

REVIEW

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Expression, regulation and targeting of receptor tyrosine kinases in esophageal squamous cell carcinoma

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Abstract

Esophageal cancer is one of the most common types of cancer, which is a leading cause of cancer-related death worldwide. Based on histological behavior, it is mainly of two types (i) Esophageal squamous cell carcinoma (ESCC), and (ii) esophageal adenocarcinoma (EAD or EAC). In astronomically immense majority of malignancies, receptor tyrosine kinases (RTKs) have been known to play a consequential role in cellular proliferation, migration, and metastasis of the cells. The post-translational modifications (PTMs) including phosphorylation of tyrosine (pY) residue of the tyrosine kinase (TK) domain have been exploited for treatment in different malignancies. Lung cancer where pY residues of EGFR have been exploited for treatment purpose in lung adenocarcinoma patients, but we do not have such kind of felicitously studied and catalogued data in ESCC patients. Thus, the goal of this review is to summarize the studies carried out on ESCC to explore the role of RTKs, tyrosine kinase inhibitors, and their pertinence and consequentiality for the treatment of ESCC patients.

Keywords: Esophageal adenocarcinoma, Esophageal squamous cell carcinoma, Tyrosine kinase receptor, Kinase activity, EGFR, VEGFR, AXL, PTK7, C-MET, ALK, And PDGFR

Background

Esophageal cancer (EC) is the 8th most mundane malignancy and 6th leading cause of death ecumenical. EC can be categorized into two subtypes predicated on histology: esophageal adenocarcinoma (EAC or EAD) and esophageal squamous cell carcinoma (ESCC) bearing different epidemiology and imperil factors [1]. ESCC and EAD are imposing together a major ecumenical health quandary. Both of these have peculiar geographic distribution as former is more prevalent in India, China, and Iran and later one is prevalent in North American, UK and Australia [2]. EAC arises from metaplastic Barrett's esophagus (BE) and related to gastro-esophageal reflux (GER) and obesity. The most important risk factors for ESCC are alcohol and tobacco. Difference between the two subtypes is not limited to epidemiology or risk factors but rather extends to treatment approaches [3].

The pathophysiology of different malignancies is driven in part by the growth factor receptors and growth factors mediated signaling. Among these signaling pathways, receptor tyrosine kinases (RTKs) are of special interest as these play an important role in the signaling of tumor cells, in different cellular processes like proliferation, migration, differentiation, cross-talk, metabolism and programmed cell death [4, 5].

RTKs are class of enzymes that lead to phosphorylation at the tyrosine (Y) residue of a protein using Adenosine triphosphate (ATP). The sequencing of the human genome led to identification of ~ 518 protein kinases [6]. Occurrence of TKs is restricted to metazoans only. Among 90 known TKs: 58 belong to RTKs and 32 to non-receptor tyrosine kinases (NRTKs). RTKs are activated by ligand binding to their extracellular domain. A number of proteomics studies have been carried out on ESCC [7–12], but only one study based on an in vivo labeling technique stable isotope labeling with amino acids in cell culture (SILAC) was focused on the phospho-tyrosine (pY) profiling using ESCC cell lines [13]. RTKs have been reported in a number of different malignancies including

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head and neck squamous cell carcinoma (HNSCC), oral squamous cell carcinoma (OSCC), lung adenocarcinoma, chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL).

Different tyrosine kinases, their expression, regulation and targeting in ESCC

A very first report for role of tyrosine phosphorylation was reported in 1989 by Ogawa et al. (1985), where they found an incrementation in levels of tyrosine phosphorylation in different cancers including EC utilizing monoclonal antibody against O-phosphotyrosine (PTYR) [14]. In recent years, a number of studies reported expression of different RTKs in ESCC (Fig. 1). The details about the architecture, domains, signal peptide and gene ontology based information has been provided for different tyrosine kinase receptors in Table 1. Additionally, a number of tyrosine kinases (TKs) have been assessed for their therapeutic value in ESCC either at in vitro or in vivo levels using tyrosine kinase inhibitors (TKIs). Here, we are presenting an update

of the studies focusing on the expression of RTKs or studies where RTKs were targeted in ESCC (Table 2).

