INTERNATIONAL JOURNAL OF RESEARCH CULTURE SOCIETY ISSN: 2456-6683 Volume - 5, Issue - 8, Aug - 2021
Monthly Peer-Reviewed, Refereed, Indexed Journal Scientific Journal Impact Factor: 5.743
Received on : 12/08/2021 Accepted on : 28/08/2021 Publication Date: 31/08/2021

Linking EGFR with epigenetic control by Long non coding RNA in Oral cancer

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Abstract: *Therapeutic out come and prognosis of oral cancer is highly correlated with EGFR expression. The advent of Long non coding RNAs (LncRNAs) as epigenetic controllers has opened new facets and area for furtherance of scientific search. This review deals in brief about the various information on epigenetic control of EGFR by LncRNAs in oral cancer. Glimpses prove that epigenetic information on EGFR control may prove to be vital in overcoming resistance to EGRF/TKI related therapy.*

Key Words: *Long non-coding RNA, EGFR, Oral Cancer, Epigenetic.*

1. INTRODUCTION:

The cancer menace in the oral region is a major concern to both the scientific community as well as the therapeutic sector. Ranked in the sixth position globally, this site for this cancer offers 50% overall 5 year survival to its patients (1). Often referred to its higher classification, head and neck cancer, oral cancer dominates with approximately contributing to 85 percent of all head and neck cancer (2). Worth mentioning is the fact that brain cancer does not fall under the head and neck cancer.

2. TYPES OF ORAL CANCER :

There are various ways cancer nomenclature are assigned eg origin eg. Lung , ovarian etc, tissue type carcinoma, sarcoma, etc. and various other methods. Since our mouth i.e. our oral cavity and its components, are composed of different types of cells, the cancer in this region is generally refered to cellular types. Briefly the various types are listed below

Squamous cell carcinoma: this is the most common of all subtypes and contribute to greater than 90percent of cancers of oral origin. Normally these cells are principally found lining the oral cavity and throat region (2). These are more commonly referred to as Head and neck squamous cell carcinomas (HNSCCs) (3).

Verrucous carcinoma: a lesser aggressive type and rare subtype of squamous cell carcinoma contributing to approximately five percent of cancer of oral origin. It is rather slow growing and metastasis (spead of the cancer to other parts) is rare or local (2).

Minor salivary gland carcinomas: this type of cancer, are situated in the numerous minor salivary glands that line the mouth and throat. This type of cancer has various forms depending on the orin site of the salivary gland. Thus this is further sub-divided into adenoid cystic carcinoma, mucoepidermoid carcinoma and polymorphous low-grade adenocarcinoma (2).

Lymphoma : these are cancers developed in the lymphnodes of immune components like the tonsils and other lymphatic nodes in the oral cavity (2).

3. HEAD AND NECK SQUAMOUS CELL CARCINOMAS (HNSCCS) :

As HNSCC is by far the most common of all the oral cancers, the rest of this review will discuss this type of cancer. Furthermore the incidence of this cancer is projected to rise further by 30 percent by 2030 (4).

HNSCC has two broad principle forms HPV-positive HNSCC and HPV-negative HNSCC. This division is to categorize if the malignancy has the involvement of Human papilloma virus or if it is independent of this viral component (5). To deal with HPV related oral malignancies various vaccines has evolved in the pharmaceutical market however HPV-negative HNSCC are strongly associated with smoking and other tobacco intake involving the oropharyngeal route (5).

Interestingly, over expression of a cellular growth factor known as Epidermal Growth Factor is strongly associated to HPV-negative HNSCC (6). It is estimated that 80-90 percent of HPV-negative HNSCC have over expression of this growth factor (7). Moreover such over expression adversely affects clinical outcome and five year survival of patients (8-11). Several therapeutic approaches targeting this molecular signature or its downstream components are being used to treat HPV-negative HNSCC (6).

4. EGFR :

Epidermal growth factor also known as Human Epidermal Growth Factor Receptor1 (HER1) is a 170kD glycoprotein situated on cell surface of epidermal cells. It was the first of its type to be discovered and is grouped under ErbB family of RTK (receptor tyrosine kinase) (6-7). Its altered expression, maybe due to mutation or overexpression, is found is various cancers including breast, lung skin etc. the receptor has a tyrosine kinase domain in the cytosolic end and is capable of down stream mediation of various signaling cascades involving pathways like PLCγ, ERK 1/2, p38 MAPK, PI3-K/Akt and more with the cell (12). EGFR is activated by several soluble ligands like epidermal growth factor (EGF), Transforming Growth factor Alpha (TGF-alpha), Heparin-binding EGF-like growth factor (HB-EGF), amphiregulin, betacellulin, epigen and epiregulin (13). EGFR can also get activated by homodimerization or heterodimerization with other epidermal growth factor receptors. The activation of the EGFR initiates its down stream signaling cascade which triggers survival, proliferative and migration entities in cells and more prominently in cancer cells (13).

There are limited success with various antibodies directed against EGFR or with the use of kinase inhibitors. Relapse and resistance are not rare and does pose to be a problem in the long term disease outcome (14). This has propelled scientist to look for other potential avenues to control or stem EGFR in oral malignancies.

