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Review

Post-transcriptional regulation of the mitochondrial H^+-ATP synthase: A key regulator of the metabolic phenotype in cancer☆

Imke M. Willers, José M. Cuezva *

Departamento de Biología Molecular, Centro de Biología Molecular Severo Ochoa, CSIC-UAM, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), ISCIII, Universidad Autónoma de Madrid, 28049 Madrid, Spain

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ABSTRACT

A distinctive metabolic trait of tumors is their enforced aerobic glycolysis. This phenotype was first reported by Otto Warburg, who suggested that the increased glucose consumption of cancer cells under aerobic conditions might result from an impaired bioenergetic activity of their mitochondria. A central player in defining the bioenergetic activity of the cell is the mitochondrial H^+-ATP synthase. The expression of its catalytic subunit β-F1-ATPase is tightly regulated at post-transcriptional levels during mammalian development and in the cell cycle. Moreover, the down-regulation of β-F1-ATPase is a hallmark of most human carcinomas. In this review we summarize our present understanding of the molecular mechanisms that participate in promoting the "abnormal" aerobic glycolysis of prevalent human carcinomas. The role of the ATPase Inhibitor Factor 1 (IF1) and of Ras-GAP SH3 binding protein 1 (G3BP1), controlling the activity of the H^+-ATP synthase and the translation of β-F1-ATPase mRNA respectively in cancer cells is emphasized. Furthermore, we underline the role of mitochondrial dysfunction as a pivotal player of tumorigenesis. This article is part of a Special Issue entitled: Bioenergetics of Cancer.

1. Introduction

The term cancer is used to define a set of heterogeneous diseases in which abnormal cells divide without control and are able to invade other tissues. The primary cause of cancer development was initially attributed to genetic mutations [1]. However, some properties of cancer cells cannot be explained only by mutations and it has been accepted that the tumor microenvironment [2] and other epigenetic events [3] contribute to cancer development and its behavior. A phenotypic trait of tumors is its peculiar aerobic glycolytic metabolism [4–7], a hallmark that has been recently added to other alterations acquired by cancer cells in their progression to malignancy [8]. The enforced aerobic glycolytic metabolism of tumors and cancer cells was first discovered by Otto Warburg many years ago [9,10]. Because the availability of oxygen was known to repress the cellular rates of glucose consumption (Pasteur effect) [11], Warburg suggested that the increased aerobic glycolysis observed in carcinomas should result from an impaired bioenergetic activity of mitochondria [9,10]. His hypothesis was heatedly debated [12–14] and mostly abandoned until the last decade of the previous century when radiation oncologists put back into stage Warburg's postulates [15–17].

Nowadays, the increased aerobic glycolysis of tumors is out of question and has been underlined by the widespread clinical application of tumor imaging by ^{18}F-2-deoxyglucose (FDG) positron emission tomography (PET), for the diagnosis, staging and follow-up of cancer patients [15,16]. The boost in aerobic glycolysis is a requirement for tumorigenesis because it ensures the provision of the building blocks and reducing power required for the biosynthesis of the macromolecules that are needed for proliferation [6,18,19]. It has been argued that some cancer cells growing *in vitro* depend on oxidative phosphorylation as the main energy provision pathway [20–22]. However, transcriptomic, proteomic and functional studies in prevalent human carcinomas indicate that an enhanced glycolysis and a repressed bioenergetic activity of mitochondria are required for tumor progression [23–29]. Moreover, other studies have demonstrated and summarized the metabolic, molecular and functional alterations of mitochondria in cancer cells [30–35].

Several mechanisms directly promoting glycolysis, the inhibition of mitochondrial function or both have been proposed aimed at explaining the Warburg phenotype of cancer cells and tumors [4,6,17,19,36–41]. Some authors suggest that the shift to a glycolytic phenotype results from adaptation to the hypoxic environment where the tumor grows. Others support that the aforementioned change is the result of mutations in oncogenes, tumor suppressors and proteins related to signal transduction pathways (myc, Akt, p53, HIF1-α, and

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* Corresponding author. Centro de Biología Molecular Severo Ochoa, Universidad Autónoma de Madrid, 28049 Madrid, Spain. Tel.: +34 91 196 4618; fax: +34 91 196 4420.
E-mail address: jmcuezva@cbm.uam.es (J.M. Cuezva).

