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Editorial

Translation and cancer

Translation is a process during which proteins are synthesized form mRNAs via highly coordinated actions of transfer RNAs (tRNAs), ribosomes and a large number of auxiliary proteins, known as translation factors [1]. Translation can be divided into four distinct phases: initiation, elongation, termination and ribosome recycling [1]. Since translation is one of the most energy consuming processes in the cell, and acts as a critical step in the control of gene expression, its regulation is one of the most crucial homeostatic mechanisms [2]. Indeed, translational dysregulation leads to a number of pathological states including cancer [3].

The first clue suggesting that aberrant translation plays a role in cancer came in 1896, when Pianese observed that cancer cells have enlarged and irregularly shaped nucleoli [4], which are the sites of ribosome biogenesis. Subsequent studies have implicated a large number of the components of the translational machinery in oncogenesis and tumour progression [3]. Accordingly, elevated protein synthesis is a common feature in the vast majority of malignancies irrespective of their tissue of origin [3]. In addition to these quantitative changes in protein synthesis, qualitative changes in translation of a subset of mRNAs, stemming from alterations in one or more components of the translational machinery, engender changes in the proteome that favour neoplastic growth [5]. These quantitative and qualitative distinctions between translational programmes of malignant versus normal cells are thought to provide sufficient therapeutic window to target the translational apparatus in cancer, while causing minimal toxicity in healthy tissues [6]. The presence of genetically heterogeneous cancer cells in the same tumour bed significantly hampers targeted cancer therapies [7]. However, activation of a number of oncogenes (e.g. RAS, PIK3CA, MYC) and/or loss of tumour suppressors (e.g. PTEN, TSC1/2, NF1, TP53) stimulates the translational apparatus [6]. Therefore, therapeutic approaches to impede translation in malignant cells hold the promise to overcome intra-tumour genetic heterogeneity.

In the last five decades, a significant research effort has been devoted to fathom the molecular underpinnings of translation [8]. This led to the understanding of a number of mechanisms, which play pivotal roles in regulating translation in homeostasis, and when dysergulated lead to cancer [6]. Based on these findings, several strategies to target malignant translational machinery have been devised and evaluated in preclinical models and in the clinic [6]. However, to design more efficient means to target dysregulated translation and translate these findings to the clinic, a number of important fundamental questions await to be answered.

In this special issue of BBA-GRM entitled "Translation and cancer" a number of world leading experts have been asked to provide critical reviews of the literature highlighting achievements and remaining gaps in knowledge in the field of translation as follows: Roux and Gao cover the role of dysregulation of major signalling pathways that regulate translation in cancer including the mammalian/mechanistic target of rapamycin (mTOR) and mitogen activated protein kinases (MAPK). Proud discusses the role of MAPK-interacting protein kinases (MNKs) in neoplasia. The MAPK/MNK and mTOR signalling pathways impinge on the eukaryotic translation initiation factor 4E (eIF4E). The MAPK/MNK pathway directly phosphorylates eIF4E, whereas the mTOR pathway increases eIF4E availability via the phosphorylation and the inhibition of a family of translational suppressors eIF4E-binding proteins (4E-BPs) [9]. Polunovsky and Bitterman describe the role of eIF4E-mediated translational control in neoplasia, with a focus on its role in cancer induction, and discuss potential eIF4E-centred cancer prevention strategies. eIF4E is a cap-binding subunit of the eIF4F complex that recruits mRNA to the ribosome during initiation [10]. The eIF4F complex also comprises a large scaffolding protein eIF4G, and a DEAD box helicase eIF4E that facilitates scanning of 5′UTR towards the initiation codon [10]. The role of eIF4A in malignancy and development of strategies to target its aberrant activity are examined by Chu and Pelletier. eIF4G recruits ribosome to the eIF4F complex via interaction with the multifactorial translation initiation factor eIF3 [11]. Hershey covers the role of eIF3 subunits in neoplasia. In addition to eIF4E, mTOR regulates translation of mRNAs that contain 5′-terminal oligopyrimidine tract (TOP mRNAs) that encode components of translational machinery [12], which is deliberated by Meyuhas. Gentilella, Kozma and Thomas discuss the role of mTOR and dysregulated ribosome biogenesis in cancer, whereas Woods, Hannan, Pearson, and Hannan outline potential anti-neoplastic therapeutic strategies to exploit interplay between p53 and ribosome biogenesis. eIF6 has been shown to play a role in ribosome biogenesis and regulate translation by binding to the 60S ribosomal subunit, thereby preventing its association with 40S [13]. Brina, Miluzio, Ricciardi, and Biffo review emerging roles of eIF6 in cancer. eIF5A has been implicated in regulation of initiation, elongation, nuclear export and mRNA stability and it is characterized by a unique post-translational modification whereby a single lysine residue in eIF5A is modified into hypusine [14]. The role of eIF5A in cancer and potential targeting of the hypusination pathway in the clinic is covered by Hershey and Mathews. The role of translational control under stress in the context of neoplasia is examined by Leprivier, Rotblat, Khan, Jan, and Sorensen, whereas Anderson, Kedersha and Ivanov elaborate on the role of stress induced mRNPs which contain components of the translational apparatus (i.e. stress granules and P-bodies [15]). Phosphorylation of eIF2α which limits ternary complex levels (ternary complex consists of eIF2, GTP and initiator tRNA) plays a major role in stress-induced translational reprogramming [8]. Koromilas will highlight the role of eIF2α phosphorylation and related pathways in cancer.

