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THE WARBURG EFFECT: A POSSIBLE ROLE OF CAP INDEPENDENT TRANSLATION

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Abstract:

Cancer is a complex multistep process involving tremendous changes at molecular and cellular properties of a cancerous cell. One of the main characteristics associated with the tumor cells include preferential use of glycolysis over oxidative phosphorylation to meet the high energy needs. This process is observed even in the presence of ample oxygen to fuel mitochondrial respiration and is considered to be the root cause of tumor growth and a potential hallmark of cancer. It has been found that tumor cells shows increased glycolytic capacity than normal cells and produce lactate rather than pyruvate in the process. During cancers, the expression levels of glycolytic enzymes are increased and different mechanisms like increased transcription or altered post-translational regulation has been proposed. Since hypoxia is a well known model in cancers and therefore role of cap-independent translation cannot be ignored. Furthermore, elucidation of the underlying reasons behind the increased expression of glycolytic enzymes in cancer will help us to better understand and cure cancer. This review focuses on the possible role of cap independent translation in mediating increased expression of glycolytic enzymes in cancers.

Key word: *Cancer, Warburg Effect, glycolytic enzymes, Cap independent translation, hypoxia*

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INTRODUCTION:

Glycolysis is the first and most important step in the metabolism of glucose and produce substrate for the oxidative phosphorylation. Energy demand of normal cells is compensated by oxidizing glucose completely via mitochondrial oxidative phosphorylation, as glycolysis produce only a small amount of energy. However, tumor cells frequently consume large amounts of glucose as compared to normal cells and secrete large amounts of lactate rather than oxidizing it completely. So, malignant cells use glycolysis preferentially over mitochondrial oxidative phosphorylation even in the presence of sufficient amount of oxygen [1]. In other words, the glycolytic capacity of cancerous cells is increased compared to normal cells. This shift in glucose metabolism is called the ''Warburg effect,'' and is considered to be the root cause of cancer formation and growth. Warburg effect has been shown to be the potential hallmark of cancer [2] [3] [4]. Earlier it was proposed that in cancer cells deviation toward the glycolytic process is due to a permanent impairment of oxidative metabolism and to compensate the energy needs, the glycolytic capacity is increased [4]. However, it was later on found that primary lymphocytes proliferate in the similar manner as cancer cells do and convert more than 90% of their glucose to lactate [5] [6] [7] [8]. Thus ruling out the possibility that increased glycolytic capacity is linked with the damaged oxidative metabolism or Warburg effect is unique to cancer cells. The belief was further strengthened, when it was found that the cancer cells posses absolutely fine oxidative metabolism system [9]. It should be noted here that the increased glycolytic rate in proliferating cells provides them different advantages. Firstly, high glycolytic rate allows cells to use more and more glucose to compensate energy demands. Although glycolysis produces low ATP number per glucose molecule, however if the glycolytic flux is high enough, ATP production can exceed that produced from oxidative phosphorylation [10] [4]. Such a phenomenon may be due to high rate of ATP production during glycolysis than to oxidative phosphorylation [11]. Secondly, during glycolysis a wide variety of intermediates are formed, which are needed for different biosynthetic pathways including glucose 6-phosphate for glycogen synthesis; dihydroxyacetone phosphate for triacylglyceride and phospholipid synthesis, pyruvate for alanine and malate synthesis, glycerol and citrate for lipids, nonessential amino acids, ribose sugars for nucleotides, and NADPH (through pentose phosphate pathway) to fatty acid synthesis [12]. In short, it can be stated that the Warburg effect benefits both the biosynthesis and bioenergetics.

Malignant cells are known to obtain their energy and other intermediated needs from the glycolysis. The increased glycolysis has been associated with the upregulation of the glycolytic enzymes [12]. The reason behind the upregulation of glycolytic enzymes in tumor cells has been linked with the increased transcription and altered post-translational regulation [13] [14]. However, it should be noted here that none of these processes account fully with the observed upregulation of the glycolytic enzymes. Little is known about the translational regulation like Cap-independent translation, mediated by Internal ribosome Entry Sites (IRES) of glycolytic enzymes during cancer. Cap-independent translation is an alternative strategy used by cells to maintain the translation rate of some mRNAs under stress conditions, like hypoxia (a well known phenomenon in cancer) [15]. So there is a possibility that the increased expression levels of glycolytic enzymes during cancer may be linked with the presence of cap-independent translation in such enzymes [16]. Earlier studies have documented presence of IRES elements in different cellular mRNAs and their essential roles in tumorigenesis (see table 1).

