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Current Opinion in Genetics & Development

Crosstalks between translation and metabolism in cancer

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Albeit cancer patients' heterogeneity, all tumor cells have alterations of both metabolism and translation. The simplest explanation for this common feature is that several oncogenes coordinate a translational and metabolic reprogramming that is necessary for tumor cells to thrive. Overall, at least three oncogenic pathways, namely c-Myc, RAS and PI3K-mTOR, are known to affect both translation and metabolism by stimulating glycolysis and protein synthesis. The crosstalk between metabolite production and the translational machinery is, instead, less understood. What is known is that, on one side, translation initiation factors, such as eIF4E and eIF6, drive tumor growth and regulate metabolism through selective translation of nucleotide biosynthesis, glycolysis and fatty acid synthesis rate-limiting mRNAs, and on the other, that nutrient levels regulate the translational machinery by inducing full activity of translation factors. Therefore, translation and metabolism offer several therapeutic targets to be fully exploited in future studies.

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Current Opinion in Genetics & Development 2018, **48**:75–81

This review comes from a themed issue on **Cancer genomics**

Edited by **Fatima Gebauer-Hernandez** and **Omar Abdel-Wahib**

http://dx.doi.org/10.1016/j.gde.2017.10.011

Introduction

In cancer biology two facts are very evident: first, the presence of strong alterations in the ribosomal machinery, some of which being evident already at the morphological level. Indeed, the nucleolus, the site where ribosomes are produced, appears dramatically enlarged in some tumors where it may also be considered as a predictive sign of malignancy [1]; second, following on Warburg's seminal observations [2], it is established that, in order to support growth, tumor cells switch from a respiratory to a glycolytic phenotype.

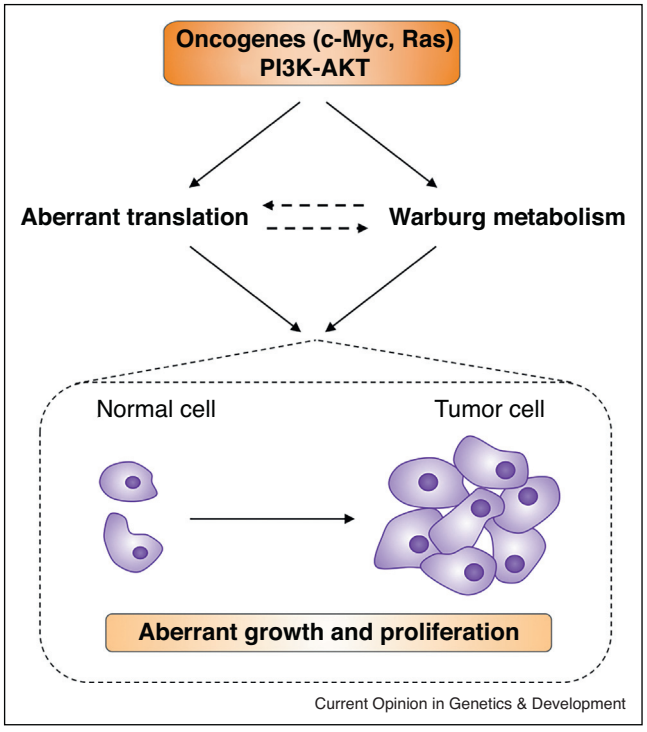
Obviously, the refinement of analytical technologies has entangled the original simplistic observations concerning the alterations of translation and metabolism. Nowadays, the literature describes translational [3] and metabolic twists [4] that are necessary for tumor cells to survive the complexity of their microenvironment. Multiple oncogenes function upstream of the metabolic and translational machineries and simultaneously coordinate the specific alterations required for malignancy. During cancer development translation and metabolism are intertwined by precise and extensive crosstalks (Figure 1).

Oncogenic pathways that co-regulate metabolism and translation: Myc, PI3K and RAS

One of the biggest challenges for cancer researchers is to unravel the metabolic features of tumor cells. A thorough discussion on this topic can be found in a recent review to which we address the reader [4]. New metabolic players, like acetate, have entered the stage and it has been shown that tumor cells can opportunistically rely on different metabolites to fulfill their extreme cellular growth needs [5]. This said, in general, cancer cells must sustain a strong glycolytic and fatty acid synthesis program, necessary for their growth, and at the same time collect, often in hypoxic environments, molecules necessary for fueling, for example glucose, glutamine and acetate. Occasionally, metabolic enzymes like IDH mutate and generate oncometabolites that are not found in normal cells [4]. Regarding translation, several translation factors are rate-limiting for tumor growth [6] and are attractive therapeutic targets [7]. The crucial question that we will briefly address in this review relates to those oncogenic pathways that co-regulate metabolism and translation.

