International Journal for Research in Applied Sciences and Biotechnology

ISSN: 2349-8889
Volume-7, Issue-6 (November 2020)

www.ijrasb.com

https://doi.org/10.31033/ijrasb.7.6.14

Role of PI3K and EGFR in Oral Cancer Progression and Drug Resistance

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ABSTRACT

Oral cancer is one of the most common cancers in the world and India. Signaling molecules play an important role in Oral Squamous Cell Carcinoma (OSCC). PI3K and EGFR signaling molecules are known to be deregulation in most cancers including oral cancer. These are associated with oral cancer progression and drug resistance. PI3K and EGFR signalling molecules have been linked to the examined resistance developed to radiation and chemotherapy. Crucial signaling molecules that function downstream of the survival pathways, particularly at points where several of these pathways crosstalk that development oral cancer and drug resistance. The main focus of this review is to discuss the role and regulation of PI3K and EGFR in oral cancer drug resistance.

Keywords- Oral Squamous Cell Carcinoma, OSCC, Oral cancer, drug resistance, PI3K, EGFR.

I. INTRODUCTION

Oral cancer is a cancerous lesion present in the mouth and is the sixth most common human malignant diseases in the world [1]. 'Oral cancer' can be of various cellular origin, but it mainly occurs in the epithelial cells of oral mucosa. It is also known as oral squamous cell carcinoma (OSCC). OSCC is the most frequently existing cancer that in the oral cavity. Oral cancer comes under the 'head and neck squamous cell carcinoma (HNSCC) and most commonly occurs in the tongue, floor of the mouth, cheek, gingival, palate and lip. Recent statistics suggests, OSCC is the most common cancer in men whereas fifth common cancer in women, in Indian subcontinent [1]. Moreover highest mortality rates (77%) occurred in the developing countries. The frequency of OSCC is higher in under-developed countries [2, 3]. In India oral cancer comprises 30% of the total malignancies [4]. There are various types of OSCC, comprising more than 90% of all malignant oral cancer [5].

Chemoresistance is a vital problem for OSCC treatment as a results usually death. The development of drug resistance limits the effectiveness of chemical agents in OSCC [6]. Chemotherapy is an important treatment strategy next to radiotherapy and surgery for the OSCC treatment. Since, the efficacy of the treatment is long-established, accumulating data indicates, these cancer cells do not undertake apoptosis easily, many of these cells endure the selection pressure, survive and metastastasize leading tumor recurrence. [7, 8]. Many novel treatment approaches have been suggested for the management of oral cancer. The progression of chemoresistance phenotype limits to the usefulness of chemical agents in the patients having oral cancer [6].

The phosphoinositide 3-kinase (PI3K) pathway is an important signaling transduction cascade controlling the regulation of cell growth, cellular processes, cell proliferation, survival as well as cell migration. PI3Ks are controlled by different stimuli such as growth factors, hormones, inflammatory mediators, neurotransmitters, antigens and immunoglobulins [9, 10]. Epidermal growth factor receptor (EGFR) is a transmembrane cell-surface receptor. It is a tyrosine kinase (TK) receptor [11] that is commonly activated in epithelial tumors. PI3K and EGFR are involved in oral cancer and drug resistance. The aim of this article is to review the current carry of PI3K and EGFR signalling molecules in oral cancer progression and drug resistance.

II. CHEMO/DRUG-RESISTANCE IN ORAL CANCER

Commonly, the treatment methods for OSCC such as surgery, chemotherapy, radiotherapy and immunotherapy last for past 20-30 years. In spite of all these progress, to treat patients, no considerable improvement in the prognosis for OSCC has been documented. So initial detection of OSCC is important aspect to deal with oral cancer [12]. Recently, Cisplatin-based concurrent radio-chemotherapy is still the agreed level of quality for treating of cancers. Currently, many new methodologies have been suggested for the treatment of oral cancer, such as targeted therapy against EGFR and induction chemotherapy [13]. Intrinsic and acquired drug/ chemoresistance agents contribute to treatment failure in oral patients. Several factors are involved in chemoresistance. Several mechanisms initiate to chemoresistance in OSCC. As chemotherapeutic agents and the prevention of side effects have shown marked improvements, induction (neoadjuvant) chemotherapy

