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Involvement of Epidermal Growth Factor Receptor (EGFR) Signaling in Renal Cell Carcinoma Progression and Therapeutic Implication

Ghulam Raza[1], Kareem Khan[2]

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Abstract

Renal cell carcinoma (RCC) is the common type of kidney cancer linked to alteration of lipid, glucose, and amino acid metabolism. Early stage RCC has prognosis with overall 5-year survival rate of 90%, and the RCC has unfavorable prognosis when the disease metastasizes. Loss of or carrying mutated tumor suppressor gene *VHL* is the cause of HIF elevation leading to initiation of RCC. The epidermal growth factor receptor (EGFR) is a transmembrane protein, contributes to crucial role in cellular expansion, multiplication, and survival. EGFR overexpression in RCC is 40-80% and EGFR signaling pathway is dysregulated in various malignancies including RCC. RCC is not primarily governed by EGFR. Several critical pathways are dysregulated in RCC, that are mediated by EGFR including VHL-HIF pathway, PI3K/Akt/mTOR signalig, and VEGF-induced angiogenesis leading to tumor growth and RCC progression. Inhibition of angiogenesis was observed upon EGFR blockade. EGFR overexpression in RCC is linked to higher tumor grade, metastatic disease, worse prognosis, poor survival, and resistance to therapies. EGFR-mediated RCC progression is either due to higher EGF expression or elevation of EGFR in the cell membrane. Therefore, targeting EGFR in RCC is a robust strategy to inhibit EGFR-driven disease progression. In this review, we pointed out the potential role of EGFR in RCC and associated molecular mechanisms that are closely related to initiation and progression of RCC. Herein, we also highlighted the therapeutic implication of targeting the EGFR in RCC.

Key words renal cell carcinoma, epidermal growth factor receptor, VHL-HIF pathway, PI3K/Akt/mTOR, VEGF, angiogenesis

1. Department of Pathology, King Edward Medical University/Mayo Hospital, Lahore, Pakistan.
2. Medical College, Aga Khan University, Karachi, Pakistan.
Correspondence: Ghulam Raza (Department of Pathology, King Edward Medical University/Mayo Hospital, Lahore, Pakistan; Email: raza26pk@gmail.com).

Introduction

Renal cancer is among the more prevalent forms of cancer. Most of the renal cell carcinoma (RCC) were diagnosed with metastasis and the overall survival rate is very low. There are numerous types of RCC, among them clear cell renal cell carcinoma (ccRCC) exhibits the most aggressive histological type. The particular reason for overall low survival rate and poor prognosis in RCC is due to resistance to conventional and standard radiotherapy and chemotherapy. The ccRCC is the most common subtype, and other rare subtypes including renal medullary carcinoma, multiocular clear cell RCC, neuroblastoma-associated carcinoma, papillary RCC, and chromophobe RCC. ccRCC exhibits less favorable outcomes in comparison to papillary and chromophobe RCC [1]. Primary risk factors for ccRCC are smoking, obesity, and von Hippel-Lindau (VHL). If the ccRCC is diagnosed within the kidney, surgical detection and nephrectomy are conducted. In this case, patients' survival rate is around 92% and if the disease metastasizes locally or systemically, the survival rate is dropped (**Figure 1**) [2]. The morphology of ccRCC is rich lipid and glycogen build up in the cytoplasm of the tumor cells. The alteration of metabolism of glucose, lipids, and amino acids is leads to the clear cell phenotype [3].

The molecular mechanism of RCC is complex. To improve the therapeutic intervention and increase the sensitivity, targeting potential prognostic biomarkers are the robust strategy. Meta-analysis identified three key genes including EGFR, FLT1, and EDN1 in RCC [4]. Among those EGFR is the most crucial biomarker and novel therapeutic target for treating RCC. EGFR is widely expressed in almost all cancer types including RCC and linked to disease progression, metastasis, poor outcome, and therapeutic resistance. VHL plays important functions in regulating the action of hypoxia-inducible factor (HIF) and ubiquitination. HIF is closely associated with angiogenesis. The action of VHL is suppressing tumors and loss of VHL and accumulation of HIF is the early sign of RCC. EGFR contributes to VHL loss in RCC through multiple pathways. Elevation of HIF in RCC is due to the upregulation of various growth factors including IGF, VEGF, EGF, and PDGF that activates PI3/AKT. Activation of PI3/AKT can be caused by stimulation of EGFR signaling. EGFR itself can also directly activate PI3K [5]. Additionally, EGFR suppresses autophagy in RCC leading to acceleration of RCC progression. EGFR also destabilizes E-cadherin, an epithelial marker essential for cellular adhesion. By attenuating E-cadherin, EGFR triggers the EMT initiation in RCC.

