Angiogenesis in Control and Progression of Lung Cancer

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Abstract

Lung cancer is the major cause of cancer-related mortality worldwide owing to its late-stage detection and aggressive behavior. Epidemiologically, several genetic and epigenetic factors contribute to the development of lung cancer. Angiogenesis, a critical process in tumor progression has become an important target for anti-cancer therapy particularly in lung cancer. Besides commercially available angiogenic inhibitors, numerous anti-angiogenic therapies have been developed to limit tumor growth, although, most of them have not proved beneficial in terms of long-term survival. Despite, logical advances in treatment strategies, NSCLC still remains a major health concern due to poor prognosis of the diseases state. This calls for a comprehensive analysis of signaling processes governing tumor angiogenesis and treatment options available thereof for development of a sustainable strategy to control cancer. In this review, several aspects of lung cancer have been discussed starting from its pathological characterization to the development of modern therapeutics.

Keywords: Lung cancer; Angiogenesis; VEGF receptors

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Introduction

Pro-angiogenic endothelial cell signal transduction has evolved as a target of choice in cancer research being indispensable for neovascularization and hence survival of solid tumors [1]. Tumor cells express several target features associated with their angiogenic activation that could be explored as specific targets which may cause either the destruction of existing tumor vasculature [2-5] or inhibition of the tumor angiogenesis [6-8]. Lung tissues are highly vascularised and therefore targeting tumor vessels for destruction may not be a viable option. Therefore, the next strategy may involve use of angiogenic or cell cycle inhibitors or quenchers to restrict neovascularisation and circumvent tumor growth. Although, these will be required in both scenarios, knowledge of the endothelial cell-specific growth factor receptors, their signal transduction and effector mechanisms are essential and will undoubtedly provide essential details to target or restrict human cancers. Here we discuss recent developments on one important family of endothelial growth factor receptors i.e. VEGF receptor family, implicated in lung...
cancer angiogenesis. Several excellent reviews have appeared on the same topic and related topics [9-13].

Lung Cancer: Epidemiology and pathological features

Lung cancer or *Bronchogenic Carcinoma* is a disease with an uncontrolled cell growth in tissues of the lung. The growth of these cells distorts the tissue and extracellular environment to the Lung cancer incidence and mortality rates have been increasing worldwide over the past two decades; however major drifts in the global distribution of lung cancer have occurred, reflecting the temporal changes in patterns of tobacco usage [14]. The proportion of lung cancer patients in developing countries increased from 31% to 49.9% over the past 20 years [14], and with rapidly increasing cigarette consumption in these regions [16], the trend is expected to continue. Epidemiological studies of lung cancer have identified significant gender and geographic variations. In addition, it has been observed that the proportion of female lung cancer cases in never smokers varies considerably from region to region [17-33]. Among men, the proportion of never smokers is lower with less regional variation [18-20, 29-31]. These findings are intriguing; though, it is not known whether such observed patterns among female never smokers represent an increased risk of lung cancer perhaps due to risk factors other than smoking. Contrary to the distribution curve of susceptibility of lung cancer due to inherent gender differences, increasing number of non-smoking women in Asia Pacific might explain the higher proportion of cases [34]. Despite advances in treatment modalities and imaging techniques, the prognosis and diagnosis of lung cancer remains poor, with five-year survival rate of 14% in early stages and lesser than 5% in locally advanced stages [35, 36]. While most of the patients diagnosed in an advanced stage II and III, only 20-30% of patients present with an operable disease at earlier stages [37]. In extent that may lead to metastasis, which is in term, an invasion of adjacent tissue and infiltration beyond the lungs. Primary lung cancers are carcinomas of epithelial cells that make up the major portion of the lung. The most common cause of cancer-related death in men is lung cancer and it remains the second most common in women, responsible for almost 1.6 million deaths worldwide annually [14,15] (Figure 1).

India, the main reason for late diagnosis is the poor referral of patients, health awareness and delayed recognition. Figure 2 depicts the molecular evolution of lung cancer and possible points of therapeutic intervention.