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APC/C-Cdh1) that in turn promote changes in the expression of genes involved in cellular energetic metabolism [42–47]. The occurrence of mutations in mtDNA [48–51] and/or in nucleus-encoded genes related with the metabolic and bioenergetic function of the organelle [52–54] has been suggested to be responsible for the metabolic shift experienced by cancer cells. More recently, and because the cell division cycle is tightly constraint to aerobic glycolysis [55,56], the glycolytic phenotype of cancer has been ascribed to the inevitable metabolic reprogramming experienced by the cells as a result of the onset of cellular proliferation [4,6,19].

In this review, we will stress the relevance of mitochondrial dysfunction as a central player of tumorigenesis. We will emphasize the mechanisms that participate in controlling the content and activity of the H^+-ATP synthase, which is a bottleneck component of oxidative phosphorylation [57,58] and one of the confirmed targets of the altered bioenergetic phenotype of human [19,59] and rat [60] carcinomas. Other aspects of the energetic metabolism of cancer have been recently summarized elsewhere [4,18,19,40].

2. Localization of the mRNAs of oxidative phosphorylation and the biogenesis of mitochondria

The bioenergetic phenotype of mammalian cells is adjusted upon changes in environmental and/or physiological conditions by regulating the activity of its mitochondria [41,61]. Regulation of mitochondrial biogenesis is mainly exerted at the level of transcription in the nucleus and by replication/transcription in the mitochondrial genome [62]. Additionally, mechanisms that control the localization [63–65] and translation [60,66,67] of nucleus-encoded mRNAs of mitochondria contribute to define the bioenergetic phenotype of the cell.

Remarkably, the sorting of nucleus-encoded mRNAs to the vicinity of mitochondria is a conserved feature in both yeast and mammalian cells [63,68]. RNA sorting affects the mRNAs that encode core components of mitochondrial complexes [64,69,70] and involves the cytoskeleton and *cis*-acting elements placed in the 3′-untranslated region (3′UTR) of the mRNAs [64,65,71,72]. The Pumilio (PUF) family of RNA binding proteins (RNABPs) binds the 3′UTRs and modulates mRNA expression in a wide variety of eukaryotic species [73]. Puf-associated mRNAs display conserved binding sites and usually fall into the same functionally annotated pathway [74–76]. In this regard, Puf3p specifically associates with 256 mRNAs in *S. cerevisiae*, 90% of which are nucleus-encoded mitochondrial proteins highly enriched in mitochondria-bound polysomes [75,77]. Consistently, yeast strains over-expressing Puf3p exhibit respiratory dysfunction, abnormal mitochondrial morphology and motility [75,78]. A second class of 224 mitochondria-associated transcripts that lack Puf-binding sites and whose expression and localization are not affected by PUF3 deletion has been described [77], suggesting the existence of at least two pathways for mRNA sorting to mitochondria.

The subcellular localization and translation of the mRNA encoding the catalytic subunit of the mitochondrial H^+-ATP synthase (β-F1-ATPase) has been studied both in yeast and in rat liver cells [63,66,69,79,80]. In yeast, β-F1-ATPase mRNA (ATP2) is preferentially sorted to the vicinity of mitochondria by the 3′UTR [71,79,80]. Deletion of the 3′UTR in the ATP2 gene leads to deficient protein import and reduced ATP synthesis, mtDNA depletion and respiratory dysfunction [79,80]. Interestingly, ATP2 mRNA was not found as a Puf3p target and belongs to the aforementioned class of Puf3-independent mitochondria-localized mRNAs for which the *trans*-acting factors remain to be identified [75,77]. In rat hepatocytes, β-F1-ATPase mRNA (β-mRNA) is present in a large ~150 nm ribonucleoprotein (β-RNP) complex preferentially associated to the outer mitochondrial membrane [63,69] that contains components of the translational machinery [81]. The assembly and appropriate subcellular localization of β-RNP requires two distal *cis*-acting elements, one placed in the open reading frame (ORF) and the other in the 3′UTR [82], and a common set of *trans*-acting proteins [82]. Recently, similar findings have been obtained for the yeast β-mRNA [71], offering a possible mechanistic explanation for a co-translational import process of the β-F1-ATPase precursor into mitochondria, although post-translational import of the precursor protein has been documented to operate in *in vitro* systems [83].

