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Review Article

A walk through the process of translation: eIF4E in resected surgical margins in oral squamous cell carcinoma

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ABSTRACT

Head and neck squamous cell carcinoma (HNSCC) represent includes cancers of the oral cavity, larynx, and oropharynx. In relation to Oral squamous cell carcinoma (OSCC), a panel of markers such as p53, eIF4E, Cyclin D 1, MMP-9, and others has been evaluated histopathologically tumor-free/clear surgical margins. The present review summarizes the importance of one of the markers associated with protein translation. eIF4E has a significant role process of tumorigenesis and has the potential to target various molecules associated with Hallmarks of cancer. Lastly, relevant findings from studies done in relation to OSCC have been tabulated.

1. Introduction

While epigenetic modifications will alter the expression of potential oncogenes and tumor suppressor genes, genetic mutations primarily impact the activities of the related proteins. Significant research has been done on how these changes are regulated and how they work. However, little research has been done on the relationship between protein translation or the generation of nascent proteins from mRNAs and the development and spread of human malignancies.[1]

In general, the three main stages of protein translation are called initiation, extension and termination. The first stage in "cap-dependent translation" is symbolized by the Eukaryotic Initiation Factor 4F (eIF4F) complex's formation and binding to the mRNA 5'-cap. The DEAD-box helicase eIF4A, along with eIF4E and eIF4G, make up the heterotrimeric complex known as eIF4F. The way that eIF4E attaches to the 7-methylguanosine (7-m-GTP) cap is unusual.[2]

The eIF4E complex's limiting element that plays a crucial part in controlling translation initiation rates, is known as eIF4E.

On chromosome 4q23 is where eIF4E, or eukaryotic initiation factor 4E, is located. It is a 24-kD polypeptide that is both present in the eIF4E pre-initiation complex and in free form. It has a role in cellular mRNA delivery to the eIF4F complex to aid in ribosome loading and mRNA translation, and also in mRNA export.[3]

Translation is prevented under baseline conditions by eIF4E's continued association with 4E-binding proteins (4E-BPs). However, the 4E-BPs are released from eIF4E by phosphorylation of the 4E-BPs through signal transduction pathways that are controlled by growth hormones and dietary status.[4]

The 4E-BPs separate from eIF4E once it has been phosphorylated by PI3K or mTOR, allowing it to join the eIF4F (which also comprises eIF4A, eIF4G, and eIF4B) complex.

At many levels, eIF4E's accessibility is controlled. A 4E-binding protein (4E-BP) interaction has an inhibitory effect

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because it sequesters eIF4E by interacting with the same binding site that eIF4G recognizes, blocking the formation of the eIF4F complex.

2. Protein Translation in Eukaryotes

Initiation, extension, and termination are the three main phases of protein translation. The rate-limiting stage in translation is initiation, and the most crucial process is the development of the translation initiation complex (eIF4F). The components of eIF4F are eIF4A, eIF4E, and eIF4G.[5]

There are three subunits of eIF4F in mammals

1. eIF4E, a polypeptide of 24 kDa that directly engages the cap structure.
2. eIF4A, a 50 kDa polypeptide with RNA-dependent ATPase activity that works with another initiation factor to initiate transcription.
3. It is believed that eIF4B releases the mRNA 5' secondary structure.
4. eIF4G, a polypeptide with a high molecular weight that acts as a scaffold for the construction of the ribosomal translation.[6]

eIF4F interacts with polyA tail-binding protein (PABP) and assembles on the structure of 5′ m7G-capped RNA.

Eukaryotic translation Initiation Factor 4E (eIF4E) activity is necessary for translation to begin since it is the rate-limiting step in protein synthesis.

The cellular proteome is altered by an increase in eIF4E by preferentially up regulating the translation of transcripts with long and structured 5′ UTRs, many of which encode growth-promoting or cancer-associated proteins. This does not enhance the pace of translation overall. Because of this, eIF4E is regarded as a key factor in the multistep carcinogenesis process.[7]

Several processes, including phosphorylation, interaction with translational repressors, and transcription, affect the levels or activity of eIF4E.[8]

The other members of Cap Guided Initiation of Translation include – eIF4A, eIF4B and eIF4G.