**Figure 1** Estimated cancer mortality and deaths worldwide (Adapted from American Cancer Society. Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013)

**Figure 2** Distinct histological features of lung cancer in smokers and non-smokers (Adapted from Sun et al. 2007)

Lung cancers are catalogued into four major types and multiple minor or rare forms [38]. For clinico-pathological reasons they are often divided into the broad categories of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLCs are further divided into three major types, squamous cell carcinoma (SCC), adenocarcinoma and large cell carcinomas. Since large cell carcinomas invariably represent undifferentiated
or poorly differentiated forms of the other types of cancers, it is therefore loosely framed and the criteria for its diagnosis generally show a discrepancy. Fundamentally, all major histological types of lung carcinoma are directly or indirectly associated with smoking, though the association is stronger for SCC and for SCLC than for adenocarcinoma [39]. By comparison, adenocarcinoma is the most common form of lung cancer in never smokers [18, 23,40]. The histological spectrum of lung cancer demonstrates geographic variations but there has been a major global trend with a decrease in SCC and a sharp rise in adenocarcinoma [41] as shown in Figure 3. This changing histological pattern has occurred over a period of a few decades, and such a rapid change in the histological spectrum of a major form of human cancer is highly unusual, if not unique. This trend has been hypothesized to be due to the widespread usage in many countries of cigarettes with lowered tar and nicotine content. Smokers compensate for the reduced nicotine content by altering their smoking behaviour, and the net result is changes in the anatomic location and histological type of lung cancer, rather than the anticipated reduction in incidence [41-44].

![Figure 3 Molecular Evolution of Lung Cancer](image)

**Figure 3 Molecular Evolution of Lung Cancer.** Generalized graphical representation of lung cancer progression through genetic/epigenetic abnormality to tissue metastasis.

**Environmental, Biological and Genetic factors in Lung cancer development**

To date, epidemiological studies have identified several genetic, environmental, viral and hormonal factors associated with lung cancer risk. Other non-smoking-related risk factors such as chromium, asbestos, arsenic, silica, cadmium and nickel, as well as air pollutants, lung disease related history, and dietary factors have also been implicated [45-47]. So far the smoking of cigarettes is the main contributor to lung pathologies including cancer as well [48]. The causal relationship between smoking and lung cancer is well established with a 10- to 20-fold increased risk of lung cancer even in occasional smokers compared with never smokers [40] (Figure 4). The disease is largely preventable, since most of the cases occur due to smoking of tobacco [14]. In the United States, smoking is estimated to account for 87% of lung cancer cases (85% in women and 90% in
men) [49]. Among female smokers, the lifetime risk of developing lung cancer is 11.6% and among male smokers the risk is 17.2%. This risk is significantly lower in nonsmokers: 1.3% in men and 1.4% in women [50]. Cigarette smoke contains over 60 known carcinogens [51], which include nitrosamine, benzopyrene and more importantly, radioisotopes from radon decay sequence. Additionally, nicotine is considered to be the key component that appears to suppress the immune response to malignant growths in exposed tissue [52]. There are evidences of lung cancer is highly correlated with gender as PAHs, thus smokers in men are shown to contain high mutagenic (PAH) and ER pathways have also been described [82]. Some evidence from animal studies [58], have explained by ETS exposure along with experimental evidences showing the implications of respiratory tract. Epidemiological studies of miners [57], and thereby inhaled, where they get adhered to the epithelial lining from the decay sequence. Additionally, nicotine is considered to be the key component that appears to suppress the immune response to malignant growths in exposed tissue [52].