Table 1: Shows presence of IRES elements in different cellular mRNAs

Gene	Reference
AML1/Runx1 (Runt-related transcription factor 1/ acute myeloid leukemia 1 protein	[17]
Apaf-1 (apoptotic protease-activating factor-1)	[18]
Cat-1 (cationic amino acid transporter)	[19]
c-IAP1 (cellular inhibitor of apoptosis protein 1)	[20]
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cyp24a1 (Cytochrome P450 family 24 subfamily A member 1)	[21]
EGR (early growth response)	[22]
EGFR/ERBB1/HER1 (epidermal growth factor receptor)	[23]
Hox (homeobox)	[24]
Hif1α (hypoxia-inducible factor 1-alpha)	[25]
c-Jun	[26]
c-myc	[27] [28]
l-myc	[29]
n-myc	[30]
p16INK4a/CDKN2A	[31] [32]
p27	[33] [34] [35]
p53	[36] [37]
p120	[38]
SNAT2 (sodium-coupled neutral amino acid transporter)	[39]
c-src	[40]
SREBP-1a (sterol-regulatory-element-binding protein 1a)	[41]
VEGF (vascular endothelial growth factor)	[42] [43] [44]
XIAP (X-chromosome-linked inhibitor of apoptosis)	[45] [46]
Zeb2	[47]

In human cells, >90% of mRNAs utilizes cap-dependent mechanism for translation purposes. Such a process involves the binding of eukaryotic initiation factor 4F (eIF4F) complex (eIF4E, eIF4A, and eIF4G) to the 5'- m7GpppN cap on the mRNA. Later on 40S subunit is recruited to the 5′ end of the mRNA as a 43S complex (40S, eIF1, eIF2, eIF3, eIF5, eIF1A and Met-tRNAi). After the formation of initiation complex on the 5′ cap, the 40S subunit scans the mRNA (5′–3′ direction) until a start codon (AUG) is recognized. When 40S subunit meets the initial codon the larger subunit (60S) joins, forming an 80S ribosome and protein synthesis start [48] (see figure 1A). It should be noted here that the protein synthesis is an energy consuming process [49] and therefore during cellular stresses like hypoxia, cap-dependent translation is inhibited to conserve energy and nutrients [50]. To cope with the stress conditions, tumor cells utilize an alternate mode of translation namely cap-independent translation [16]. Such an alternate mode of translation, directly recruit the translation initiation complex to the IRES element (present in the 5'-UTR) of these mRNAs (see figure 1B) and is considered to be an efficient mode of translation, when cap-dependent protein synthesis is impaired [51]. It has been found that during stress condition like hypoxia, IRES elements remains active to carry cap independent translation [42] [52].