Fig. 1 offers schematic illustrations of two putative pathways by which the RNP containing β-mRNA (β-RNP) could be sorted throughout microtubules to the mitochondrial periphery [63]. The β-mRNA interacts with shuttling RNA binding proteins [84] that deliver their cargo by specific interactions with kinesin and dynein motor proteins. Translation of the mRNA could occur in the tracking β-RNP up to the sequence in the ORF which acts as a translational repressor (Fig. 1A) [82]. Anchoring the β-RNP to the mitochondrial membrane releases the repressor allowing co-translational import of the encoded protein [85]. The finding of a translational machinery in rat liver β-RNPs [81] and the localization-dependent translation of yeast β-mRNA support this pathway [71]. Alternatively, the β-RNP might be sorted in a translation repressed state until it reaches the mitochondrial membrane (Fig. 1B) by the interaction of a repressor with β-mRNA that impedes the recruitment of the translational machinery until the β-RNP is anchored to mitochondria.

3. The “altered” bioenergetic phenotype of human tumors

The finding of an alteration in the expression of the H^+-ATP synthase in rat [60] and many different human [24,27,28,86] carcinomas concurrent with the induction of glycolytic markers, strongly supported the original Warburg's hypothesis [59,87]. This proteomic feature was defined as the “bioenergetic signature of cancer” [4,24] and has been largely confirmed and extended to different carcinomas [26,88–92] (see [4] for a recent review). More recently, we have functionally supported the relevance of Warburg's postulates after the demonstration that the rates of glucose capture assessed by FDG-PET imaging inversely correlate with the bioenergetic signature in lung carcinomas [17]. Moreover, by the generation of HCT116 colon cancer cell lines expressing different levels of β-F1-ATPase, to assess the contribution of mitochondrial bioenergetics in cancer progression [41], we have demonstrated that the activity of oxidative phosphorylation defines the rate of glucose utilization by aerobic glycolysis [41].

Quantitative assays, using high-affinity monoclonal antibodies against proteins of the “bioenergetic signature” of the cell [93] have revealed an unanticipated finding: tumors from different tissues and/or histological types have the same proteomic signature of energetic metabolism (β-F1-ATPase/GAPDH ratio), indicating that cancer abolishes the tissue-specific differences in the bioenergetic phenotype of the cell [93]. In other words, energetic metabolism represents an additional hallmark of the phenotype of the cancer cell [6,8] and a promising target for the treatment of diverse neoplasias [4,93].

4. Repression of β-F1-ATPase expression in development and in cancer

The establishment of the bioenergetic function of mitochondria in the mammalian liver occurs soon after birth [94]. In this process, pre-existing fetal mitochondria are transformed into functional organelles [94] by concerted transcriptional and post-transcriptional regulation of the nuclear and mitochondrial genomes [95–98]. Regarding post-transcriptional regulation of the metabolic pathways that develop in liver mitochondria soon after birth, the prenatal storage of transcripts encoding enzymes of β-oxidation [99], the TCA cycle and its anaplerosis [99,100], ketone body metabolism [101] and the urea cycle [102,103] has been described. In particular, the mRNAs encoding nucleus (β-F1-ATPase) and mitochondrial (ATPase 6–8) subunits of the H^+-ATP synthase [95] and of adenine nucleotide translocase [104]