RTKs alone or in combination with other treatments (e.g. chemotherapy or radiotherapy) have achieved breakthrough advances in the management of a number of hard-to-treat malignancies (e.g. melanoma, renal cell carcinoma or oncogene driven non-small cell lung cancer) [15, 16].

Epidermal growth factor receptor (EGFR) in ESCC

The epidermal growth factor receptor (EGFR or ERBB1) is a surface protein, a member of the ERBB growth factor receptor family, which initiates signal transduction by activation of a receptor-associated tyrosine kinase (TK); ERBB family also includes ERBB2 (Her2), ERBB3, and ERBB4. The members of the EGFR family have three regions, a transmembrane domain, an extracellular ligand binding region, and an intracellular region with TK activity [17]. These members have been reported to play an important role in tumor cell proliferation,

Table 1 Biological Characteristics of Some of the Receptor Tyrosine Kinases Reported in Esophageal Squamous Cell Carcinoma

Name of the receptor (HGNC Official Name)	Gene Symbol	Gene Locus	Ligand	Structural Feature of the Class		Primary Localization	Alternate Localization	Function
				Domain	Motif			
Epidermal growth factor receptor	EGFR	7p11.2	EGF	Three FU, one REC, one TM, and one TYK domain	One SP	Plasma Membrane	Endosome, Clathrin-coated vesicle, Cytoplasm	Stimulate proliferation of different cell types
Insulin like growth factor I receptor	IGF1R	15q26.3	IGF1/IGF2	One FU, one TM, one TYK, two REC, three FN3, and one TM domain	One SP	Plasma membrane		Regulation of cell growth and survival
MET proto-oncogene	MET	7q31	HGF	One TYK domain, One PSI, One SEMA, four IPT domains	One SP	Plasma Membrane	Cytoplasm	In biological processes like cellular proliferation, motility, migration, & invasion
Vascular endothelial growth factor receptor	FMS related tyrosine kinase 1	FLT1	13q12.3	VEGF	One SP	Plasma Membrane	Extracellular	Transmembrane receptor protein tyrosine kinase activity cell communication, signal transduction, and stimulate angiogenesis
	Kinase insert domain receptor	KDR	4q12	VEGF				
Platelet derived growth factor receptor	PDGFRA	4q12	PDGF	Three Ig LIKE, one IGC2, one TM, and one TYK domain	One SP	Plasma membrane	Extracellular	Growth, differentiation and cell death controls
	PDGFRB	5q32						
ALK	ALK	2p23.2-p23.1	Heparin (an activating ligand)	One TM, one TYK domain, one LDLA, & one MAM	One SP, two NPXY	Plasma membrane	Cell surface	Embryonic brain development, Important role in the genesis and differentiation of the nervous system
Protein tyrosine kinase 7	PTK7	6p21.1	No known ligand (Context-dependent signaling switch for the Wnt pathways Wnt)	Five IGC2, two Ig LIKE, a TM, & a TYK domain	One SP	Plasma Membrane	Cytoplasmic expression	Cell adhesion, migration, polarity, proliferation, actin cytoskeletal reorganization and apoptosis

FU Furin-like repeats, REC cheY-homologous receiver domain, TM Transmembrane domain, SP Signal peptide motif, NPXY Asn-Pro-X-Tyr, TYK Tyrosine kinase domain, LDLA LDL receptors, the class A, KRINGLE Kringle Domain, FZ Frizzled domain

Note: primary and secondary localization of the receptor tyrosine kinases are either based on the information annotated in the Human Protein reference Database (HPRD, <http://hprd.org>) or the human protein atlas (HPA, <https://www.proteinatlas.org>)

Table 2 Summary of the selected clinical experiences with different agents targeting Receptor Tyrosine Kinases in ESCC