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has become available for HNSCC [14]. However, a huge number of HNSCC patients show poor response to combination chemotherapy; thus, drug resistance remains unresolved for head-and-neck oncologists [15]. Early stage cancers of the oral cavity are treated with surgery, radiotherapy and chemotherapy, while advanced stage cancers are normally treated with multi-modality regime, sequential, including surgical resection of primary tumors followed by radiotherapy with or without chemotherapy [16]. Chemoresistance is a well identified phenomenon in which cancer cells become tolerant/resistance to therapeutical/ pharmaceutical treatment. Efforts to increase the efficiency of radiotherapy, particularly in local advanced cancer, include concomitant chemo-radiotherapy (CT-RT) or altered fractionated radiotherapy [17]. Chemotherapy, cisplatin-based chemoradiation residue the standard for locoregionally advanced OSCC/ HNSCC [18]. Although advances in radiotherapy and surgery , that remain the standard treatment choice, the mortality frequency has remained mostly unchanged for decades, with a 5-year survival rate of about 50% [19].

III. PI3K SIGNALING PATHWAY IN ORAL CANCER AND DRUG RESISTANCE

PI3K signaling pathway is a key signaling transduction cascade controlling the regulation of cell growth, cellular processes, cell proliferation, survival as well as cell migration. PI3Ks are controlled by different stimuli such as growth factors, hormones, inflammatory mediators, neurotransmitters, antigens and immunoglobulins [9, 10]. Activation of receptor protein tyrosine kinases by various external stimuli leads to the generation of a second messenger called phosphatidylinositol 3,4,5 triphosphate (PIP3), which is generated from phosphatidylinositol 4,5-bisphosphate (PIP2) by activated PI3K. The PIP3 recruits Akt/PKB to the plasma membrane, where it is activated via phosphorylations [20]. Akt/mammalian target of rapamycin (mTOR)/ glycogen synthase kinase 3 beta are downstream molecules of phosphoinositide 3-kinase (PI3K) signaling pathway and involve in apoptosis, cell cycle and cell proliferation. Akt/PKB, as the downstream effectors of PI3K, is activated by Class 1A and Class 1B PI3K, and Class 1A and Class 1B PI3K are activated by tyrosine kinase and G-protein-coupled receptors, respectively [9]. Akt induces cell survival and suppresses apoptosis by various of stimuli. The phosphorylated Akt (p-Akt) is an activated type of Akt which plays a major role in various human cancers. Akt is a 52 kDa serine or threonine kinase with three isoforms: Akt-1, Akt-2, and Akt-3 [21]. Each isoform is comprised of three distinct regions: an N-terminal pleckstrin homology (PH) domain involved in lipid binding, a kinase domain and a C-terminal 'tail'. Many studies have identified that Akt may be a potential oncogene in humans and over-expression of phosphorylated Akt/PKB (p-Akt/PKB) has been identified in various cancer, including OSCC [22, 23]. Akt activation is linked with increased cancer cell invasion in various cancer, including OSCC cells [24]. Hence, p-Akt may be a good predictor of cancer aggressiveness. The important function of Akt is to inhibit cell death at multiple steps in the apoptosis signaling pathways. The PI3K/Akt/mTOR or PI3K/Akt/GSK3β pathway may be induced by various mechanisms, all of which more activation of the pathway in tumor cells. The activation of the PI3K/PKB pathway has an antiapoptotic effect. When activated, Akt either negatively or positively regulates the function of many different proteins in the cells [25]. Akt has been identified to phosphorylate Bad and caspase-9 which will lead to blokage of their involvement in transducing an apoptotic cascade [26, 27]. These have indicated that expression of Akt inhibits Bax conformational alter and mitochondrial translocation initiated by chemotherapeutic agents. One study informs that Akt may be phosphorylate Bax at Ser^{184} residue. It also has been proposed that PI3K/Akt pathway is linked with radioresistance both *in vivo* and *in vitro* in various cancers, including HNSCC [28]. In addition, Akt activates NFκB through phosphorylation of IκB, translocates to the nucleus and triggers transcription of Bcl-2 and Bcl-xL [29, 30]. Phosphatidylinositol 3-kinase (PI3K)/Akt cell signaling pathways are involved in cancer progression. Upregulation of the PI3K/Akt pathways in tumor cells provide the survival signals. P53 protein is post-translationally altered by a number of biological pathways including MAPK, PI3K-Akt, GSK3 etc and this leads to the alteration of the function of p53 [31].