Elevated expression of EGFR in RCC was reported ranging from 50%-90% [6, 7]. The intracellular RTK domain of EGFR is autophosphorylated leading to the stimulation of multiple pathways in RCC including RAS-RAF-MEK-ERK and PI3K-PTEN-AKT pathways resulting in tumorigenesis in RCC. EGFR EGFR-mediated pathways are dysregulated in the RCC. Thus, proper characterization of EGFR localization in RCC and neighboring normal kidney tissues is important for EGFR-dependent anticancer therapeutic targeting. EGFR expression was assessed by immunohistochemistry (IHC) in the kidney tissues of 63 patients [8]. It was found that EGFR expression in the cell membrane was remarkably higher in the RCC tumor tissues in comparison to normal tissues. Conversely, EGFR expression in the cytoplasm was remarkably higher in the normal kidney tissues compared to RCC tumor tissues [8].

Alteration of VHL in RCC

RCC is a fatal disease with poor prognosis and lower recovery rate. Numerous subtypes of RCC including papillary, clear cell, and oncocytoma. So far, no effective monotherapy, combination therapy, or chemotherapeutic agents developed yet to recover the RCC. Treatment option for RCC is limited [9]. Surgical removal is the only successful therapy for localized RCC. Other treatment options are thermal ablation, active surveillance, radiation, immune therapy, and targeted molecular therapy [10]. Several immunotherapies are considered to treat RCC including PD1-blocker such as nivolumab, cytokines interferon (IFN) and interleukin 2 (IL2), and tumor-infiltrating lymphocytes. However, the effectiveness of cytokine therapy is limited due to widespread severe toxicities [11]. Therefore, understanding of the mechanistic insight of RCC is necessary. Researchers are being focused on elucidating the molecular mechanism and mechanistic pathway associated with RCC. One of the crucial findings is *VHL* gene discovery [12], which was a breakthrough finding that emerged in the RCC study. *VHL* gene encodes pVHL protein. In normoxia, pVHL tightly regulates HIF actions, and targets them for proteasome-dependent degradation. Most importantly, loss of pVHL is the early sign of RCC, leading to inhibition of HIF degradation. As a result, elevation of HIF occurs in the cytoplasm and translocates to the nucleus. Upon nuclear translocation, HIF binds with hypoxia-related genes, and hypoxic condition is manifested [13]. Once these genes are activated leading to the initiation of pathways associated with blood vessel formation, proliferation, metastasize, and progression of RCC [13] [14]. HIF alfa subunits are degraded through polyubiquitination in normoxic conditions. pVHL is an E3 component that ubiquitinates HIF-α subunits in the availability of oxygen. Some proteins are present in the pVHL ubiquitin ligase complex including elongin B, elongin C, Rbx1, and cullin 2. Cytosolic chaperonin containing TCP-1 (CCT) promotes the binding of pVHL to the elongin B and elongin C to protect pVHL from ubiquitin-dependent degradation [15]. pVHL also attenuates cyclin D1 resulting inhibition of cell cycle progression. Regulation of several proteins including TGFα and EGFR is also linked to the alteration of pVHL in RCC. Several FDA-approved tyrosine kinase inhibitors are available which solely target the VHL-HIF pathway, such as sunitinib, and sorafenib. Additionally, the anti-angiogenic agent bevacizumab is also considered in this regard. The effectivity and action of these therapeutic agents are higher in RCC compared to the conventional cytokine therapies [16, 17].