DEAD-box helicase eIF4A is referred as the "Founding Member of the DEAD-box Family proteins"[9] and has been overexpressed in hepatocellular carcinoma[10] and melanoma.[11]

Since eIF4B (69.2 kDa) is said to function independently of the eIF4F complex and was determined to be not necessary for translation initiation, its involvement in the initiation of translation is not fully understood. According to a study done in 2014 by Harms u et al, the eIF4B translation initiation factor controls the eIF4A conformational cycle and boosts eIF4A activity[12] eIF4B has been aberrantly expressed in B-cell lymphoma[13] and in Leukemia.[14]

In order to carry out translation, mRNA, ribosomal subunits, and the cap-binding complex assemble around the scaffold protein eIF4G (175.5 kDa). eIF4G is a part of the eIF4F cap-binding complex, and through allosteric mechanisms, it improves eIF4E's association with the cap structure.[15] eIF4G is overexpressed in Breast cancer,[16] Cervix cancer,[17] Squamous cell lung carcinoma[18] and Nasopharyngeal carcinoma.[19]

Overexpression of the oncogenes eIF4E and eIF4G promotes cell transformation. According to studies, eIF4E, eIF4G, and eIF4A genes showed enhanced transcription or amplification in a variety of human malignancies.[20]

3. EIF4E-sensitive mRNA

Despite the fact that eIF4E functions as a general translation initiation factor, its overexpression only selectively promotes the translation of a selective mRNAs known as "eIF4E-sensitive" mRNAs, rather than dramatically promoting global protein synthesis.[21]

The 5'-untranslated regions (5'-UTRs) of mRNAs are classified into different groups by the classification and regression tree (CART) system. Class I mRNAs, also known as weak mRNAs, are thought to be poorly expressed under typical cellular conditions and feature long, structured 5'-UTRs.[22]

Long and intricately organized untranslated sections can be found at the 5' end of weak mRNAs and translationally suppressed mRNAs. Enzymes find it challenging to understand where transcription should start because of this extended region. In order to translate the message into a protein, initiation factor proteins are needed.

These fragile mRNAs or mRNAs that encode proteins crucial to the growth of cancer cells, demand cap-dependent translation, which calls for the engagement of the eIFs in the cell. mRNAs that code for proliferation-related and anti-apoptotic proteins are two examples of weak mRNAs.[23]

mRNAs with highly organized 5'UTRs translate less effectively due to their GC-rich region.

After being delivered to the cytoplasm, eIF4E-dependent mRNAs are referred to as weak mRNAs. Nuclear export of eIF4E-dependent mRNAs can increase when eIF4E is overexpressed because it can change the structure of the nuclear pore complex (NPC).[24]

Contrarily, strong mRNAs/housekeeping genes translate with considerably less cellular apparatus like eIFs and typically code for biologically vital proteins, such as those required for a cell's critical metabolic functions.

Strong mRNAs are only slightly impacted by changes in eIF4F complex formation, whereas weak mRNA translation is selectively and disproportionately accelerated when eIF4E is overexpressed or hyperactive.[23]

4. eIF4E and the Translation of Malignancy-associated Proteins

Increased translation of mRNAs with significant secondary structure in their 5' UTR is produced by overexpression of

eIF4E.

The growth-promoting gene products ornithine decarboxylase, cyclin D1, c-Myc, VEGF, and b-FGF-2 are among those whose mRNAs are less competitive.[25]

4.1. Ornithine decarboxylase-ODC

The first and most important step in the synthesis of polyamines is the ornithine decarboxylase-ODC. In addition to acting as antioxidants, polyamines are crucial for maintaining DNA structure and the DNA double strand break repair mechanism. ODC protein levels are 30 times higher in cells that overexpress eIF4E.

4.2. Cyclin D1

The D-type cyclins (D1, D2, and D3) control how mammalian cells advance through the G1 phase of the cell cycle. The start of the G1 phase is when these proteins are stimulated. The cyclin D1 mRNA is transported from the nucleus more effectively by eIF4E.In order to enter the S phase, cyclin D1 and polyamines are both necessary, and transformation has been associated with a rise in their expression.

4.3. C-Myc

The biological processes of cell development, proliferation, and apoptosis are all thought to be regulated by c-Myc. A wide variety of human cancers are affected by activated oncogenic c-Myc, which is also linked to aggressive tumors with a worse prognosis.

