. DOI: 10.1038/nature06494

[99] Rao S, Lee S-Y, Gutierrez A, Perrigoue J, Thapa RJ, Tu Z, et al. Inactivation of ribosomal protein L22 promotes transformation by induction of the stemness factor, Lin28B. Blood. 2012 Nov 1;**120**(18):3764-3773. DOI: 10.1182/blood-2012-03-415349

[100] Landau DA, Tausch E, Taylor-Weiner AN, Stewart C, Reiter JG, Bahlo J, et al. Mutations driving CLL and their evolution in progression and relapse. Nature. 2015 Oct 22;**526**(7574):525-530. DOI: 10.1038/nature15395

[101] Ljungström V, Cortese D, Young E, Pandzic T, Mansouri L, Plevova K, et al. Whole-exome sequencing in relapsing chronic lymphocytic leukemia: clinical impact of recurrent RPS15 mutations. Blood. 2016 Feb 25;**127**(8):1007-1016. DOI: 10.1182/blood-2015-10-674572

[102] Shi Z, Fujii K, Kovary KM, Genuth NR, Röst HL, Teruel MN, et al. Heterogeneous Ribosomes Preferentially Translate Distinct Subpools of mRNAs Genome-wide. Molecular Cell. 2017 Jul 6;**67**(1):71-83.e7. DOI: 10.1016/j.molcel.2017.05.021

[103] Bhat P, Shwetha S, Sharma DK, Joseph AP, Srinivasan N, Das S. The beta hairpin structure within ribosomal protein S5 mediates interplay between domains II and IV and regulates HCV IRES function. Nucleic Acids Research. 2015 Mar 11;**43**(5):2888-2901. DOI: 10.1093/nar/gkv110

[104] Hertz MI, Landry DM, Willis AE, Luo G, Thompson SR. Ribosomal protein S25 dependency reveals a common mechanism for diverse internal ribosome entry sites and ribosome shunting. Molecular and Cellular Biology. 2013 Mar;**33**(5):1016-1026. DOI: 10.1128/MCB.00879-12

[105] Meyuhas O. Ribosomal Protein S6 Phosphorylation. Four Decades of Research. Int Rev Cell Mol Biol. 2015;**320**:41-73. DOI: 10.1016/bs.ircmb.2015.07.006

[106] Myasnikov AG, Kundhavai Natchiar S, Nebout M, Hazemann I, Imbert V, Khatter H, et al. Structure-function insights reveal the human ribosome as a cancer target for antibiotics. Nature Communications. 2016 Sep 26;**7**:12856. DOI: 10.1038/ncomms12856

[107] Huang B-T, Zeng Q-C, Zhao W-H, Tan Y. Homoharringtonine

contributes to imatinib sensitivity by blocking the EphB4/RhoA pathway in chronic myeloid leukemia cell lines. Med Oncol Northwood Lond Engl. 2014 Feb;**31**(2):836. DOI: 10.1007/s12032-013-0836-9

[108] Tujebajeva RM, Graifer DM, Karpova GG, Ajtkhozhina NA. Alkaloid homoharringtonine inhibits polypeptide chain elongation on human ribosomes on the step of peptide bond formation. FEBS Letters. 1989 Nov 6;**257**(2):254-256. DOI: 10.1016/0014-5793(89)81546-7

[109] Lü S, Wang J. Homoharringtonine and omacetaxine for myeloid hematological malignancies. Journal of Hematology & Oncology. 2014 Jan 3;**7**(2). DOI: 10.1186/1756-8722-7-2

[110] Gilles A, Frechin L, Natchiar K, Biondani G, Loeffelholz O von, Holvec S, et al. Targeting the Human 80S Ribosome in Cancer: From Structure to Function and Drug Design for Innovative Adjuvant Therapeutic Strategies. Cell 2020 Mar 5;9(3). DOI: 10.3390/cells9030629

[111] nBruno PM, Liu Y, Park GY, Murai J, Koch CE, Eisen TJ, et al. A subset of platinum-containing chemotherapeutic agents kills cells by inducing ribosome biogenesis stress. Nature Medicine. 2017 Apr;**23**(4):461-471. DOI: 10.1038/nm.4291

[112] Bywater MJ, Poortinga G, Sanij E, Hein N, Peck A, Cullinane C, et al. Inhibition of RNA polymerase I as a therapeutic strategy to promote cancer-specific activation of p53. Cancer Cell. 2012 Jul 10;**22**(1):51-65. DOI: 10.1016/j.ccr.2012.05.019

[113] Devlin JR, Hannan KM, Hein N, Cullinane C, Kusnadi E, Ng PY, et al. Combination Therapy Targeting Ribosome Biogenesis and mRNA Translation Synergistically Extends Survival in MYC-Driven Lymphoma. Cancer Discovery. 2016 Jan;**6**(1):59-70. DOI: 10.1158/2159-8290.CD-14-0673

[114] Lee HC, Wang H, Baladandayuthapani V, Lin H, He J, Jones RJ, et al. RNA Polymerase I Inhibition with CX-5461 as a Novel Therapeutic Strategy to Target MYC in Multiple Myeloma. British Journal of Haematology. 2017;**177**(1):80-94. DOI: 10.1111/bjh.14525

[115] Khot A, Brajanovski N, Cameron DP, Hein N, Maclachlan KH, Sanij E, et al. First-in-Human RNA Polymerase I Transcription Inhibitor CX-5461 in Patients with Advanced Hematologic Cancers: Results of a Phase I Dose-Escalation Study. Cancer Discovery. 2019;**9**(8):1036-1049. DOI: 10.1158/2159-8290.CD-18-1455