VHL loss: underlying mechanism of RCC formation

The tumor suppressor gene, *VHL* resides on chromosome 3p25. Mutation in one *VHL* allele leading to VHL disease and *VHL* gene inactivation in RCC occurs by point mutation results in impairment of suppressing tumor function of pVHL. pVHL contributes a pivotal function in the regulation of cellular oxygen in normoxic environment. HIF-1α and HIF-2α are activated in hypoxia and degraded in normoxic environment by the action of proline hydroxylases. Hydroxylation of proline residues P402 and P564 within the oxygen-mediated degradation domain (ODD) of the HIF-1α subunit occurs by proline hydroxylases. HIF-1α Hydroxylation is necessary for the recognition by VHL and polyubiquitinated degradation [18]. This tightly regulated cellular process maintains HIF-1α activation only in the hypoxic condition. However, the HIF-1α overexpression is manifested in the lack of VHL action [19]. Loss of VHL is carried out by numerous crucial factors including point mutation in the *VHL* gene, auto-degradation, and pVHL depletion [19]. HIF-1α stabilization occurs in loss of pVH*L* leading to abundant of HIF-1α even in normoxia which impairs normal cellular processes resulting in cell proliferation, angiogenesis, and cell cycle progression. Higher angiogenic phenotype arises in RCC due to the overproduction of HIF-induced VEGFA in the absence of pVHL action [20]. Heterotrimeric complex with VHL was formed with extra

proteins of 16 kDa and 9 kDa, whilst, the complex was not formed in the mutation of the *VHL* gene [20]. Under normoxia, VHL downregulates VEGF, platelet-derived growth factor B (PDGFB), and glucose transporter 1 (GLUT1) [21]. It was also reported that there are several targets of HIF-1α including VEGF, PDGF, and GLUT1. These all proteins exerted elevated expression levels in RCC compared to the non-malignant cells.

pVHL resides in the compartment of the cytoplasm and nucleus. pVHL consists of two mutational regions named alpha and beta domains. The α domain of pVHL directly binds to elongin C, and the beta domain directly binds to HIFα subunits [22] [23]. Different *VHL* mutations with respect to HIF regulation including Type 1, Type 2A, and Type 2B alleles. Among them, Type 2A pVHL mutant exhibited higher residual HIF-binding affinity compared to other mutants which is regarded as lower risk of RCC [24-26]. Patients detected with Type 1 and Type 2B *VHL* mutations form renal cysts having lost the WT allele of *VHL* and overproduction of numerous *HIF* gene products. Restoration of pVHL function by gene transfer does not alter cellular growth, although suppresses tumor formation in xenograft model [27, 28].

Correlation between EGFR and VHL in RCC

Elevated EGFR expression is found in several tumor types, which is linked to the initiation of numerous signaling pathways resulting in tumor progression and unfavorable prognosis. VHL contributes to EGFR degradation in the proteasome. Thus, EGFR is upregulated in the alteration of pVHL in RCC. It was revealed that VHL loss turns to HIF-mediated TGFα expression and EGFR activation [29]. EGFR mutation has been detected in various cancers and EGFR mutation is one of the primary reasons for tumor progression. Studies reported that EGFR mutation was not detected in RCC patients indicating EGFR-KRAS pathway is not the reason for tumor progression and oncogenicity in RCC [30, 31]. Overexpression of EGFR increases the action of VEGF leading to angiogenic phenotype in RCC [32]. It was revealed that HIF initiates the TGFα/EGFR pathway in VHL-altered RCC cells and it was demonstrated that HIF-mediated tumorigenesis was attenuated in VHL-negative RCC cell lines when EGFR was inhibited by shRNA [33]. Suppression of growth of in vivo tumor was observed in VHL loss in RCC cells upon EGFR silencing. Inhibition of TGFα abrogates autonomous proliferation of VHL-deficient cells. EGFR and VHL expression, correlation, and survival rate in RCC were shown in **Figure 2**. Study reported that HIF-2α expression activates EGFR in VHL-competent 786-0 and A498 cells indicating HIF-2α mediates autonomous cellular multiplication by EGFR activation via TGFα signaling [34]. Whilst, remarkable TGFα protein expression was not observed in cells that express HIF-1α, which suggest HIF-1α is unable to activate EGFR and autonomous cellular proliferation (**Figure 3**) [33].