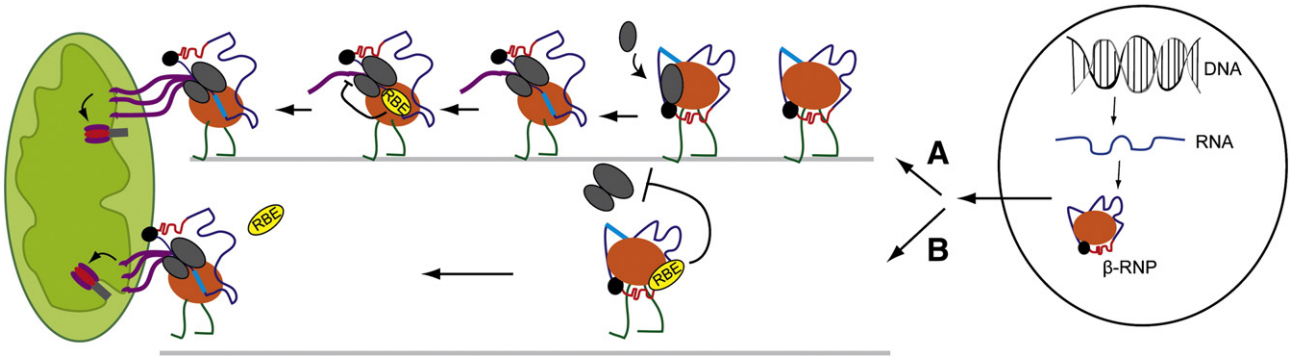

Fig. 1. Sorting the β-RNP to mitochondrial periphery. The nucleus-encoded β-mRNA (blue line) is transcribed in the nucleus and assembled into a large ribonucleoprotein complex (β-RNP, orange). The *cap*-structure (black circle) and 3′UTR (red) of the mRNA are shown. After nuclear export, the β-RNP migrates through microtubules (gray line) propelled by motor proteins (green legs) towards the mitochondrial vicinity. A, Translation of the mRNA could be initiated in the traveling β-RNP up to a *cis*-acting element (light blue) in the ORF, which is targeted by an RNA binding element (RBE) that acts as a translational repressor. The small and large ribosomal subunits are depicted as gray ellipses. When the β-RNP is anchored to the mitochondrial membrane the pre-sequence of the precursor protein (purple) is recognized by the import machinery, the repressor is released and translation proceeds concurrent with protein import. B, Translation of β-mRNA is impeded in the migrating β-RNP until it reaches the mitochondria by the inhibitory action of RBE.

which are required for the development of oxidative phosphorylation are also stored in the fetal liver. The accumulation of the former two transcripts is due to an increase in their stability during fetal development [95,97]. However, these mRNAs are maintained in a silenced/repressed state until the time of birth, when they become preferential substrates of their translational machineries [66,95,96,98] to trigger the functional differentiation of the organelle [94]. The bioenergetic coupling of the neonatal mitochondria also requires the intra-mitochondrial accumulation of adenine nucleotides [94] by ATP-Mg/Pi mitochondrial transporters (SCaMCs) [105,106], contributing to minimize the high H^+-leak of the fetal organelle [107,108].

A conserved translational repression mechanism for regulating the expression of β-F1-ATPase in fetal rat liver [66] and in rat hepatomas [60] has been documented suggesting that it might contribute to the altered bioenergetic phenotype observed in cancer cells [59,60,87]. Remarkably, the inhibition of mitochondrial biogenesis observed in As30D and FAO hepatomas occurred, as in the case of fetal hepatocytes [95,97], in a situation of a concurrent accumulation of oxidative phosphorylation transcripts mediated by an increase in their stability [60]. The repression of β-mRNA translation in fetal hepatocytes and in hepatomas [60] was demonstrated by various approaches [81,95,96] including the specific repression of β-mRNA translation in *in vitro* assays and the recapitulation of such inhibition on chimeras that contained the 3′UTR of the transcript [60,66].

Mechanistically, translational regulation could be explained by differences in the affinity of the mRNA to the translational machinery, as well as by the action of regulatory proteins and miRNAs that bind sequence elements within the mRNA for controlling its translation [66,109–112]. In this regard, we have described that the 3′UTR of rat β-mRNA is essential for translation of the transcript due to its ability to interact with components of the translational machinery [66]. The activity of the 3′UTR in translation is comparable to that previously described for the sites that promote internal initiation of translation (IRES) found in viral and other cellular RNAs [113,114]. That is, the 3′ UTR behaves as a translational enhancer both *in vitro* [66,115] and in transfected cells [116]. This activity of the 3′UTR is essential for conferring the appropriate bioenergetic phenotype to daughter cells during cellular proliferation because it drives the synthesis of β-F1-ATPase at the G2/M phase of the cycle [67] when *cap*-dependant translation is partially inhibited [117].

More recently, we have demonstrated that the 3′UTR of human β-mRNA is also required for efficient translation of the transcript [118]. Remarkably, we illustrated that the diminished expression of β-F1-ATPase in prevalent human carcinomas (lung, breast and colon) is exerted at post-transcriptional levels [118] and also accompanied by a specific translation masking event of the β-mRNA [118]. Contrary to the findings in rat [60], we observed that human breast and lung tumor extracts were unable to recapitulate the translational inhibitory effect on RNA chimeras that contained the 3′UTR of human β-mRNA [118]. These results indicate the existence of mechanistic differences among mammals for controlling the expression of the transcript and suggested that in human tissues, in addition to the 3′ UTR, other elements of the transcript are required for its appropriate translation masking in cancer.