Study	Type of the study	Number of patients	Indication	Primary outcomes
i. EGFR-targeting agents:				
Dutton et al. (2014)	Phase III	Total number: 450 patients ESCC: 106	Gefitinib for esophageal cancer progressing after chemotherapy	The use of gefitinib as a second-line treatment in esophageal cancer in unselected patients does not improve overall survival (for all patients as well as for both histology subgroups).
Iison et al. (2011)	Phase II	Total number: 30 patients ESCC: 13.	Erlotinib in patients with previously treated squamous cell and adenocarcinoma of the esophagus	Overall, erlotinib had limited activity in patients with esophageal cancer with some responses observed in ESCC.
Rodríguez et al. (2010)	Phase II	Total number: 173 ESCC: 19	Perioperative concurrent chemotherapy, gefitinib, and hyperfractionated radiation followed by maintenance gefitinib in locoregionally advanced esophagus and gastroesophageal junction cancer.	Gefitinib did not worsen CCRT toxicity; maintenance gefitinib proved difficult.
Zhai et al. (2013)	Phase II (pilot study)	18 patients	Concurrent erlotinib and radiotherapy for chemoradiotherapy-intolerant ESCC patients	For ESCC patients who cannot tolerate chemoradiotherapy, concurrent erlotinib and radiotherapy were tolerable and effective.
Huang et al. (2016)	Phase II	281 patients	Icotinib in Patients with Pretreated Advanced ESCC with EGFR overexpression or EGFR Gene Amplification	Overall, icotinib showed favorable activity in patients with advanced, previously treated ESCC with EGFR overexpression or amplification (in terms of response rate, overall survival and progression-free survival).
Janmrat et al. (2006)	Phase II	Total number: 36 patients ESCC: 9	Gefitinib in second-line treatment of advanced esophageal cancer patients	Overall, gefitinib has a modest activity in second-line treatment of advanced esophageal cancer. However, the patient outcome was significantly better in female patients and in patients demonstrating high EGFR expression or ESCC histology.
ii. VEGF/VEGFR-targeting agents:				
Janjigan et al. (2015)	Phase II	Total number: 35 patients ESCC: 5 patients	Sorafenib in chemotherapy-refractory esophageal carcinoma	For all patients: 8 week Kaplan-Meier estimated progression-free survival (PFS) was 61% (90% CI 45 to 73%). Median PFS was 3.6 months (95% CI 1.8 to 3.9 months), with median overall survival OS 9.7 months (95% CI 5.9 to 11.6 months).
Horgan et al. (2016)	Phase II	Total number: 61 patients ESCC: 12 patients	Adjuvant sunitinib following chemoradiotherapy and surgery for locally advanced esophageal cancer	For all patients: median survival was 26 months with a 2 and 3-year survival rate of 52% and 35%.

migration, angiogenesis and progression towards metastasis. Therefore, it has become an important therapeutic target in NSCLC, breast cancer and HNSCC.

EGFR overexpression and amplification was frequently observed in ESCC and correlated with advanced tumor stage and poor prognosis [18]. Among

some ESCC cases, not only EGFR but EGF ligand was also expressed proving the involvement of an autocrine loop [19–21].

Moreover, overexpression of HER2–4 has been reported to be present in 30–80% of the ESCC cases. Overexpression of EGFR was correlated with poor

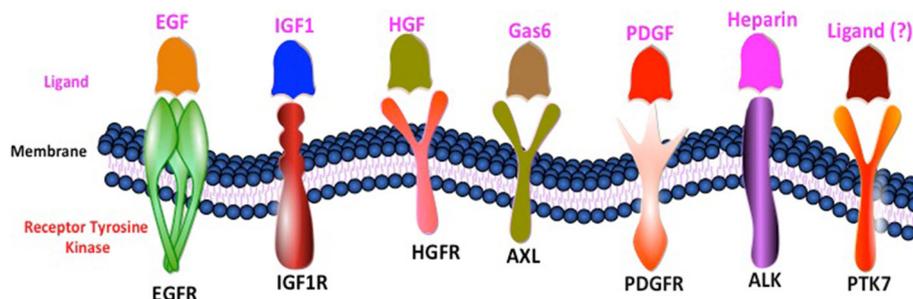


Fig. 1 Different Receptor Tyrosine Kinases with their respective ligands reported in Esophageal Squamous Cell Carcinoma

prognosis [22]. Overexpression of EGFR and its ligand EGF (epidermal growth factor) have been reported long back in ESCC cell lines (TE1, TE2 & TE8) [23]. Since then a lot of progress has been made in the field. The abundance of the EGFR was reported to be 20-fold higher in esophageal cancer as compared with normal esophageal mucosa [24].

Overexpression of EGFR was observed specifically in 68% of the ESCC patients and it was significantly correlated with clinical stage, tumor invasion, and poor survival outcome [25]. In a radioimmunoassay, a positive correlation was found between overexpression of EGFR and poor prognosis in primary ESCC tumors [26]. EGFR overexpression was further associated with lymph node metastasis as well [27].