Impact of EGFR on O-GlcNAcylation and O-GlcNAc-transferase in RCC

O-GlcNAcylation and O-GlcNAc-transferase (OGT) expression is remarkably higher in RCC cell lines and renal carcinoma tissue samples compared to non-malignant cells. Attenuation of OGT abrogated RCC cell proliferation and cell cycle transition along with higher apoptosis demonstrates elevated O-GlcNAcylation and OGT upregulation promoted the oncogenicity in the development of RCC. It was reported that in A431 and A549 cells, EGFR was O-GlcNAcylated and found direct interaction with OGT without the requirement of any mediators [35]. Furthermore, it was found EGFR co-immunoprecipitation with OGT in human RCC cell lines and demonstrated EGFR and PI3K/AKT were downregulated in OGT knockdown RCC cell line, 786-O. On the reverse strand of EGFR, EGFR-AS1 is transcribed which has partial

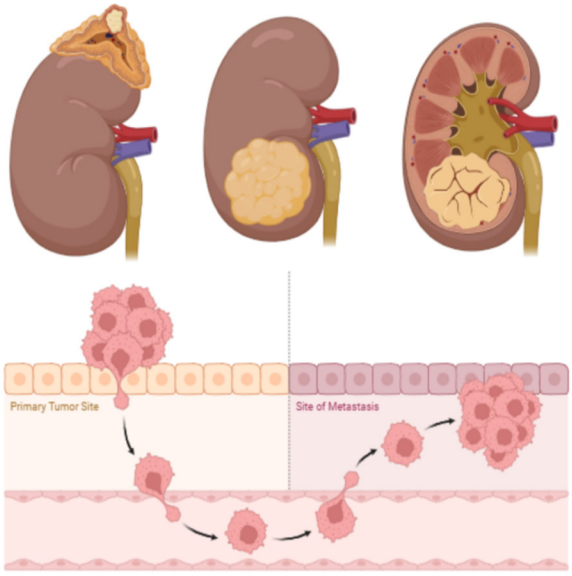

Figure 1. Formation of tumors in RCC. Overall survival rate is 5 years in RCC if the disease is localized in the kidney and the survival rate is dropped if the disease gets metastasized.

complementary sequence of *EGFR*. The *EGFR* is highly expressed by the elevated expression of *EGFR-AS1* and the study reported that *EGFR-AS1* mediated tyrosine kinase inhibitor resistance in squamous cell carcinoma and unfavorable prognosis was identified in hepatocellular carcinoma (HCC) [36, 37]. It was studied that as *HCC*, *EGFR-AS1* is also expressed at high level in RCC and promoted RCC by invasion, proliferation, and metastasize. EGFR-AS1 increased the expression of *EGFR* by raising the mRNA stability in RCC [38]. RCC cell migration and invasion were inhibited by abrogating EGFR-AS1 [38].

EGFR signaling and autophagy regulation in RCC

The transmembrane protein, lysosomal-associated transmembrane protein 4B (LAPTM4B) resides in the endosome and lysosome and overexpressed in various cancers. Upregulated LAPTM4B transforms normal cells to oncogenic by promoting migration, expansion, and invasion through PI3K/AKT pathway [39, 40]. Beclin 1 is an active component of the initiation of autophagy. EGFR regulates autophagy by stimulating PI3K/AKT/mTOR, EGFR-RAS, and EGFR-Beclin 1. The EGFR pathway triggers activation of PI3K/AKT which suppresses autophagy and EGFR inhibits autophagy initiation through phosphorylating and attenuating Beclin 1 [40-43]. Simultaneously, EGFR signaling activates mTOR leading to the formation of mTOR complex (mTORC) and the mTORC1 suppresses autophagy by phosphorylating ULK1 which interferes with ULK1-AMPK interaction. Subsequently, autophagy is prevented by interfering with the complex formation of ULK1-FIP200-ATG13 [41, 44, 45]. Activated EGFR suppresses autophagy, whereas, in metabolically-stressed conditions LAPTM4B forms complex with inactive EGFR to initiate autophagy for the survival of cancer cells [46, 47]. LAPTM4B activates the EGFR pathway by abrogating lysosomal degradation. LAPTM4B also inhibits autophagy due to the blockade of EGF-activated enzyme-somal degradation leading to the activation of EGFR signaling. EGFR and LAPTM4B are both overexpressed in multiple cancer types including RCC. It was demonstrated that LAPTM4B is overexpressed in RCC and upon downregulating LAPTM4B reduced the proliferation of RCC cells by promoting cellular apoptosis. LAPTM4B is largely co-related with CD8 T-cells which are poorly expressed in high-grade RCC compared to advanced RCC. LAPTM4B enhanced immune-escape leading to promoting cancer cell survival, proliferation, and tumor progression in RCC [48].