Environmental exposures

ETS (environmental tobacco smoke) is a mixture of sidestream smoke released by the burning tip of the cigarette or other smoking device (such as a cigar or pipe) and mainstream smoke exhaled by the smoker [56]. Sidestream smoke being the main component of ETS; consists largely, although diluted in the air, carcinogens that are inhaled by the smoker [56]. However, the overall evidence suggests that ETS is a relatively weak carcinogen and most lung cancers in never smokers cannot be explained by ETS exposure alone. Radon is a radioactive gas produced from the decay of naturally occurring uranium in soil and rocks. Though chemically inert, radon decays into active products that attach themselves to particulate matter in the air and thereby inhaled, where they get adhered to the epithelial lining of respiratory tract. Epidemiological studies of miners [57], along with experimental evidence from animal studies [58], have established a causal relationship between occupational radon exposure and lung cancer development. [59]. However, collective analyses of these studies indicate that residential radon exposure is associated with a small but detectable increase in risk of lung cancer, although the risk is much greater among smokers owing to the synergistic effects of radon and smoking [60, 61].

Cooking oil vapours and indoor coal burning

The high rates of lung cancer among female never smokers in Asia have led to studies evaluating the potential role of passive environmental factors, like exposure to indoor coal burning and cooking oil vapours. Volatile substances generated from cooking oils have been shown to be mutagenic and contain carcinogenic polycyclic aromatic hydrocarbons (PAHs), as well aldehydes and other mutagens [62-65]. Indoor coal burning for heating and cooking in homes without adequate ventilation has also been implicated as a risk factor. Emissions from the incomplete combustion of coal have been shown to contain high concentrations of mutagenic PAHs [66]. Studies have shown that there is a significant correlation between indoor air benzo[al]pyrene (BAP) concentration and high lung cancer mortality rates, particularly from Adenocarcinoma [67]. Some large case-control studies have reported that household coal burning is a significant risk factor for lung cancer [68-70].

Hormonal factors

The higher proportion of lung cancer in female compared with male suggests a possible role for gender-dependent hormones in the development of lung cancer. Oestrogen receptors (ER and ER) are expressed in healthy lung tissue and lung tumors in both women and men, however the data is not consistent as to whether ER expression is gender biased or not [71-73]. ER appears to be expressed more frequently than ER in lung tissue [72], and its expression in NSCLC tumours is associated with improved survival, whereas the expression of ER is a poor prognostic factor [74, 75]. In vitro studies have also shown that oestrogens stimulate the proliferation of NSCLC cells through oestrogen receptor-mediated signalling, whereas anti-oestrogens inhibit growth [71,72; 76-78]. In addition, oestrogens can potentially alter the metabolic activation of carcinogens such as PAHs, thus promoting carcinogenesis [79]. It has also been postulated that oestrogen may directly act as a carcinogen, by process of metabolic conversion to catechol oestrogens [80, 81]. Interactions between the epidermal growth factor receptor (EGFR) and ER pathways have also been described [82]. Some studies have found that the augmentation of hormone replacement therapy (HRT) is associated with an increased risk of lung cancer and poorer survival while as early menopause is associated with a decreased risk of lung cancer [83- 85]. Conversely, other studies have reported that HRT use is associated with a decreased risk of lung cancer, primarily among smokers [86, 87].

Figure 4 The Risk of lung cancer is highly correlated with cigarette smoking. Adapted from OncoProf.net, by Caen University School of Medicine
Genetic factors

Genetic factors play a crucial role in initiating and progression of lung cancer lesions. The observation that only 10-20% of smokers develop lung cancer suggests that individuals might differ in their susceptibility to environmental risk factors. A recent analysis of 11 studies of lung cancer found that family history was associated with a 1.5-fold increased risk of lung cancer [88]. A large linkage analysis of 52 families has identified a major susceptibility locus for inherited lung cancer on chromosome 6q23-25 [89], and the search for a lung cancer susceptibility gene in this region is ongoing. Differences in DNA repair capacity might also contribute to susceptibility to lung cancer, owing to the lower capacity to repair DNA. Polymorphisms in DNA repair genes responsible for nucleotide excision repair (ERCC1, ERCC2 and XPA), base excision repair (XRC1 and OGG1), DNA double-strand break repair (XRCC3) and mismatch repair pathways (MLH1 and MSH2) have been studied in association with lung cancer risk [90].