IV. EGFR SIGNALLING PATHWAY IN ORAL CANCER AND DRUG RESISTANCE

EGFR is a transmembrane cell-surface receptor. It is a tyrosine kinase (TK) receptor [11] that is commonly activated in epithelial tumors. The corresponding mRNA is encoded from 28 exons spanning approximately 190,000 (nucleotides) on chromosome 7p12. It belongs to the ErbB family of receptor tyrosine kinases that also includes ErbB2 (HER-2 or Neu), ErbB3 (HER-3) and ErbB4 (HER-4) [32]. Overexpression of EGFR protein and mRNA is linked with poor prognosis, more tumor growth, metastasis and resistance to protein and chemotherapy [33]. EGFR plays a major role in various human malignancies. It has been identified, overexpressed in up to 90% of cases in OSCC [34]. EGFR activation is found to be linked with the malignant phenotype, blockage of apoptosis, increased proliferation, metastasis and resistance to radiochemotherapy, including OSCC [35]. The activated EGFR leads to the activation of several intracellular signaling pathways, including ERK and Stat-3 pathways [36]. ERK and Stat-3 are the important signaling molecules that come under EGFR [37]. Aberrant activation of the EGFR signaling axis has

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ISSN: 2349-8889
Volume-7, Issue-6 (November 2020)

https://doi.org/10.31033/ijrasb.7.6.14

been found to play a major role in HNSCC [38]. All these evidences suggest the possible role of EGFR for OSCC progression and chemoresistance. There are the several signaling molecules that lie downstream of EGFR [37]. EGFR activation has been documented in OSCC [34, 39]. EGFR is linked with inhibition of apoptosis, and resistance to radiation and chemotherapy in wide array of tumors, including OSCC [40, 41]. Similarly, aberrant induction of the EGFR signaling has been observed to fuel the progression of HNSCC [38].

V. SUMMARY AND CONCLUSION

Oral cancer is one of the most common cancers in the world and India. Cancer of oral cavity, mainly OSCC are highly prevalent in India. The scientific community involved in the areas of advanced cancer research is increasingly aware of the necessity to analyze the drug resistant mechanisms in different population and to come up with suitable treatment modalities and combination of drugs to treat the patients effectively. There are many ways these oral tumor cells develop resistance to drugs and evade signalling mechanism. Deregulation and activation of PI3K and EGFR signalling molecules are involved in oral cancer progression and drug resistance. Elevated expression of these signalling molecules are associated with many cancers progression, including OSCC and found resistance to radio-chemo-therapy. PI3K and EGFR are major contributor to the observed oral cancer progression and resistance to drug. These signalling molecules protect the oral cancer cells from most chemotherapy drugs, causing drug resistance. Since, this review contributes to the better understanding of oral sqamous cell tumors and drug resistance through PI3K and EGFR signalling molecules.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the Department of Biotechnology (DBT), New Delhi, Project No. BT/PR4624/MED/30/701/2012 and the CLS, CUJ is supported by DBT BUILDER Programme No. BT/PR9028/INF/22/193/2013.

AUTHORS' CONTRIBUTIONS

RM and MA reviewed the literature, drafted and finalized the manuscript and equal contributions

COMPETING INTERESTS

All authors declare that there are no competing interests and this work has not been published elsewhere.

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