The *EGFR* amplification has been associated with diseases outcome in ESCC. ESCC patients with low copy number observed to have longer survival as compared with patients with high copy number of *EGFR* gene. *EGFR* amplification has been associated with advanced pathological stage and tumor lymph node metastasis [28].

Downstream pathways activated by signaling through EGFR family members include the MAP kinase pathway and the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. The known ligands of the EGFR are EGF & transforming growth factor- α (TGF- α). Binding of a ligand to the EGFR causes it to dimerize either with itself or with another member of the ERBB family. Dimerization further leads to activation of TK, the downstream phosphorylation and activation of other effector signals [29]. In case of lung adenocarcinoma patients, somatic mutations present in the TK domain of *EGFR* responds well to TKIs targeting EGFR, but these TKI sensitive mutations in EGFR are very rare in ESCC patients [30, 31].

Small molecules or antibodies against EGFR used for ESCC The expression of EGFR in ESCC varies between 33.3–72.1% with a significant association with occurrence of metastasis, involvement of lymph node and survival [32, 33–35]. The immunohistochemical study revealed that EGFR staining was restricted to the plasma membrane of the malignant cells in 71.2% of ESCC cases. In contrast, for pEGFR immunoreactivity was nuclear [36].

TKIs are a class of oral, minuscule molecules that inhibit ATP binding within the TK domain, leading to consummate inhibition of EGFR autophosphorylation and signal transduction. A number of anti-EGFR antibodies or small molecules have been tested in different malignancies including ESCC. In this context, there is a strong rationale for investigation of biological agents targeting EGFR family in ESCC. Gefitinib and erlotinib are

EGFR-TKIs, which selectively block EGFR signaling through competitive reversible binding at intracellular EGFR-TK domain. EGFR has been studied extensively in relation to lung adenocarcinoma to target the mutant EGFR using erlotinib [37, 38]. TKIs of EGFR could be either reversible or irreversible. Among reversible TKIs are erlotinib, and gefitinib and the irreversible category includes afatinib, dacomitinib, and osimertinib.

Erlotinib and ESCC The trade name for Erlotinib is Tarceva. Erlotinib has been used to treat the NSCLC patients [37]. Erlotinib bind to the TK domain of EGFR in a reversible manner and blocks the EGFR pathways by competing with ATP of the EGFR-TK domain. There were two clinical trials where Erlotinib was used for treatment of ESCC patients [39, 40]. The results of those trials have been summarized in Table 2.

Gefitinib and ESCC Gefitinib (trade name Iressa) have been used for different types of solid malignancies. It inhibits EGFR *via* interruption of the EGFR signaling in the target cells. It is a reversible TKI of EGFR. Gefitinib was tested in ESCC TE8 cell line (with moderate type of tumor differentiation) [41]. In an *in vitro* study on ESCC cell lines (TE8, T.T and T.Tn), Gefitinib inhibited cellular proliferation in a dose-dependent manner, induced cell cycle arrest, inhibited ligand induced autophosphorylation of EGFR, downstream signaling pathways including Ras/Raf/MAPK and PI3K/Akt, and cell death [42].

Dutton and coworkers conducted a phase III study to evaluate gefitinib as a treatment for advanced esophageal cancer progressing on chemotherapy. Unfortunately, gefitinib was ineffective in proving overall survival (for both ESCC and EAD) [43]. There were two additional trials where gefitinib has been used for treatment of ESCC patients. The results of those have been summarized in Table 2 [43–45].

Gefitinib and erlotinib are reversible TKIs. These are reversible ATP mimetics that compete for ATP binding in the EGFR TK domain and competitively inhibit the binding of ATP to the EGFR TK domain [46]. This results in inhibition of EGFR phosphorylation (a post-translational modification) and downstream signaling. The irreversible EGFR TKIs are similarly ATP-mimetics, but those have the ability to bind covalently to cysteine residue at 797 position of EGFR [47].