4.4. VEGF and b-FGF-2 (Vascular endothelial growth factor (VEGF and Fibroblast growth factor-2 (FGF-2))

Both VEGF and FGF-2 are important angiogenesis regulators and have been linked to accelerating tumor growth. In eIF4E-transfected cells, VEGF and FGF-2 mRNA are linked to the heavy polysomes, suggesting that enhanced expression is accomplished through their translational upregulation.

4.5. Hallmarks of cancer and eIF4E

The distinguishing characteristics serve as an organizational framework for explaining the complexity of neoplastic disease.

The six hallmarks of cancer, which are distinct and overlapping capacities that promote tumor growth and metastasis, continue to offer a strong framework for comprehending the biology of cancer.[26]

4.6. Sustaining proliferative signaling

When eIF4E is overexpressed, there is an increase in the translation of mRNAs that encode a variety of components that encourage proliferation without the need for outside stimuli. For example-IGF, Cyclin A, D1, D3, and E1.

4.7. Evading growth suppressors

The ability of NIH 3T3 cells overexpressing eIF4E to avoid contact inhibition and form foci was demonstrated. It has also been demonstrated to aid in the translation of a number of cyclins (A, D1, D3, E1), which can override signals that inhibit growth.

4.8. Enabling replicative immortality

The two fundamental obstacles to replicative immortality are aging and telomere shortening. Since its overexpression in primary human mammary epithelial cells (HMECs) is unable to reverse telomere-dependent crisis and mortality, eIF4E appears to be insufficient to maintain replicative immortality.

4.9. Resisting cell death

By boosting the translation of survival factors like BCL-XL, MCL-1, BIRC2, Survivin, and others, eIF4E encourages resistance to cancer cell death. Resistance to the generation of both mitochondrial- and endoplasmic reticulum-mediated apoptosis is promoted by up regulation via overexpression of eIF4E.

4.10. Inducing angiogenesis

Vascular endothelial growth factor A and fibroblast growth factor 2 are produced by cancer cells and are favorable for the proliferation of endothelial cells and the vascularization of the tumor. eIF4E regulates the translation of these factors.

4.11. Activating invasion and metastasis

The epithelial-mesenchymal transition (EMT) and invasion caused by transforming growth factor (TGF) require translational regulation via eIF4E overexpression, availability, and phosphorylation.

4.12. Emerging hallmarks and enabling characteristics

By increasing the synthesis of proteins involved in mitochondrial transport, the cellular energy system, eIF4E overexpression may have an impact on the dysregulation of cellular energetics, a new hallmark.

5. Results

An updated review of English language literature showed only few articles in which oral cavity was considered as a separate entity.(Table 1) Majority of the studies have been done in relation to head and neck squamous cell carcinoma in which oral cavity is just a subset.

Table 1: Tabulation of different studies using IHC technique for eIF4E in oral cavity

Author details/year	Aim of the study	Site vise distribution	eIF4E +	eIF4E -	Conclusion
Cherie-Ann O. Nathan et al, 1997[26]	To detect proto-oncogene eIF4E in surgical margins which may predict recurrence in head and neck cancer	Floor of mouth	2	1	eIF4E may be a potential prognostic predictors of HNSCC aggressiveness and has a possible role of in multistep tumorigenesis process.
		Base of tongue	2	0	
		Lip	1	1	
		Total	**5**	**2**	
Cherie-Ann O. Nathan et al, 1999[28]	To analysis surgical margins with the molecular marker eIF4E	Oral cavity	5	6	Elevated levels of eIF4E in tumor margins may identify patients who could benefit from additional therapy.
		Maxilla	0	2	
		Total	**5**	**8**	
Cherie-Ann O. Nathan et al, 2000[27]	To analysis eIF4E, p53 and MMP-9 in resected tumor free surgical margins	Oral cavity	6	7	eIF4E appears to be the most significant predictor of recurrence in HNSCC compared with other well-known factors associated with recurrence.
Jagtar Singh et al, 2015[29]	To assess prognostic significance of the molecular markers, p53 and eIF4E, in the histologically tumor free surgical margins of HNSCC	Floor of mouth	13	1	Expression of eIF4E appears to be a more marked prognosticator compared with p53.
		Tongue	2	1	
		Lips	4	1	
		Total	**19**	**3**	
Bindhu Joseph et al, 2019[30]	To evaluate the potential role of elF4E and p53 as predictive biomarkers in resected margins of oral cancers	Tongue	1	4	Overexpression of p53 and eIF4E in histologically negative margins of oral cancers may represent a subset of patients with more aggressive tumors who may benefit from early institution of adjuvant radiation.
		Floor of mouth	0	1	
		Gingivobuccal sulcus	1	10	
		Retromolar trigone	0	2	
		Buccal mucosa	8	13	
		Total	10	30	
Bindhu Joseph et al, 2019[30]	Evaluation of elF4E in histologically negative margins	Buccal mucosa	15	0	eIF4E has a potential to serve as a clinical biomarker of aggressive tumor behavior even prior to morphological changes.
		Gingivobuccal sulcus	8	0	
		Tongue	5	0	
		Hard Palate	1	0	
		Total	27	0	