Involvement of EGFR in stimulation of PI3K/AKT in RCC

PI3K induces phosphorylation at the 3-OH group of the inositol ring. PI3K is divided into 3 groups including class I, II, and III, which are divided based on their structure and lipid substrate preferences. Among three groups, class I PI3K was widely studied and contributes crucial function in different cancer types. Numerous growth factors i.e. epidermal growth factor (EGF), insulin-like growth factor (IGF), and platelet-derived growth factor (PDGF) activate PI3K through different pathways. Then, the activated PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate to form phosphatidylinositol 3,4,5-trisphosphate on the cell membrane leads to the initiation of downstream signals. The *AKT* is one of the downstream targets and activated AKT drives cellular growth, cell cycle progression, oncogenicity, and tumorigenesis. Genetic alteration was detected in the PI3K/AKT signaling pathway in RCC. *AKT* mutations were identified in RCC, the common mutations were *E40K* in *AKT1* and *E17K* in *AKT3* [49]. The VHL/HIF and PI3K/AKT signaling pathways are correlated in RCC, and interplay between these two pathways drives the progression of RCC. Elevation of HIF due to loss of *VHL*

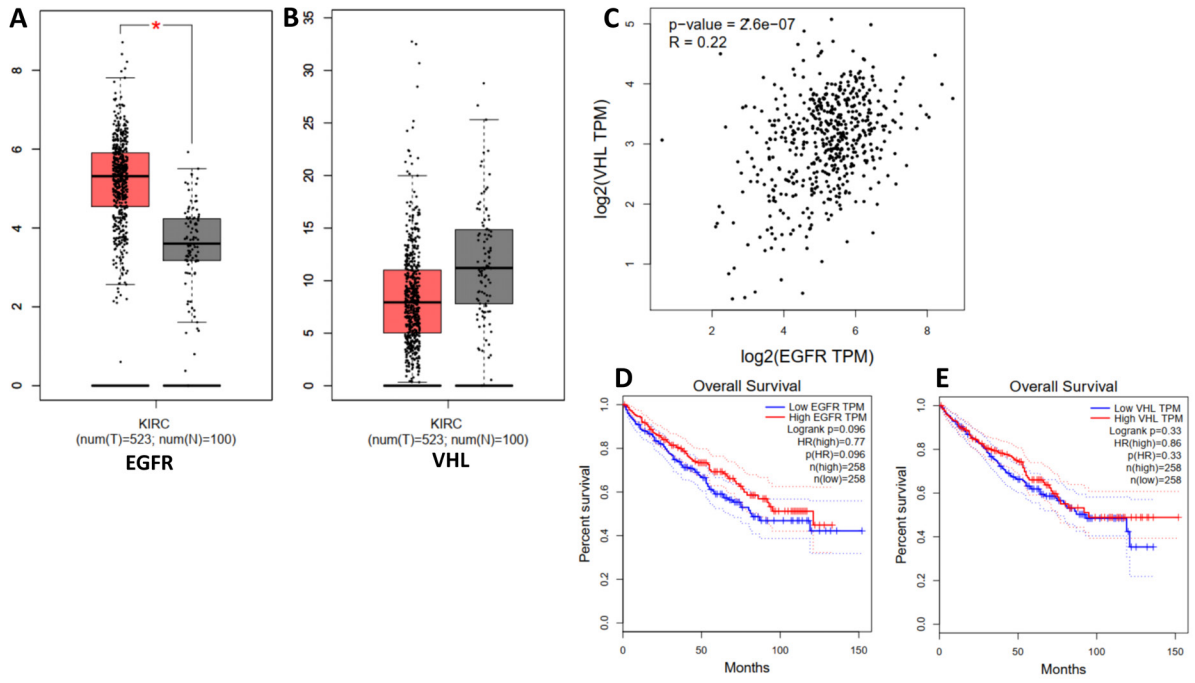

Figure 2. GEPIA plots. A: Box plot of EGFR expression in normal tissues (N) and tumor tissues of kidney renal clear cell carcinoma (T). B: Box plot of VHL expression in normal tissues (N) and tumor tissues of kidney renal clear cell carcinoma (T). C: Correlation of EGFR and VHL in RCC. D: The survival plot of low and high EGFR expression in RCC. E: Survival plot of low and high VHL expression in RCC.