Icotinib and ESCC Icotinib is a small-molecule EGFR TKI, which binds to the ATP binding pocket of EGFR protein, and interrupts downstream signaling in a reversible manner [48]. EGFR overexpression and response to icotinib was studied in ESCC. An overexpression of EGFR was observed in 49% of the cases and it was

correlated with clinical stage and lymph node metastasis significantly. Among a total of 62 ESCC patients treated with Icotinib, 17.6% were with high EGFR expression as compared with 0% patients with low to moderate expression of EGFR. Overall, the study suggests that overexpression of EGFR could be used in predicting the efficacy in icotinib treated ESCC patients [49].

Icotinib was clinically evaluated for the treatment of previously treated advanced ESCC patients who either had overexpression or amplification of EGFR in a single arm, multi-centric phase-II clinical trial [50]. The results have been summarized in Table 2.

Afatinib and ESCC Afatinib (trade name Gilotrif in US) is a dual tyrosine kinase inhibitor of EGFR & ERBB2. These have been extensively used in lung adenocarcinoma, [38] lung squamous cell lung cancer, [51] and HNSCC [52]. In the xenograft derived from ESCC cell line KYSE270, treatment with Afatinib lead to reduction in the tumor volume in a dose dependent manner [53]. Afatinib was also tested in a pre-clinical study on ESCC cell lines (HKESC-2 and EC-1) where the IC50 was observed in lower μM range. The cell death induced by Afatinib in ESCC cell lines was mediated by PARP-1 cleavage by the suicide proteases. There was no synergy observed between afatinib and the corner stone drug 5-fluorouracil (5-FU) and cisplatin [53]. From a clinical viewpoint, afatinib was not yet formally evaluated in ESCC, hence its use cannot be justified in this indication.

Lapatinib and ESCC Another TKI, Lapatinib is a reversible dual tyrosine kinase inhibitor of the EGFR and HER2 [54]. Lapatinib was tested in a panel of ESCC lines where it inhibited the Her2 phosphorylation; its amplification in HER2 overexpressing cells. Furthermore, Lapatinib inhibited proliferation of ESCC cells, induced cell death, and led to accumulation of EGFR and HER2 on the cell surface. In a combination of either trastuzumab or cetuximab with lapatinib, an increase in antibody-dependent cell-mediated cytotoxicity (ADCC) of 15–25%, and 15–30% was observed, respectively [55]. From a clinical standpoint, lapatinib was formally evaluated for esophageal/gastroesophageal/gastric adenocarcinoma with HER2 overexpression, but not in ESCC [56].

VEGFR (vascular endothelial growth factor receptor) in ESCC

Therapies directed against VEGF receptor (VEGFR) are the focus of major ongoing research in solid tumor malignancies. Folkman and others have provided compelling evidence linking tumor growth and metastasis with angiogenesis [57]. The ligand for VEGFRs is VEGF.

There are three subtypes of VEGFR including VEGFR1, VEGFR2, and VEGFR3. These are alternative splice variants of VEGFR, an outcome of alternative RNA splicing [58]. Among identified angiogenic factors, VEGF is the most potent and specific and has been identified as a crucial regulator for both normal and pathologic angiogenesis. VEGF produces a number of biologic effects, including endothelial cell mitogenesis, migration and induction of proteinases, leading to remodeling of the extracellular matrix, increased vascular permeability, and maintenance of survival for the newly formed blood vessels [59]. VEGF exerts its angiogenic effects by binding to several high-affinity transmembrane receptors, most notably VEGFR1 and VEGFR2. An overexpression of VEGFR1 and VEGFR2 has been reported in ESCC cell lines. Furthermore, treatment of these cell lines with anti-VEGFR1/2 antibodies inhibits proliferation of ESCC cells denotes validity of VEGFRs as the genuine targets in ESCC [60]. Additionally, varied expression of *VEGFR1*, *VEGFR2*, and *VEGFR3* at transcriptional level was observed in ESCC [61]. VEGFR1 & VEGFR2 were reported in > 42% & 40% of the ESCC cases, respectively with cytoplasmic expression. VEGFR1-expressing cases were found to be associated with poor nodal status. There was no association between clinicopathological factors & prognosis with VEGFR2 expression [62]. VEGFR3 expression was significantly higher in sera of ESCC patients as compared with healthy donors [63].