6. Discussion

Following the physical examination of the lesion, it would be fruitful to understand the exact size and the extent of the lesion. This is made possible by using noninvasive imaging modalities such as computerized X-ray scan (CT scan), ultrasonography (US), magnetic resonance imaging (MRI), bone scan, positron emission tomography (using FDG, PSMA etc) followed by minimally invasive biopsy (needle aspirations) or invasive (surgical) biopsy coupled with histo-pathological examination to establish the identity and stage of the cancer.[31]

The properties of the malignant cells that dictate tumor behavior are conferred by genetic changes. The pathobiology of HNSCC cannot be properly predicted by a single molecular event, though. Recent advances in high-throughput assays enable the identification of changes in a wide range of gene targets. Finding HNSCC-specific genetic changes may be used as clonal molecular signatures to distinguish tumor cells from their healthy counterparts.

These molecular HNSCC signals could be used clinically as diagnostic, prognostic, and therapeutic biomarkers once they have been identified. This method can result in verified marker panels for HNSCC-specific candidate gene probes that are used for screening. Since genetic changes can place before cancer phenotypes manifest, they may be used as biomarkers for early detection.[32]

Saliva from HNSCC patients contains exfoliated cancer cells with genetic changes. As a result, it provides a possible non-invasive source to look at genetic changes in patients with HNSCC.[33]

Many studies are upcoming in relation to noninvasive methods to detect HNSCC at an early stage. Hypermethylation of NID-2 is highly specific for HNSCC. The high specificity is noted in salivary and serum samples, facilitating accurate and non-invasive prognostication of HNSCC.[34] Further studies are needed to be done in order to obtain non-invasive prognosticators for OSCC.

The primary treatment for oral cavity and lip squamous cell carcinoma is surgery. An important factor in predicting both the rate of recurrence and long-term patient survival is the surgical margin status.[35]

The ideas around recurrence are connected to the limitations of standard histologic examination, which calls for alternative techniques. Incorporating molecular data into the study will not only enable the discovery of the cancerized field that cannot be histologically identified but also provide a more sensitive and precise determination of the residual tumor cells.

The Royal College of Pathologists defines clear/adequate margins as those that are 5 mm or farther away from the invading tumor cells in their guidelines for the histological assessment of surgical margins.[36]

Similar to this, a distance of 1 to 5 mm is seen to indicate close margins, and less than 1 mm is thought to indicate involved or positive margins.[36]

Close and positive margins are viewed as inadequate, while clear margins are considered sufficient.[37] From a clinical perspective, patients with clear but near margins are frequently thought to have positive or insufficient margins.[38] Margin status is used to guide the use of adjuvant treatments such radiation therapy, systemic chemotherapy, and revision surgery as well as to predict the prognosis of the patient. After surgery, pathologists often check the edges of the resected tissues to see if tumor cells are present. Positive surgical margins frequently associated with an increased chance of locoregional tumor recurrence, thus surgeons may remove extra tissues until negative or 'oncologically safe' surgical margins are established.

After margin-free surgical resections, locoregional recurrence rates range between 16 and 20%,[39] and the 5-year survival rate is 64.8%,[40] indicating that the examination of margins is still the most reliable predictor of survival.

The unique three-dimensional anatomy of the oral cavity subsites makes precise interpretation of surgical margins a crucial and difficult task, making adequate surgical margins in lip and oral cavity SCC particularly tricky to obtain.

The surgeon's ocular examination and palpation are highly relied upon in current methods for determining the borders of tumors. Recent decades have seen little advancement in methods for determining the extent of resection, with intraoperative evaluation primarily relying on frozen section (FS) histopathologic analysis.[41] A more recent and efficient method for better identifying and defining margin status in conjunction with histopathology assessment is Molecular Surgical Margin (MSM) assessment.