Viral factors

Although it has been estimated that 15-25% of human cancer may have a viral aetiology; two viruses, the Jaasiekte sheep retrovirus (JSRV) and human papilloma virus (HPV), have been speculated to have a role in the pathogenesis of lung cancer. HPV is considered to be an evidential causative agent for most human cervical cancers, and might be having a role in other malignancies [91]. HPV16 and HPV18 infections, oncogenic variants of HPV were reported to have significantly higher prevalence in females having older than 60 years having lung cancer [92, 93]. JSRV, a -retrovirus, is highly infectious in sheep. Surviving sheep eventually develop a low-grade tumors resembling bronchioloalveolar carcinoma (BAC) through the activation of the phosphatidylinositol 3- kinase -Akt pathway. The ability of JSRV to initiate the progression of peripheral lung cancers has led to the assumption that the virus/ viral particles could be linked with development of human lung cancers.

Molecular changes in lung cancer

Prominent differences in the molecular alterations of the three major genes involved in the pathogenesis of lung cancers; KRAS, TP53 and EGFR, have been found in lung cancers, (Figure 5) providing evidence that these cancers arise through different molecular mechanisms. Mutations in TP53 are one of the most frequent changes identified in human tumour cells, and the common mutations (usually in the DNA binding domains of the gene) lead to the generation of mutant forms with altered amino acid sequences that lack DNA binding activity. Although mutations in TP53 occur in lung cancers arising in both smokers and never smokers but they occur less frequently in never smokers [94, 95]. In addition, the TP53 mutational signature (that is, the ratio of transitions, transversions and deletions) and the mutational spectrum (that is, the distribution of mutations along the gene) are distinct in lung cancers in smokers and never smokers [96]. These differences in TP53 mutational frequency, spectrum signature support the hypothesis that tobacco-related carcinogens are unlikely to be an important factor in the pathogenesis of lung cancers in most never smokers.

Figure 5 Prioritizing of signal transduction in smokers via (b) continuous loop formed by Ras signal activation compared to (a) archetypal EGFR signalling in never smokers, in lung cancer progression.

The EGFR protein belongs to a family of four surface receptor tyrosine kinases and is overexpressed in many cancers, including about 50% of lung cancers [97]. EGFR forms heterodimers or homodimers with other family members on binding to one of several ligands thereby initiating a cascade of signalling events that activate the proliferation, anti-apoptotic signalling, angiogenesis, invasion and metastasis [97]. These multiple effects are initiated by the activation of three major pathways: the Akt pathway that leads to survival through the inhibition of apoptosis; activation of the Ras-mitogen-activated protein kinase (MAPK) pathway that leads to increased proliferation; and STAT signalling with effects on many other functions. These observations led to the development and widespread clinical testing of small-molecule tyrosine kinase inhibitors (TKIs) including erlotinib (Tarceva) and gefitinib (Iressa) [98-100]. Although these inhibitors had little or no effects in treating most NSCLC cases, yet dramatic responses were observed in some patients. Subsequently, various mutations were identified in the EGFR tyrosine kinase domain associated with drug sensitivity
and treatment response [101, 102]. EGFR mutations, and hence TKI response is recorded to occur in specific lung cancer subtypes: East Asian ethnicity adenocarcinoma histology, never smoking status and female gender [97, 103]. EGFR mutations are the first specific genetic mutation associated with never smokers, and increasing smoke exposure is negatively correlated with mutation [104, 105]. Significantly, EGFR mutations target the same NSCLC subpopulations associated with higher proportions of lung cancers arising in never smokers. A combination of mutations, polymorphisms, and amplifications targeting the same allele may have a role in the increased susceptibility of East Asians to develop EGFR mutations [106]. The same factors may have a role in the high proportion of adenocarcinomas occurring in never smoking East Asian women.

Ras proteins function downstream of the EGFR signalling pathway to mediate cell proliferation [107]. Oncogenic missense mutations in KRAS result in the loss of intrinsic GTPase activity that is required to return Ras proteins to their inactive, GDP-bound form [107]. Therefore, the intrinsic negative-feedback control of Ras activity is lost, leading to the constitutively activated mutated Ras. Several distinctive features characterize KRAS mutations in lung cancer. KRAS mutations are limited to NSCLCs (predominantly adenocarcinomas), and are never present in SCLCs [103, 108, 109]. KRAS mutations also predict poor survival [110] and resistance to EGFR TKI therapy [111]. The activated forms of tobacco-related carcinogens such as NNK and BAP form adducts within KRAS, specifically at codon 12.