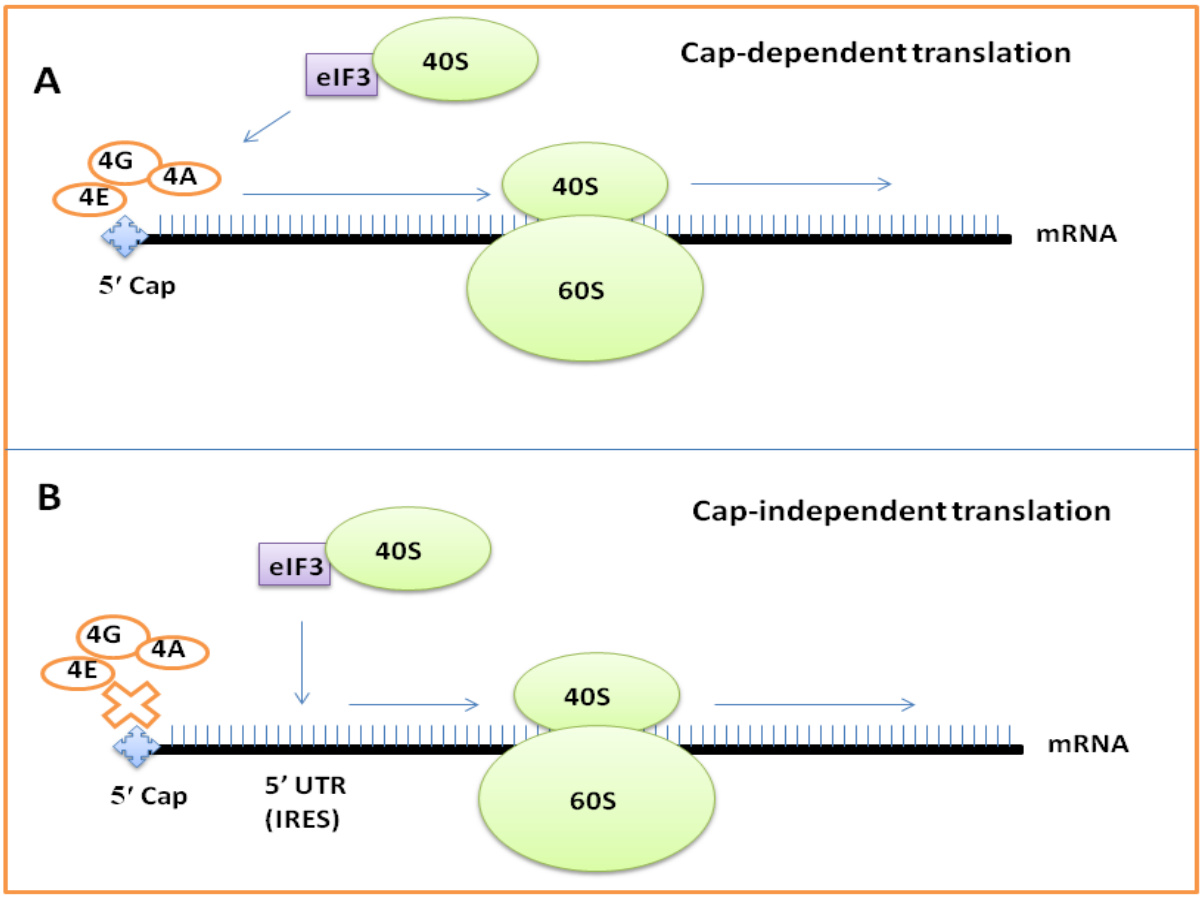

Figure 1: Shows protein translation in normal and stress conditions. A) Cap dependent translation: Eukaryotic initiation factor binds to the 5'- cap on the mRNA, followed by recruitment of 40S subunit to the 5′ end of the mRNA to form as a 43S complex. The 40S subunit scans the mRNA (5′–3′ direction) until a start codon (AUG) is recognized, flowed by the union of larger subunit (60S) to form forming an 80S ribosome and protein synthesis start. **B) Cap independent translation:** This alternate means of translation occurs under cellular stress and involves direct recruitment of the translation initiation complex to the IRES element (present in the 5'-UTR) of few mRNAs and is considered to be an efficient mode of translation.

Presence of long 5′ untranslated region (5′ UTR) in mRNAs is an indicative of the chances of cap-independent translation and we have found such long sequences in various glycolytic mRNAs. The molecular mechanism of cap-independent translation mediated by IRES is not fully known, however it is clear that IRES elements act differently. It should be kept in mind that for efficient initiation of translation most of the IRESs depend on canonical translation initiation factors and non-canonical IRES transacting factors (ITAFs). One such ITAF is polypyrimidine tract binding protein (PTB) at the IRES sequence rich in the pyrimidine regions and modulates the activity of the IRES elements. Also, binding of PTB to the pyrimidine sequences has been found to enhance during stress conditions like with hypoxia (24). Apart from the presence of long 5′ UTR sequences in the glycolytic mRNAs, we also found many PTB consensus sequence elements (CCUC) in the 5-UTRs of various glycolytic enzymes.

CONCLUSION:

Presence of long 5′ UTR in different glycolytic enzymes like Phosphofructo kinase (PFK1) (Gene ID: 5213), Hexokinase 2 (HK2) (Gene ID: 3099) and Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Gene ID: 2597) increases chances of cap-independent translation. As earlier discussed that in tumor cells expression level of glycolytic enzymes is increased and the reason behind such phenomenon can be attributed to cap-independent translation. There is a need to study the cap independent translation of glycolytic enzymes and activation of IRES activity in tumor cells. The information presented in the review will be critical in understanding the molecular mechanism behind the

increased glycolytic capacity of tumor cells and thus effective in devising anticancer therapy.

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