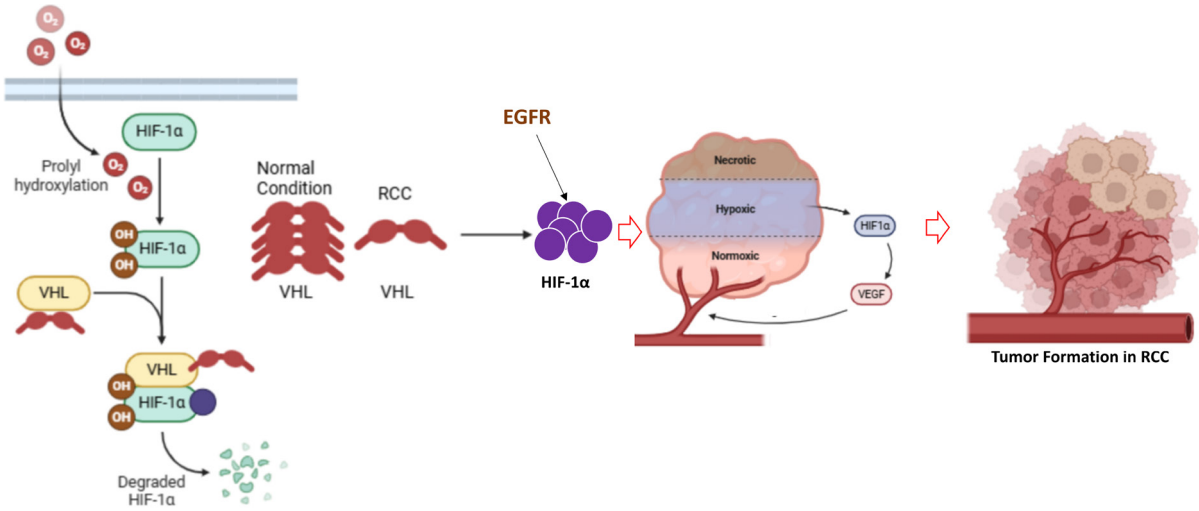

Figure 3. VHL-HIF1α pathway. Loss of VHL turns to elevation of HIF1α leads to initiation of RCC and tumor formation. EGFR contributes to the alteration of the VHL-HIF1α signaling pathway in RCC.

promotes augmentation of numerous growth factors including EGF, IGF, PDGF, and VEGF that activates PI3K/AKT in RCC [50]. EGFR is the upstream activator of the PI3K/AKT pathway. EGFR mediates the stimulation of PI3K/AKT by association with the p85 subunit of PI3K on phosphorylated EGFR [51]. EGFR enhances PI3K/AKT initiation promoting cell survival and proliferation. EGFR and PI3K/AKT both are dysregulated in multiple cancer types including RCC. Furthermore, mTORC1 and mTORC2 were activated subsequently which upregulates HIF expression [52, 53]. It was revealed that mutation of *PI3K*/*AKT* is relatively lower and the AKT activation is higher in RCC compared to other cancer types [54]. Besides, PI3K/AKT activation by signals originating from extracellular compartments, and transmembrane receptors, shortage of glucose also mediates phosphorylation of AKT and is activated in multiple cancer types including RCC. AKT is phosphorylated at Thr308 residue through the formation of higher protein association with PDK1 and glucose-dependent protein in lower glucose state in RCC [55, 56]. Inhibition of isoforms of AKT is a novel approach in RCC. AKT inhibitor, MK2206, and kinase inhibitor, GDC0068 were examined in RCC clinical trials [57, 58]. Moreover, anti-angiogenic therapy and targeting PI3K/AKT/mTOR pathway are promising approach that were tested in RCC. Activation of autophagy and initiation of apoptosis were manifested by inhibiting the PI3K/AKT/mTOR pathway in RCC [59, 60].