Both KRAS and EGFR mutations target the peripheral airways and give rise to lung adenocarcinomas [112, 113]. However, activation of both signalling pathways appears to be redundant in lung cancer progression as KRAS and EGFR mutations in lung tumors are almost entirely mutually exclusive [108].

VEGFR signalling and Angiogenesis

Angiogenesis, the process by which capillaries sprout from pre-existing blood vessels, tightly regulated by feedback loops of large number of pro-angiogenic and anti-angiogenic factors. The formation of new vessels from an existing vascular network may occur by two distinct processes; sprouting angiogenesis and intussusceptive angiogenesis. The process of sprouting angiogenesis is regulated by growth factors, such as VEGF. Sprouting angiogenesis leads to the vascularisation of previously non-vascularized space and is vigorously implicated during early to late embryogenesis, and in various pathological conditions such as cancer or rheumatoid arthritis. Intussusceptive angiogenesis refers to the splitting of an existing vessel, a mode of angiogenesis far from being as extensively studied. Intussusceptive angiogenesis is estimated to play a major part during vascularization of the lung. Cells will normally only proliferate in proximity to vessels, where there is sufficient supply of oxygen and nutrients. Through the process of intussusception, vessels will expand in tune with the tissue and vice versa. Intussusceptive angiogenesis has been shown accountable for angiogenesis in tissue expansion. There is of yet no mechanism that describes how intussusceptive angiogenesis could vascularize non-vascularized tissues.

Angiogenesis and Tumor survival

Tumor cells have an absolute requirement for a persistent supply of nutrients transported through new blood micro-vessels to nourish their growth. Thus, tumor vascularization makes a vital process for the progression of cancer from a small localized tumor to an enlarging tumor with the ability to metastasize [114]. The importance of angiogenesis in tumor growth and metastasis is well established [115]. Numerous cellular factors and signalling pathways, both stimulatory and inhibitory, participate in the angiogenic process. When the critical concentration of proangiogenic factors reaches the threshold, the “angiogenic switch” positively regulates the neovascularature, promoting tumor growth and metastasis [116]. The angiogenic process is a complex series of sequential and coordinated cellular and molecular events. When tumor cells are more than 100–200 μm from the nearest nutrient vessel, oxygen deprivation, or hypoxia, occurs within the tumor microenvironment [117]. Hypoxic cells undergo various intracellular changes, including stabilization of hypoxia inducible factor-1α (HIF-1α), which activates transcription of mediators involved in tumor progression and metastasis. One key proangiogenic mediator is the secreted protein identified as vascular endothelial growth factor (VEGF), or vascular permeability factor, a potent angiogenic factor that mediates proliferation, activation, invasion, migration, and permeability of endothelial cells.

There are seven distinct molecules identified in the VEGF family (VEGF-A, -B, -C, -D, -E, -F, and placental growth factor, PlGF) that bind three structurally homologous tyrosine kinase receptors: VEGFR-1, -2, and -3. Neuregulin-1 (NRP-1) and neuregulin-2 (NRP-2) originally identified as non-kinase receptors for the semaphorins, also bind specific isoforms of the VEGF family members [118]. Each VEGF family member has a specific binding profile with respect to the receptors. Vascular endothelial growth factor (VEGF) can bind to VEGFR1/Fit-1or to VEGFR2/Flik-1/KDR. These molecules play an important role in angiogenesis during development, wound healing and in the pathogenesis of tumour neovascularization. Figure 6 depicts the signalling pathway of the major tyrosine kinase receptor, VEGFR2 involved in angiogenesis. Patients with NSCLC or breast cancer with VEGF positive tumours were found to have a poorer prognosis than those tumours which lacked VEGF [119, 120]. Study [121] has shown that 5/12 human hematopoietic tumour cell lines expressed both VEGF and FIt-1 (VEGFR1) mRNA, indicating a potential autocrine pathway in these tumour cells. The importance of vascular endothelial growth factor and
Figure 6 Schematic of the intracellular signaling downstream of activated VEGFR-2. The numbers represent phospho-tyrosines of VEGFR-2, ovals correspond to signal mediators and boxes indicate outcomes associated with the various signal transduction pathways. DAG, diacylglycerol; EC, endothelial cell; eNOS, endothelial nitric oxide synthase; FAK, focal adhesion kinase; HSP27, heat-shock protein-27; MAPK, mitogen-activated protein kinase; MEK, MAPK and ERK kinase; PI3K, phosphatidylinositol-3 kinase; PKC, protein kinase C; PLC, phospholipase C; Shb, SH2 and -cells; TSAd, T-cell-specific adaptor.