Tumorigenesis is a multi-step process that propels a normal cell toward a malignant phenotype by accumulating early genetic events.[42]

Early signs of genomic instability in HNSCC, such as mutations and amplifications, point to loss of heterozygosity (LOH) and may predispose a cell to tumorigenicity even when it still exhibits histological normality.[43] As a result of these molecular changes, abnormal protein expression and function are produced, which affects cellular functions that control DNA repair, apoptosis, cell cycle progression, and proliferation.[44]

eIF4E has a crucial role in the malignant transformation, tumor progression and drug resistance in case of solid tumors.[45] The aberrant expression of several genes associated to cell cycle, vascular expansion, and cell survival can be caused by overexpression of eIF4E, which can specifically promote the translation of weak mRNA that is not expressed or is only faintly expressed in normal cells.[46] In comparison to normal tissue, tumor tissue expresses eIF4E at a much higher level. The expression of eIF4E increases as the tumour spreads. Additionally, eIF4E overexpression will raise the risk of cancer recurrence. As a result, the expression of eIF4E is a sign of tumor development, malignant transformation, metastasis, and a bad prognosis. Additionally, it is an accurate molecular marker for tumor detection.[46]

Numerous researches have been conducted in relation to head and neck, breast, and colon solid cancers. It's interesting to note that HNSCC has 100% expression of eIF4E. Clinically, overexpression of eIF4E is frequently seen in a range of human tumor types, and it is typically linked to disease progression, a higher risk of tumor recurrence, and tumor-related death.

In relation to head and neck squamous cell carcinoma, studies have analyzed the eIF4E marker using various techniques such as IHC, Western blot and PCR. Looking at subset of oral cavity various studies with relevant findings were evaluated and their findings are tabulated. (Table 1)

As early as (1997), Nathan et al conducted analysis to detect proto-oncogene eIF4E in surgical margins. Upon IHC analysis in subsets of oral cavity such as Floor of the mouth, Base of tongue and lip, overexpression of eIF4E was noted in 5 patients. Another study conducted by Nathan et al (1999) in 13 tumor free surgical margins revealed 5 margins for overexpression of eIF4E in surgical margins. These 5 patients with overexpression of eIF4E in surgical margin may benefit from additional therapy post-surgical resection of primary tumor.

In order to understand the molecular pathology of p53, MMP-9 and eIF4E in H/P tumor free surgical margins, Nathan et al. (2000) analyzed these 3 oncogenes and

concluded that eIF4E was positive in 6 surgically resected tumor free margins.

Comparative analysis conducted by Jagtar Singh et al., (2015) and Bindhu Joseph et al, (2019) have concluded that eIF4E appears to have more marked properties as a prognosticator compared to p53.

7. Conclusion

Immunodiagnostic demonstration of overexpression of eIF4E in histopathologically negative surgical margins may contribute to the early detection of residual disease or field change and direct management protocols; such patients would stand to benefit from early initiation of adjuvant therapy and mTOR inhibitors which improved loco-regional control of recurrences.[30]

Knowing the nature of eIF4E in HNSCC it would be beneficial to target this factor at various stages of tumor progression. No specific agent has been detected till date but various trials are ongoing and many agents are in different stages of clinical trials.

According to Sahu et al, oral cancers and cancers of head and neck are considered to be categorized under the heading of malignant solid tumors and hence numerous therapeutic agents are studied under the term of solid tumors.[47] Examples of these agents which target eIF4E include- LY2275796 (Phase I) and Ribavirin (Phase II).[46]

The drug target landscape is evolving, progressively moving away from conventional drug targets and toward more difficult "undruggable" targets. Proteins without an enzymatic activity, which make up around 80% of all human proteins, are frequently among these targets. PROTACs, PROteolysis-TArgeting Chimeras, are heterobifunctional small molecule compounds, which consists of a ligand for the target protein, a linker, and a ligand to recruit E3 ligase. It can solve the conundrum of the recognized issues with using targeted medications because it is a new approach to the research and development of novel small molecule drugs.[48] There are several agents which are being tested in different stages of clinical trials especially for solid tumors. Hopefully the near future will show some progress in this field and have a molecule specific for OSCC.

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None.

9. Conflict of Interest

None.

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