Impact of EGFR splicing in RCC formation

Somatic mutation-mediated oncogenic function and transition of normal cells to malignant cells were extensively studied. Besides, alternative pre-mRNA splicing contributes to a major role in cancer development also emerged in several cancer types. RTKs are alternatively spliced although the function of the splicing variant in tumor development requires to be explored. DNA levels of EGFR alternations is not common whilst, RNA splicing of EGFR can be higher which majorly impacts clinical outcomes. Alternative splicing of *EGFR* was identified in RCC tumor tissues [61, 62]. It was unveiled that EZH2 mRNA splicing variants are highly enhanced in RCC tissues along with multiplication, invasion, and oncogenicity in RCC cells [63]. Novel EGFR splicing variant EGFR_pr20CTF was detected in RCC using RNA-sequencing. 71.7% among 99 patients, the EGFR_pr20CTF splicing variant was identified in RCC tumors. In the same study, three distinct splice forms were identified which were alpha, beta, and gamma. The study reported that the EGFR_pr20CTF splicing variant was found in less than 0.2% of non-RCC tumors of 1091 patient samples. Therefore, this splice variant is solely specific to RCC [64].

Role of EGFR in activation of Epithelial Mesenchymal Transition to trigger RCC

Epithelial Mesenchymal Transition (EMT) is a mechanism initiating cancer cells to acquire invasive and metastatic characteristics promoting cancer progression [65]. Through the EMT process, epithelial cells lose the primary characteristics such as adhesion and acquire mesenchymal properties such as invasiveness leading to invasion, metastasis, and resistance to therapy. EMT plays an essential role in the pathophysiology of RCC. EMT in RCC is associated with increasing recurrence rate, therapeutic resistance, and unfavorable prognosis. Therefore, targeting the molecular pathway of EMT is a potential approach to treat RCC and facilitate the outcome of the patients [66]. EGFR has major contributions to the initiation and progression of EMT in RCC. E-cadherin, claudins, and occludins are the essential proteins in epithelial cells that maintain cellular adhesion, and polarity of the cells. Loss of these essential epithelial markers is the primary sign the EMT development.

EGFR is a major contributor in the alteration of E-cadherin, claudins, and occludins through multiple pathways. Galectin-7 is a galectin family protein that plays a primary role in regulating cellular adhesion through directly interacting with E-cadherin [67-69]. E-cadherin is abundant at the adherent junctions of the epithelial cells. Several proteins including β-catenin maintain

the integrity of the E-cadherin. EGFR also forms a complex with E-cadherin [70, 71]. However, it was reported that EGFR activation can suppress the function of E-cadherin [72, 73]. EGFR also decreases the stabilization of E-cadherin by enhancing E-cadherin internalization and altering the interaction of E-cadherin with the cytoskeleton by decreasing its expression on the cell surface [74]. It was revealed that upon EGF treatment in the cancer cells, β-catenin phosphorylation occurs at the Tyr654 and Tyr142 residues associated with reducing affinity to the E-cadherin leading to EMT progression [75, 76] in RCC and other cancer types. Sunitinib is an RTK inhibitor, widely used in treating cancer, particularly RCC. However, many patients remain unresponsive to the sunitinib treatment due to the major cause of EGFR-mediated EMT. In vitro study suggested that pEGFR was enhanced and followed by expression of mesenchymal markers was elevated upon treatment of sunitinib in the RCC cell line 786-O [77]. This study demonstrates that sunitinib mediated EMT via phosphorylation of EGFR in the 786-O cells which was alleviated by combination treatment with erlotinib. Besides, some other RCC cell lines such as Caki-1/SN were observed as resistant to sunitinib. Upon sunitinib treatment in the Caki-1/SN cells leading higher phosphorylation of EGFR [77].