In esophageal cancer, VEGF was overexpressed in 30–60% of patients, with several studies demonstrating a correlation between high levels of VEGF expression, advanced stage, and poor survival in patients undergoing esophagectomy. VEGF expression level is a predictor of tumor differentiation, TNM stage, distant metastasis, and overall survival (OS) in resectable ESCC cases [64]. In ESCC, expression of VEGF was associated with angiogenesis and progression of the disease [65, 66]. VEGF-targeting agents were evaluated mainly in EAD. Examples of small molecule VEGF-TKIs evaluated in clinical studies with mixed histology populations include sorafenib and sunitinib.

Sorafenib One phase II study for sorafenib in chemotherapy-refractory esophageal carcinoma was carried out which incorporated both ESCC and EAD. Results for all patients suggested the ability of sorafenib to stabilize chemotherapy-refractory disease; however, these results were not stratified according to histology. The results of this clinical trial have been summarized in Table 2 [67].

Sunitinib Sunitinib targets VEGFRs, PDGFR- β , and c-Kit [68]. A phase II clinical study evaluated adjuvant sunitinib following chemoradiotherapy for locally advanced

esophageal cancer (both histologies). Results for all patients suggested that adjuvant sunitinib was poorly tolerated, with no signal of additional benefit over standard therapy. The results of the clinical trial has been summarized in Table-2 [69].

C-MET in ESCC

The MET proto-oncogene encode for protein c-MET, which belongs to RTK family. c-MET is also called as hepatocyte growth factor receptor (HGFR). It gets activated upon binding to its ligand hepatocyte growth factor (HGF). MET has been reported to overexpress in ESCC [70]. MET expression was observed in ~21% of the ESCC cases and interestingly it was correlated with PD-L1 (a ligand for PD1 receptor) expression [71].

MET is an emerging target and TK receptor for HGF [72]. MET had been reported in $\geq 50\%$ of the ESCC cases at mRNA and protein levels [73]. Amplification of *MET* oncogene was found in 4–10% of gastric cancer cases [74]. Activation of the MET oncogene leads to multiple downstream pathways that promote the cancer phenotype. The most common c-MET small molecule inhibitor evaluated in gastrointestinal cancers is tivantinib. The principal clinical experiences with c-MET inhibitors were with gastric/gastroesophageal/esophageal adenocarcinomas [75, 76]. On the other hand, there are no fully published clinical data about c-MET TKIs in ESCC till now.

AXL in ESCC

AXL is a receptor tyrosine kinase, which belongs to TYRO3/AXL/MER. Overexpression of AXL has been reported in large number of malignancies including lung, colorectal [77], liver, oral squamous cell carcinoma (OSCC) [54], cutaneous squamous cell carcinoma [78], breast [79], HNSCC [80], pancreatic [81], and EAD [82]. In ESCC, expression of AXL kinase was observed in 80% of the total ESCC cases and correlated with the progression of the diseases [83]. In an in vitro model of ESCC, cells were found to be preferentially sensitive to foretinib (a c-MET, AXL and vascular endothelial growth factor receptor inhibitor) than lapatinib (HER2 inhibitor). Interestingly, both the agents had synergistic effect together indicates a possibility to use them together in vivo for an effective option in ESCC patients [83]. In ESCC cell lines (KYSE70 and KYSE180), AXL was playing an important as it exerted resistance towards PI3K α via EGFR/PKC/mTOR pathway [84]. From a clinical perspective, none of the AXL inhibitors reached final phases of drug development in the indication of ESCC.

ALK in ESCC

Anaplastic Lymphoma Kinase (ALK) is also known as ALK tyrosine kinase receptor or CD246. Gene fusion

may lead to exchange between two genes of either genetic code or regulatory DNA sequences. The translated products of gene fusion have been proved to be very important in cancer research [85]. A protein can be product of gene fusion, which could give rise to it by joining parts of two different genes. Some of the classical gene fusion examples involving a kinase-coding gene are *EML4-ALK* in lung adenocarcinoma [86], *ALK-RET* in colorectal cancers [87], and *VCL-ALK* in renal cell carcinoma (RCC) [88]. Similar cases were observed in ESCC, where fusion protein TPM4-ALK was detected in two separate proteomics based studies [89–91]. There is a need to study these gene fusion events associated with ALK to define their exact function and significance in relation to ESCC in different populations. However, beyond the basic science findings, ALK inhibitors were not formally evaluated in the setting of ESCC and no recommendation can be made about the use of any of these agents.