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Wurth and Gebauer discuss the role of RNA-binding protein-mediated regulation of translation in tumour initiation and progression, whereas Faye and Holcik focus on proteins that act as trans-acting factors (ITAFs) to regulate cap-independent translation via internal ribosome entry sites (IRES). Finally, Grewal highlights recent advances in knowledge on the role of tRNAs in cancer.

We are indebted to all the authors for taking their time to write these outstanding reviews. We are also thankful to the executive editor Prof. Joseph Reese for giving us this opportunity, and we are particularly grateful to Andy Deelen and Don Prince, the Special Issue Journal Manager, for having huge tolerance for our tardiness and extraordinary efforts in bringing this special issue to publication. We would also like to thank the past and present members of our labs and all of our collaborators. Topisirovic would in particular like to thank Prof. Roderick McInnes, who enabled him to focus on science by avoiding nonsense.

References

[1] J.W. Hershey, N. Sonenberg, M.B. Mathews, Principles of translational control: an overview, Cold Spring Harb. Perspect. Biol. 4 (2012).
[2] I. Topisirovic, N. Sonenberg, mRNA translation and energy metabolism in cancer: the role of the MAPK and mTORC1 pathways, Cold Spring Harb. Symp. Quant. Biol. 76 (2011) 355–367.
[3] D. Silvera, S.C. Formenti, R.J. Schneider, Translational control in cancer, Nat. Rev. Cancer 10 (2010) 254–266.
[4] G. Pianese, Beitrag zur histologie und Aetiologie der carcinoma histologische und experimentelle, Beitr. Pathol. Anat. Allg. Pathol. 142 (1896) 1–193.
[5] J. Pelletier, J. Graff, D. Ruggero, N. Sonenberg, Targeting the eIF4F translation initiation complex: a critical nexus for cancer development, Cancer Res. 75 (2015) 250–263.
[6] M. Bhat, N. Robichaud, L. Hulea, N. Sonenberg, J. Pelletier, I. Topisirovic, Targeting the translation machinery in cancer, Nat. Rev. Drug Discov. 14 (4) (2015) 261–278.
[7] P.L. Bedard, A.R. Hansen, M.J. Ratain, L.L. Siu, Tumour heterogeneity in the clinic, Nature 501 (2013) 355–364.
[8] A.G. Hinnebusch, The scanning mechanism of eukaryotic translation initiation, Annu. Rev. Biochem. 83 (2014) 779–812.
[9] P.P. Roux, I. Topisirovic, Regulation of mRNA translation by signaling pathways, Cold Spring Harb. Perspect. Biol. 4 (2012).
[10] N. Sonenberg, A.G. Hinnebusch, Regulation of translation initiation in eukaryotes: mechanisms and biological targets, Cell 136 (2009) 731–745.
[11] R.J. Jackson, C.U. Hellen, T.V. Pestova, The mechanism of eukaryotic translation initiation and principles of its regulation, Nat. Rev. Mol. Cell Biol. 11 (2010) 113–127.
[12] S. Levy, D. Avni, N. Hariharan, R.P. Perry, O. Meyuhas, Oligopyrimidine tract at the 5′ end of mammalian ribosomal protein mRNAs is required for their translational control, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 3319–3323.
[13] A. Miluzio, A. Beugnet, V. Volta, S. Biffo, Eukaryotic initiation factor 6 mediates a continuum between 60S ribosome biogenesis and translation, EMBO Rep. 10 (2009) 459–465.
[14] M.H. Park, K. Nishimura, C.F. Zanelli, S.R. Valentini, Functional significance of eIF5A and its hypusine modification in eukaryotes, Amino Acids 38 (2010) 491–500.
[15] C.J. Decker, R. Parker, P-bodies and stress granules: possible roles in the control of translation and mRNA degradation, Cold Spring Harb. Perspect. Biol. 4 (2012) a012286.

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