5. *Trans*-acting factors that regulate β-F1-ATPase mRNA translation

The control of the translation of β-mRNA during development [66] and in hepatomas [60] involves specific proteins that bind the rat transcript. The binding of these proteins is regulated by the energy and *redox* state of the cell [119]. It is assumed that the binding of proteins to the 3′UTR of β-mRNA sterically hinder the initiation of translation [59,66]. With these findings in mind, we have pursued the molecular and functional characterization of the rat and human 3′UTR β-mRNA interacting proteins. By improving a MS2-based affinity chromatography procedure [84], we have identified that the AU-rich element-binding protein HuR interacts with the human 3′UTR of β-mRNA [120]. However, functional studies demonstrated that HuR plays an ancillary role in β-F1-ATPase expression in human cells [120].

As illustrated with RNA chimeras that contain the 3′UTR of rat β-mRNA, silencing of translation of the rat transcript is due to the specific binding of regulatory proteins to the β-mRNA [60,66]. However, the 3′UTR of human β-mRNA does not interact specifically with human breast and lung tumor proteins [118]. Moreover, chimeras containing the 3′UTR of human β-mRNA do not recapitulate translational inhibition by tumor extracts [118]. These findings forced us to search for the set of RNA binding proteins that interact with the full-length human β-mRNA by the MS2-based methodology [84]. We have identified nine RNA binding proteins that interact *in vitro* with β-mRNA [84]. These proteins are involved in transcription (DHX9, SFPQ, NONO, ILF3, NCL, and NPM), splicing (SFPQ and NONO), RNA export to the cytoplasm (DHX9, NCL, ILF3 and IMP1), RNA processing (SFPQ, NONO, NCL and NPM), RNA localization (NCL, NPM, SFPQ, NONO, G3BP1 and IMP1), RNA stability (IMP1 and G3BP1) and translation (ILF3, G3BP1, IMP1 and RL8) [84]. Furthermore, DHX9, NCL, NPM, ILF3, G3BP1 and IMP1 shuttle from the nucleus to the cytoplasm depending upon environmental conditions [121–124] and form part of different RNPs that are sorted throughout the cytoplasm by kinesin and dynein motor proteins [125,126].

We have studied the *in vivo* interaction of NPM1, IMP1 and G3BP1 with β-mRNA as well as the functional relevance of these proteins in controlling the expression of β-F1-ATPase [84]. We observed no

apparent *in vivo* interaction of NPM1 and IMP1 with β-mRNA [84]. However, the *in vivo* association of G3BP1 (Ras-GAP SH3 binding protein 1) with the human β-mRNA has been shown by various approaches [84]. Moreover, trimolecular fluorescence complementation assays indicate that G3BP1 interacts with the 3′UTR of β-mRNA [84] and this interaction specifically represses mRNA translation by preventing its recruitment into active polysomes [84]. Therefore, we suggest that binding of G3BP1 to the 3′UTR of the transcript might hinder the intrinsic translational enhancing activity of the 3′UTR [66,118], preventing either 43S recruitment to the mRNA or mRNA circularization [127] (Fig. 2).

G3BP1 is over-expressed in several tumors and cancer cell lines [128–130]. Consistent with its role in β-mRNA translation, the over-expression of G3BP1 in human cells inhibited the synthesis of β-F1-ATPase without affecting β-mRNA levels [84]. This mechanism of protein silencing by G3BP1 is at variance with the reported degradation of *c-myc* mRNA by the endoribonuclease activity of G3BP1 [124]. Therefore, our findings suggest that G3BP1 could play an essential role in the glycolytic switch that occurs in cellular transformation, contributing to define the bioenergetic phenotype of the cancer cell at the level of translation [84]. Since post-translational regulatory events influence the activity of G3BP1 [121,124,131,132] it is reasonable to suggest that these changes could also participate in mediating β-mRNA translation. The control of β-F1-ATPase expression in human cancer is mostly exerted at the level of translation [118]. Translational silencing is usually mediated by 3′UTR-mediated sequestration of the mRNA into RNPs [109,110] and/or by miRNA-mediated inhibition of translation [111,112]. Therefore, we cannot exclude the possibility that miRNAs could also play a role in the regulation of β-mRNA translation both in cancer and during development.

6. Other mechanism that affect the expression/activity of the H^+-ATP synthase in cancer

Recent findings indicate that promoter hypermethylation of the β-F1-ATPase gene (ATP5B) limits the expression of the protein in chronic myeloid leukemia cells, compromising the bioenergetic activity of mitochondria and contributing to adriamycine resistance [133].