5. EPIGENETICS :

In today's world proteomics information has received further boost with neo knowledge from other scientific spheres like epigenomics, transcriptomics and metabolomics (15). In the past few couple of decades, with advanced genome related analyses of the eukaryotic transcriptome, it has been brought to light that majority of the human DNA is transcribed, though only 2 % may have protein entity (16). This evidently projected a more complex collection of information than only those related to protein expression (16). An extensive transcription from antisense regions, overlapping sequences, and non-coding RNA (ncRNA) expression was found (16). lncRNAs circulating in blood have emerged as a new class of confident cancer biomarkers (17). The fact that these RNAs are protected from RNase makes them a stable biomarker and can be measured from body fluids such as whole blood, plasma, urine, gastric juice, and saliva (18). Various independent studies have demonstrated the feasibility of these RNAs for diagnosis of malignancies and possibly may also act as predictive and prognostic marker (17).

6. LONG NON CODING RNA :

Long non-coding RNA (LNCRNA) are typically more than 200 nucleotides long without any prospect of protein coding potentialities. Though previously considered non-functional, due their inability to transcribe any protein, these nucleotides are now proven modulators of cellular function (19). Their distribution being both in the nucleus and cytoplasm, exercise their regulation by epigenetic modification, modulation of transcriptional or translational activities of the cell (19).

Long non coding RNAs are named from their region of origin. Briefly they are as follows:
sense lncRNAs – originates from the sense strand and may overlap with protein encoding region
antisense lncRNA- originates from the anti sense strand of a protein encoding region,
bidirectional promoter lncRNAs – originates within 1 kb of promoters antisense to the protein-coding sequence,
intronic lncRNAs – originates from an intron region of agene encoding a specific protein
intergenic lncRNAs - originates between two genes coding for proteins
enhancer lncRNAs - originates from an enhancer region of a sequences encoding protein
Circular RNAs - typical circular structure with 3′- and 5′-ends that are covalently linked.

7. EGFR AND LNCRNA IN ORAL CANCER :

So far only three of the Long non coding RNAs has been experimentally linked with EGFR in oral cancer. They have been discussed at separate sections.

Long noncoding RNA EGFR-AS1

LncRNA EGFR-AS1 is an antisense long non-coding RNA arising from the antisense stand of the gene *EGFR* (20). It has been reported that it is positively correlated with EGFR expression thereby promoting tumorigenesis (20). Furthermore a study with this LncRNA revealed that SNP in exon 20 results in a single nucleotide variant within EGFR-AS1 which alters splicing of EGFR such that sensitivity of EGRF resistant strains becomes susceptible to anti-EGFR therapy (14).

Interestingly Rho-associated protein kinase 1 (ROCK I) is a serine threonine kinase associated with modulation of actin cytoskeleton. Actin cytoskeletons modulations are required for vital processes in cancer development mainly epithelial to mesenchymal transition (EMT) leading to cellular invasion and metastasis (21). Epigenetic control of ROCK1 is done by miR-145 as the miRNA sponges ROCk1 mRNA and prevents its translation

into its protein form (22). As it seems LncRNA EGFR-AS1 competes with mRNA of ROCK1 for binding with miR-145 thereby allowing the mRNA to get translated into protein and cancer progresses unabated.

In another study, in colorectal cancer, it was found that EGFR-AS1 may be involved in regulation of miR-133b/EGFR/STAT3 signalling cascade (23).

In a study with oral cancer a correlation with LincRNA EGFR was established with suggestive data predicting its anti-apoptosis potential in cancer cells (24). In another study with hepatocellular carcinoma, Lnc-EGFR was found to up-regulated T reg differentiation and down-regulated CTL activity thereby create immunosppressive environment for cancer progression and metastasis (25).

Long non-coding RNA ELDR (LINC01156)

Another long non-coding RNA, LncRNA ELDR, overexpression was found to increase PCNA expression and induce proliferation followed by colony formation in **Oral squamous cell carcinoma** (OSCC) where as deplesion of the said RNA revered the phenomenon cause by over expression (1). The investigators further found the said non coding RNA to partner with ILF3 (Interleukin Enhancer Binding Factor 3) and regulate the expression of Cyclin E1 along with the phosphorylation status of retinoblastoma (RB) protein. siRNA designed against LncRNA ELDR ameliorated the adverse effects of the LncRNA, thereby proving its importance and role in progression of oral cancer.

In humans LncRNA ELDR expression was found to be high in oral cancers and this LncRNA was situated downstream of EGFR gene on Chromosome 7 on the opposite stand making it an anti-sense LincRNA.

LINC00052

LINC00052, Long intergenic non-protein coding RNA, has been found to be upregulated in oral cancers. This LncRNA targets and sponges a miRNA miR-608, which is responsible for **sponging both mRNAs of EGFR** and Bcl-xL . Turning off of miRNA-608 by LINC00052 ensures two folded advantage for cancer, primarily release of the control of EGFR expression and attenuation of intrinsic mode of apoptosis induced by Bcl2 depletion (26).

Long Non-Coding RNA CRNDE

In another study Long Non-Coding RNA CRNDE revealed that it down regulates the expression of eukaryotic translation initiation factor 4A3 (eIF4A3), mucin 1 (MUC1), and phospho-EGFR thereby directly contributing to enhancement of cancer progression (27)

Long non-coding RNA KCNQ1

Long non-coding RNA KCNQ1, an anti sense long noncoding RNA, promotes esophageal squamous cell carcinoma by sponging miR-133b and activating the EGFR/PI3K/AKT pathway (28) .

8. CONCLUSION:

If one runs a TARNIC , a free online software by MD Anderson Cancer Center on non-coding RNA interaction analysis, trying to identify the interaction of LncRNAs with EGFR mRNA, we shall find as many as 244 entries. Though not all of these entries shall bear any substantial clinical relevance, however there is no doubt that many will. Direct study of EGFR and LncRNA in oral cancer is scanty, there is no doubt that these LncRNAs as epigenetic players contribute enormously to clinical outcome and therapeutic potentials.

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