The first oncogene to be found with a pleiotropic role on metabolism and translation is c-Myc. The Myc proto-oncogene is regulated post-transcriptionally (Figure 2a) and contributes to the genesis of human cancers by acting as a transcriptional modulator coordinating cell growth (Figure 2b). Myc induces the expression of a variety of metabolic enzymes involved in the glycolytic and fatty acid synthesis switches [8] and in nucleotide biosynthesis [9] but, most importantly, some of its transcriptional targets are rRNAs, tRNAs and several Initiation Factors, including eIF4E, eIF2α, eIF4A1 and eIF4G1 [10]; thus, Myc overexpression results in an amplification of the translation machinery itself. Genetic evidence shows that haploinsufficiency of ribosomal proteins and translation factors reduces Myc-induced oncogenesis [11],

Figure 1



Scheme showing the link between mRNA translation and metabolism in cancer. Activation of oncogenes (e.g., c-Myc, RAS) and/or aberrant activity of specific signaling pathways (e.g., PI3K-AKT) lead to changes in both the translatome and metabolic activity, in turn supporting tumorigenesis. Changes in the translation efficiency of specific mRNAs implicated in cellular metabolism may critically contribute to the Warburg effect, a typical feature observed in most cancer cells. On the other hand, since translation is the most energy-demanding process in the cell, metabolic changes can *per se* affect the translatome of cancer cells.

strengthening the importance of Myc-dependent augmentation of translation during tumorigenesis. Accordingly, downregulation of Myc leads to a higher resistance to age-related pathologies, such as cancer, and is accompanied by reduced translation and downmodulation of nutrient sensing pathways [12]. In summary, we can establish a strict correlation between the levels of c-Myc, the abundance of translational machinery components and the activation of anabolic pathways.

Translation and metabolism are also regulated by the PI3K signaling pathway, one of the most frequent pathways found amplified in tumor cells (Figure 3). Downstream of PI3K stands the nutrient sensor kinase mTOR. Activation of mTOR upon nutrient-rich conditions results in the amplification of the translational machinery and the glycolytic and fatty acid synthesis pathways [13] (Figure 3) by a mechanism that is different from the one elicited by Myc. mTORc1 (mTORcomplex1) is a protein kinase complex that activates translation at the level of initiation and elongation. The best-known substrates of mTORc1 are 4E-BP proteins. When dephosphorylated, 4E-BPs bind to eIF4E impeding its recruitment to the eIF4F complex, while, when phosphorylated, 4E-BPs are detached from eIF4E in turn allowing eIF4F complex formation. Hence, 4E-BP phosphorylation unleashes the translational activity of the eIF4F complex [14]. Emerging evidence indicates that mTOR may concomitantly act as a controller of anabolic metabolism also by other means, for example by direct regulation of *de novo* purine and pyrimidine synthesis through different transcriptional and post-translational mechanisms and by promoting lipogenic gene expression through multiple inputs [15].

Tumor cells often present mutations in the RAS pathway. RAS mutations prevent the cellular response to mTOR inhibitors [16]. Similarly to the PI3K pathway, also the oncogenic RAS pathway converges simultaneously on both the translational and metabolic machineries inducing increased translation, glycolysis and fatty acid synthesis [17] (Figure 3). The molecular mechanism by which these effects occur are, however, still elusive. What is clear is that the effects on translation are partly driven through Mnk kinases [6] (Figure 3).

Other oncogenic pathways are likely to co-regulate translation and metabolism. Among these, the Hippo pathway is emerging [18].

Translation acts upstream of metabolism and exerts a feed-forward loop on cellular growth

The activity of translation factors is frequently rate-limiting for tumor formation. Initiation is commonly held as the rate-limiting step of translation and is regulated by several initiation factors which act downstream of signaling pathways [6]. Perhaps the puzzling thing is that initiation factors, in spite of being evolutionarily conserved and expressed in all cells, may regulate translation of specific mRNAs. The explanation for this phenomenon lies on their capability to preferentially stimulate translation of transcripts bearing specific nucleotide sequences. Sequences sensitive to activation of the mTOR-eIF4F axis have been well characterized and are generally found in mRNAs that are important for cell cycle progression and enzymatic processes. Among these sequences are complex 5′ UTR structures, that require the action of helicases to be unwound and melted for efficient ribosome scanning, the process by which a ribosome reaches the initiating codon [19] and specific cis-regulatory sequences, not necessarily complex or structured, which provide a special dependency on eIF4E, for example PRTEs [9]. In other cases translation initiation is regulated through a completely different mechanism: small translatable open reading frames not coding for functional proteins, which lie upstream of the main Open Reading Frame (uORFs), can act as functional barriers [20] which interfere with correct scanning of the downstream ORFs. Such inhibitory effects can be lost under specific stress