Moreover, we have recently shown that the inhibitor peptide of the mitochondrial ATPase, called ATPase Inhibitory Factor 1 or IF1 [134–136] is up-regulated in human breast, colon and lung carcinomas when compared to paired normal tissues [137]. IF1 function has been mostly described as an inhibitor of the hydrolase activity of the H^+-ATP synthase when mitochondrial respiration is impaired [135,136,138]. In this situation the pH of the mitochondrial matrix becomes more acidic and IF1 becomes activated and capable of binding β-F1-ATPase to prevent a useless waste of energy [135,136,139]. More controversial is the role of IF1 as an inhibitor of the synthase activity [140–144]. Since the binding of IF1 to β-F1-ATPase is regulated by the energetic state of mitochondria [135,136] and cancer cells display high mitochondrial membrane potentials [145], in principle one would expect that IF1 cannot inhibit the H^+-ATP synthase in cancer. However, we have over-expressed IF1 and its pH-insensitive H49K mutant [135,146] and found that the expression of these peptides triggers a decrease in the activity of the H^+-ATP synthase, the up-regulation of aerobic glycolysis and a concurrent increase in the mitochondrial membrane potential, mimicking the effects of the H^+-ATP synthase inhibitor oligomycin [137]. Conversely, siRNA mediated silencing of IF1 in cells expressing high levels of IF1 triggers the down-regulation of aerobic glycolysis and an increase in the activity of the H^+-ATP synthase [137]. Therefore, it is reasonable to suggest that the binding of the H^+-ATP synthase by IF1 depends also on the mass-action ratio and, in situations of increased IF1 expression such as in certain tumors and cancer cells [137], the protein inhibits both the synthetic and hydrolytic activities depending upon the energetic state of mitochondria and yet uncharacterized post-transcriptional mechanisms that could regulate the binding activity of IF1 to the H^+-ATP synthase. In agreement with our proposal, recent findings indicate that deletion of IEX-1, a stress-inducible gene that apparently targets IF1 for degradation, results in the inhibition of the ATP synthase activity *in vivo* [144]. Therefore, the regulated expression of IF1 provides the cancer cell with an additional mechanism to regulate its energetic metabolism which has further consequences for tumor growth [137].

7. Energetic metabolism and cancer progression

A perturbation profiling approach, to characterize the metabolic changes that occur during transformation to a cancerous state, demonstrated that increased energy production by glycolysis in response to aberrant mitochondrial respiration accompanies the acquisition of the fully transformed state [147]. In apparent contrast, it has been reported that transformation of human mesenchymal stem cells promotes an increase in their dependency on oxidative phosphorylation [148]. However, when these transformed cells were implanted into nude mice an increase in glycolysis was observed accompanied by the down-regulation of genes of the TCA cycle [148]. Likewise, it has been reported that H-RasV12/E1A transformed cells show an activation of oxidative phosphorylation at an early stage of transformation [149]. However, as the tumorigenic potential of the cells increases an enhancement of glycolysis and a diminished activity of mitochondrial respiration are observed [149]. Consistent with these findings, we have recently demonstrated that for *in vivo* tumor progression the previous selection of cancer cells with a cellular

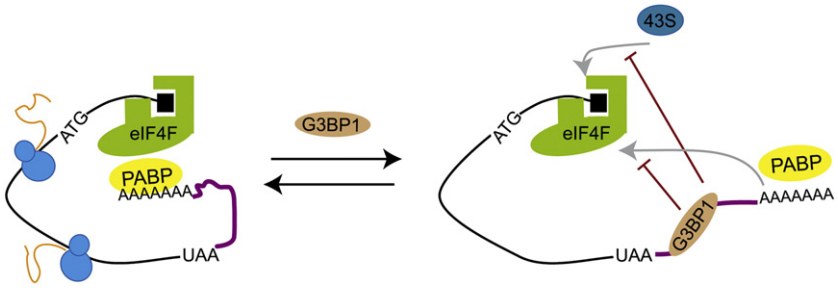

Fig. 2. Mechanism of translational repression of β-mRNA by binding of G3BP1 to the 3′UTR of the transcript. The mRNA is efficiently translated in a circular way by the 5′–3′ communication established by the interaction of the scaffolding eIF4F complex (green) and PABP (yellow). Binding of G3BP1 to the 3′UTR (purple) of β-mRNA (black) inhibits the translation of the transcript at the level of initiation. G3BP1 binding could mask the translational enhancing activity of the 3′UTR and prevent the interaction of the mRNA with the 43S ribosome and/or hinder mRNA circularization.

phenotype in which the bioenergetic activity of mitochondria is repressed is required [41]. The acquisition of this metabolic trait is not based on a permanent genetic change rather it represents a reversible feature that results from the metabolic adaptation of the cells to the *milieu* where tumor cells develop *in vivo* [41].