RIN1 promotes RCC through EGFR signaling

Ras and Rab1 interactor 1 (RIN1) is a Ras effector protein, associated with unfavorable prognosis. RIN1 regulates cell adhesion and migration by interacting with Abl kinase. The effect of RIN1 expression and its action in ccRCC is not well studied. Rab25 plays a pivotal role in recycling EGFR in kidney cells. Rab25 is one of the Rab GTPases which is crucially upregulated in RCC. RIN1 has a major contribution in activating EGFR in ccRCC by interacting with Rab25 [78]. Rin-mediated EGFR pathway is required for Rab25-mediated tumor malignancy in ccRCC. EGFR-induced tumorigenesis was inhibited in RCC upon attenuation of RIN1. Upregulation of Rab25 is correlated with worse outcomes of the patients apparently mediates metastatic [79, 80]. Endogenous Rab25 interacts with RIN1 which was detected by co-immunoprecipitation assay and PI3K and EGFR are transported through Rab25-decorated vesicles [81]. The EGFR trafficking and recycling to the plasma membrane by Rab25 contributes to RIN1-induced EGFR signaling in RCC. Therefore, the RIN1 is a potential therapeutic agent targeting EGFR signaling in ccRCC to reduce tumorigenesis.

Therapeutic implications

In 1980, immunotherapy was first used for treating metastatic renal cell carcinoma (MRCC). Interferon α (IFNα) and interleukin 2 (IL2) had remarkable response <5-40% with few higher response (<5%). The cytokine-based therapy exhibited potential antitumor efficacy with lower toxicity [82]. So far, noncytokine-based therapies do not exhibit notable curative anti-tumor effects in patients with MRCC [83]. The mechanism of cytokine-based therapy was not fully elucidated. The possible mechanism is activation of cytotoxic T-lymphocytes, natural killer cells [84], promoting antibody-dependent cellular cytotoxicity [85-87], and inhibition of oncogenic functions [88].

Sunitinib is a selective RTK inhibitor including VEGFR and PDGFR. The potential antitumor action of Sunitinib was exerted by inhibiting angiogenesis. Sunitinib is successfully used in the RCC treatment and it is a primary intervention in RCC due to higher response rate. A phase I clinical trial of Sunitinib demonstrated notable antitumor actions in several patients with RCC.

Bevacizumab is used in the RCC treatment. The antitumor mechanism of bevacizumab is potent antiangiogenic action which neutralizes the vascular endothelial growth factor (VEGF). Human clear-cell renal carcinoma has a significantly higher blood vessel count compared to non-clear-cell renal carcinoma due to higher expression of VEGF. Bevacizumab mediated inhibition of angiogenesis leading to potent antitumor action in RCC [89].

Sorafenib is an oral multi-kinase inhibitor, and therapeutic agent for treating several cancers particularly RCC. Sorafenib possesses dual mechanisms including shrinkage of tumor growth and tumor anti-angiogenesis. In the clinical trial, sorafenib efficiently improved the total survival of the patients with lower toxicity. In the phase II clinical trial, sorafenib was well tolerated with less adverse effects. Sorafenib as a single therapeutic agent in RCC is very effective. However, to maximize the therapeutic efficacy sorafenib can be used with other therapeutic agents [90].

Cetuximab, a selective inhibitor of EGFR. The preclinical studies showed cetuximab has anti-tumor actions in RCC cell lines and remarkable xenograft tumor shrinkage in nude mice [91, 92]. However, in the phase II clinical trial patients with RCC did not exhibit objective response. The cetuximab response rate against RCC patients was much lower [93, 94].

Conclusion

In normal cellular condition, EGFR controls multiple pathways regulating cell growth, differentiation, multiplication, and survival. EGFR-mediated cellular mechanisms are well-controlled in healthy cells. However, when the EGFR gets mutated, then EGFR-mediated cellular processes are dysregulated in numerous malignancies leading to uncontrolled cellular proliferation. EGFR overexpression is seen in different tumor types. Overall patients' outcomes and prognosis are improved by therapeutically targeting EGFR in numerous cancers. Conversely, several clinical reports demonstrated that objective responses were not seen in RCC by targeting EGFR alone or in combination. Although preclinical study reports suggested significant tumor suppression and notable cytotoxic effect was observed against many RCC cell lines by inhibiting EGFR. Higher expression of EGFR was observed in some RCC subtypes, but it is unclear, more in-depth studies are required to investigate whether there is a greater involvement of EGFR in RCC.

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Ethical policy

Non applicable.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Ghulam Raza and Kareem Khan contributed to design of the work, data collection, and drafting the article. Ghulam Raza did the critical revision and approved the submission of the article.

Competing interests

The authors declare no competing interests.

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