Protein tyrosine kinase 7 in ESCC

Protein tyrosine kinase 7 (PTK7) is an orphan TK, it belongs to the category of pseudokinases as some of the key residues essential for catalytic activity of PTK7 are missing in its kinase domain [92]. PTK7 also known as colon carcinoma kinase-4 (CCK-4) [93]. Overexpression of PTK7 has been reported in a number of different malignancies including oral tongue squamous cell carcinoma (OTSCC) [94], colorectal [95], and intrahepatic cholangiocarcinoma [96]. PTK7 overexpression has been reported in ~60% of the total ESCC cases. Its overexpression was correlated with poor prognosis of ESCC [97]. PTK7 increases invasive behavior of ESCC cells via NF- κ B signaling when it is in catalytically defective form [98]. Furthermore, ESCC cell lines with higher expression of PTK7 have comparatively more refractive behaviors to radiation as compared with ESCC cells with low levels of PTK7 as evident with induction of apoptosis upon PTK7 knockdown in irradiated ESCC cells. The resistance to radiation in ESCC cells was regulated by PTK7 through NF- κ B (nuclear factor-kappa B) [99]. PTK7 can act as a co-receptor with other RTKs like VEGFR1 to regulate other signaling pathways [100]. Till now, none of the agents targeting PTK7 were approved for the management of ESCC.

Insulin-like growth Factor-1 receptor in ESCC

The insulin-like growth factor type 1 receptor (IGF-1R) is a member of the receptor tyrosine kinases (RTK) family [101]. IGFIR is a tyrosine kinase that was significantly higher in adenomatous polyps and carcinoma as compared with healthy controls, and a positive correlation was observed between serum

IGF1 and mucosal *IGF1R* mRNA expression in the polyps [102].

An improved sensitivity to radiation was found upon silencing IGF1R at in vitro and in vivo levels in ESCC cell lines [103]. Figitumumab (CP-751871, CP), an anti-IGF1R antibody (a human IgG2 monoclonal antibody, MAB) was screened in ESCC cell lines [104]. IGF1R and its ligands were found as overexpressed in ESCC as compared with normal epithelia [105, 106]. IGF1 contributes to resistant to chemotherapy agents used currently in clinic in ESCC and other cancers. Hence, there is a need of further investigations to estimate the exact role of IGF1R-IGF axis in ESCC [104]. There are established clinical development programs for IGF1R inhibitors among patients with gastric or gastro-intestinal adenocarcinoma [107], but little has been done (from the clinical perspective) in the indication of ESCC.

Platelet-derived growth factor receptor in ESCC

The platelet-derived growth factor receptor (PDGFR) is another member of RTK family [101]. PDGFR subtypes are PDGFR α , and PDGFR β . Varied expressions of PDGFR α , and PDGFR β have been reported in ESCC cells [61]. Expression of PDGFR α was studied in cancer-associated fibroblast derived from ESCC patients and observed as an essential factor in ESCC progression; and expression of PDGFR β was found to be associated with poorly differentiated tumors but not with prognosis [108]. Additionally, a downstream regulator of PDGFR stability small glutamine-rich tetratricopeptide repeat-containing protein alpha (SGTA) was upregulated in ESCC as compared with adjacent normal epithelia. An overexpression of SGTA was correlated with tumor grade. Additionally, an association between expression of SGTA and Ki-67 (a proliferation marker) was found suggesting role of SGTA in the proliferation of ESCC cells [109].

Perspective and future directions

Receptor tyrosine kinases play a very crucial role in the maintenance, growth and differentiation of cancer cells including EAD and ESCC. ESCC is a multifactorial disease, which remains a public health problem worldwide. Over the past decade, the treatment of ESCC has been evolving rapidly. In the past the performance of the systematic therapies in ESCC was disappointing. TKIs such as Erlotinib, and Afatinib led to a great success in treating lung adenocarcinoma patients. This gives a hope specially when a fair number of TKIs are in different phases of clinical trials and some are in pipeline for development.

Among many other challenges, malignancies treated with chemotherapy and/or radiotherapy develops

resistance to these treatments and become more aggressive and tends to have recurrence of the disease. Furthermore, blocking RTKs with one antibody or small molecule could trigger malignant cells to choose the alternative route for signaling and eventually that could lead to survival. This suggests the need for being vigilant of other signaling pathways, which could get activated as an alternative route after TKIs treatment.