The relevance of the cellular environment in cancer progression is quite well delineated [150]. In this regard, it has been documented that nuclei from cancer cells when transplanted into the cytoplasm of enucleated non-tumorigenic cells (Fig. 3A) [151] or into enucleated frog or mice oocytes (Fig. 3B) [152–155] are epigenetically reprogrammed and develop as normal cells (Fig. 3A) or even into normal tadpoles or mice embryos (Fig. 3B). Contrary to the latter finding implantation of the same cancer cells into nude mice resulted in tumor formation (Fig. 3B). These findings suggest a relevant tumor suppressor role for the non-tumorigenic cytoplasms [151–155] within the context of little chromosomal aberrations of the transplanted cancer nuclei. In this regard, it has been demonstrated that pharmacological treatment of cancer cells with dichloracetate (DCA), that triggers a switch to a mitochondrial-dependent pathway of energy provision, promotes *in vivo* tumor regression [41,156–158]. Likewise, induction of mitochondrial oxidative phosphorylation inhibits cancer growth in mammals [159] and prevents tumorigenicity [160,161]. On the contrary, an impaired mitochondrial respiration promotes the generation of tumors [162]. Furthermore, mtDNA and membrane damage enhances tumor progression and metastasis [163–165]. Overall, these findings highlight the role of mitochondria in the epigenetic regulation of tumorigenesis and suggest that repression of oxidative phosphorylation is a prerequisite for tumor development [41].

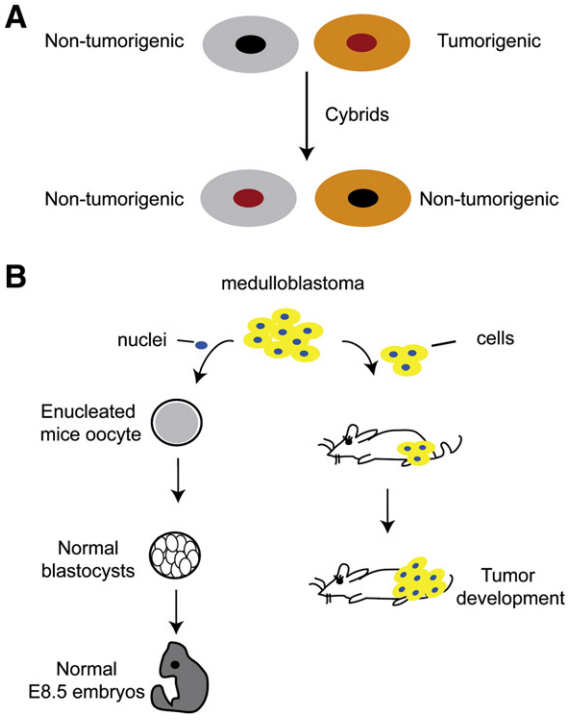

Fig. 3. The role of the cellular environment in cancer development. A, Hamster hybrid cells were derived by fusion of a non-tumorigenic (CHEF/18) nucleus (black) with an enucleated cytoplasm (orange) of a tumorigenic (CHEF/16) cell or *vice versa*. Fusions of a non-tumorigenic cytoplasm (gray) with a tumorigenic nucleus (red) suppress tumorigenicity [151]. B, Nuclei of medulloblastomas were transferred to enucleated mice oocytes and the blastocysts implanted into pseudo-pregnant female mice. The blastocysts derived normal mice embryos (E8.5) [152]. Implantation of the same medulloblastoma cells into nude mice developed tumors [152].

8. The tumor suppressor function of mitochondrial activity

Mitochondria, in addition to their essential role in the production of biological energy, also play a crucial role in the execution of cell death [166]. Cellular metabolism is molecularly and functionally integrated with cell death [167–169]. In this regard, it has been demonstrated that the execution of cell death requires an efficient oxidative phosphorylation system [170–173] and specifically the molecular components of the H^+-ATP synthase [174–177]. In fact, β-F1-ATPase expression is a predictive marker of the response to chemotherapy [92,169,178–180]. Consistently, we have demonstrated that the activity of the H^+-ATP synthase is required for the efficient execution of cell death in cells that depend on oxidative phosphorylation for provision of metabolic energy [169]. The role of the H^+-ATP synthase in the execution of cell death in the former cells is mediated by the generation of reactive oxygen species (ROS) after priming the cells with death-inducing agents [41,169], which in turn promote severe oxidative damage on cellular and mitochondrial proteins and contribute to effectively swamp the cell into death [41,169]. Mechanistically, cytotoxic drugs have been suggested to interfere mitochondrial function, most likely promoting the reverse functioning of the H^+-ATP synthase which results in mitochondrial hyperpolarization and the subsequent generation of ROS [41,169]. Otherwise, highly glycolytic cells with scarce or no dependence on oxidative phosphorylation for energy provision are resistant to death stimuli because they do not produce reactive oxygen species [169].