Keeping these points in mind, more studies preferably involving an integration of multidimensional aspect of high-throughput genomics, transcriptomics, and proteomics profiling with biomarker-matched targeted therapy either alone or in combination with immunotherapy are required to overcome this deadly disease and for improvement both in the prognosis and survival of the ESCC patients. A thorough investigation is required to explore the co-expression of RTKs in ESCC as this phenomenon is dependent on the ligand binding. A well-designed study could lead to information about what combination of TKIs could be used for these kinds of tumors. Additionally, a clear and better understanding of the tumor pathophysiology, biology of ESCC and mechanism of action of minuscule molecules or anti-tyrosine kinase receptor antibodies is required.

Further, three-dimensional (3D) model of ESCC where co-culture combination of primary ESCC cells with microenvironment component could reveal which signaling pathway or active kinase is driving the signaling of the ESCC-microenvironment milieu as that could be used as a potential therapeutic target for treatment options in ESCC. Last but not least, there is a clear need for phospho-tyrosine targeted proteomics studies in settings like iTRAQ, where primary ESCC samples could be used for identification of RTKs specific peptide/proteins in ESCC.

Conclusions

RTKs have been investigated extensively for research in relation to gastro-intestinal malignancies and a number of TKIs including reversible (erlotinib, and gefitinib), and irreversible (afatinib, dacomitinib, and osimertinib) have been tested for their efficacy in different malignancies including ESCC. The cancerous cells also evolved as those learned how to this mechanism and overcome the barriers imposed by exogenous/ intrinsic perturbations. Additionally, there is a need for development of an in vitro and/or in vivo model to test the effect of nexus between tumor-microenvironment more specifically ESCC-microenvironment interaction, and its impact on RTK signaling. The tumor-microenvironment has been reported to be associated with TKIs resistance by providing pro-survival factors secreted by the cellular components of the microenvironment. Hence, it will be of significance to identify RTKs actively involved in tumor-

microenvironment nexus or cell-tissue interactions in an *in vitro* and/or *in vivo* model. The success/failure of identifying these molecules involved in this biological nexus is directly dependent on the availability of new/novel technologies. There is an optimism in identifying the missing links/points of RTK signaling in ESCC as tools and techniques involved in 'Omic' technologies (genomics, transcriptomics, proteomics and metabolomics) could help us understanding answering these questions related with different biological dimensions of ESCC tumorigenesis if it gets integrated with system based approaches.

Abbreviations

5-FU: 5-Fluorouracil; ATP: Adenosine triphosphate; AXL: AXL receptor tyrosine kinase; BE: Barrett's esophagus; CCK4: Colon carcinoma kinase-4; CLL: Chronic lymphocytic leukemia; CML: Chronic myeloid leukemia; EAD: Esophageal adenocarcinoma; EGF: Epidermal growth factor; EGFR: Epidermal growth factor receptor; ESCC: Esophageal squamous cell carcinoma; GER: Gastroesophageal reflux; HGF: Hepatocyte growth factor; HGFR: Hepatocyte growth factor receptor; HNSCC: Head and neck squamous cell carcinoma; IGF: Insulin growth factor; IGF1R: Insulin-like growth factor I receptor; iTRAQ: Isobaric tags for relative and absolute quantitation; MAB: Monoclonal antibody; MET: Tyrosine-protein kinase Met; NRTKs: Non-receptor tyrosine kinases; NSCLC: Non-small cell lung cancer; OS: Overall survival; OSCC: Oral squamous cell carcinoma; OTSCC: Oral tongue squamous cell carcinoma; PDGF: Platelet-derived growth factor; PDGFR: Platelet-derived growth factor receptor; PDL1: A ligand for PD1 receptor; PI3K: Phosphatidylinositol 3-kinase; PTKs: Protein tyrosine kinases; pY: phospho-tyrosine; RTKs: Receptor tyrosine kinases; SGTA: Small glutamine-rich tetratricopeptide repeat-containing protein alpha; SILAC: Stable isotope labeling with amino acids in cell culture; TGF- α : Transforming growth factor-alpha; TK: Tyrosine kinase; TKIs: Tyrosine kinase inhibitors; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor

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Authors' contributions

MKK contributed to the conceptualizing and design of this study. MKK and OA drafted, checked and made critical changes in the manuscript. The authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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