Recently, using HCT116-derived carcinoma cell lines expressing different levels of β-F1-ATPase, we have confirmed that it is the activity of oxidative phosphorylation that drives OXPHOS-geared cell death in response to the action of chemotherapy [41]. An abrogated mitochondrial activity contributes to a diminished potential for ROS signaling in response to 5-fluorouracil treatment [41]. In agreement with previous findings [41,178–180], a recent study has further demonstrated that the down-regulation of β-F1-ATPase expression in chronic myeloid leukemia leads to adriamycin resistance [133]. All these findings have led us to suggest that repression of the bioenergetic function of mitochondria is one of the strategies of the cancer cell in order to ensure its proliferation by diminishing the potential to execute ROS-mediated cell death [4].

However, it should be noted that ROS act as a double-edged sword in cell physiology, being the response of the cell determined by the intensity and the duration of the ROS signal [181]. As discussed earlier, an excessive ROS production overwhelming the cellular antioxidant defense contributes to the execution of cell death. However, if the ROS signal is transient and tolerated by the antioxidant defense ROS can signal to pathways that allow proliferation and survival as in the case of cellular adaptation to hypoxia [182] and the proliferation of cells when treated with oligomycin [41,183]. Indeed, inhibition of the H^+-ATP synthase by oligomycin treatment or by the over-expression of IF1 promotes an increase in mitochondrial membrane potential [137] which is the main cellular source of ROS production [169,184]. The finding that many cancer cells over-express IF1 [137] might explain the "abnormal" high mitochondrial membrane potential observed in these cells [145]. The over-expression of IF1 in cancer cells and tumors [137] might thus contribute to trigger a ROS signal compatible with the expression of genes involved in proliferation and survival and the perpetuation of the cancer cell [164,185]. However, it should be mentioned that in some cells mitochondrial membrane potential could also be maintained by reverse functioning of the H^+-ATP synthase at the expense of ATP generated by glycolysis. In this situation, inhibition of the H^+-ATP synthase will likely contribute to acceleration of cell death by mechanisms similar to that occurring in neurons [186] and activated macrophages [187]. In any case, cancer cells have developed mechanisms to overcome the perils of excessive ROS signaling as afforded by the over-expression of the uncoupling protein UCP2 [188] and by the preferential expression of the COX4-2 subunit of the mitochondrial respiratory chain which assures a more efficient electron transfer to O_2 [189].

9. Final remarks

Overall, three independent mechanisms can affect the bioenergetic activity of mitochondria specifically targeting the H^+-ATP synthase that favor an increase in aerobic glycolysis in the cancer cell. The first one, described in chronic myeloid leukemia, is exerted by limiting the amount of the mRNA encoding the catalytic β-F1-ATPase subunit by hypermethylation of the promoter of the *ATP5B* gene [133]. A second mechanism, documented in solid breast, lung and colon carcinomas is mediated by controlling the translation of β-F1-ATPase mRNA [118] by regulatory RNA binding proteins such as G3BP1 [84]. A third mechanism involves the inhibition of the activity of the H^+-ATP synthase by increasing the mitochondrial content of its natural inhibitor IF1 [137]. Irrespective of the mechanism(s) used our findings strongly support that the Warburg phenotype of cancer cells results from an impaired bioenergetic function of mitochondria that is regulated by metabolic/epigenetic means. Glycolysis is known to provide an advantageous phenotype that favors cellular proliferation and invasion [41,190]. Moreover, limiting the activity of the H^+-ATP synthase is also expected to contribute to tumor growth because oxidative phosphorylation is required for the efficient execution of cell death. Overall, these studies illustrate the need of further basic studies aimed at characterizing the complexity of the cellular response needed for mitochondrial biogenesis in order to understand the alterations of the mitochondrial proteome that specifically affect the content/activity of the H^+-ATP synthase in cancer.

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