its receptors is established by result yielding targeting of these molecules to treat cancers. Many researchers have noted and highlighted the expression of VEGFR-2 in many cancer forms. A large body of evidence indicates that the VEGF-VEGFR signalling is involved in the pathological angiogenesis, thus promoting the diabetic retinopathy, rheumatoid arthritis and malignancy of solid tumors. VEGFR-1 (Flt-1) is involved in inflammatory diseases and tissue-specific metastasis of cancer [122, 123], while the VEGF-A and VEGFR-2 system is a direct target in the suppression of pathological angiogenesis. Anti-VEGF-A monoclonal antibody is now under phase III clinical trial, and monoclonal antibody against VEGFR-2 also has a suppressive effect on solid tumor growth in mice [124]. Many pharmaceutical companies are developing small molecules which specifically block the tyrosine kinase activity of VEGFR-2 [125, 126] although most compounds block in parallel the
tyrosine kinase activity of VEGFR-1 due to the high structural homology between the two receptors. Another target for regulating VEGFR-2 signaling could be the critical autophosphorylation site on the receptor. Downstream signaling is an important target for the suppression of endothelial cell proliferation via the VEGF-A-VEGFR-2 pathway [127]. Furthermore, a report suggests that oral administration of a bacterial-type vector (non-toxic Salmonella typhimurium) containing VEGFR-2-expressing vector DNA induces an immune response to VEGFR-2, leading to an efficient inhibition of solid tumor growth in the immunized animals [128].

Targeting growth factors and their receptors

Several strategies aimed at blocking the mitogenic signaling pathway that is activated following ligand-receptor interactions, are being thoroughly evaluated. These include growth factor antagonists (pentosan polysulphate), monoclonal antibodies, receptor dimerization inhibitors, protein tyrosine kinase inhibitors (genistein, erbstatin, tyrphostins), antisense oligonucleotides and transcriptional inhibitors [129]. Monoclonal antibodies raised against the extracellular domain of the orphan receptors for functional studies can also be used for targeting tumours overexpressing these receptors.

Angiogenic inhibitors

Inhibitors of angiogenesis prevent the extensive growth of blood vessels (angiogenesis) necessary for tumors progression and survival. Some of the inhibitors, such as bevacizumab (VEGF inhibitor), are already in clinical use. One of the main limitation with augmentation of anti-angiogenesis drugs is that all the drugs catalogue as anti-angiogenesis target separate and single angiogenic molecule however there are multiple factors responsible for stimulating blood vessel growth in normal as well as in cancer cells, therefore the other known and unknown factors continue to stimulate blood vessel growth even if an individual is put up on anti-angiogenic drugs. Other problems with drug efficacy include maintenance of stability and activity, route of administration, and precise targeting of the tumor vasculature [130]. Considering that Angiogenesis pathway is one of the primary requirements for tumorigenesis, it is worthwhile to underline the importance of VEGF signaling by carrying out expression and functional studies in various tumors.

VEGF Receptors and Lung Cancer

VEGF [131] and its receptors [132] are expressed in cancer cells, in both NSCLC [133, 134] and SCLC [135]. VEGF expression is significantly correlated with neovascularization in resected NSCLC tissues and may be used as a prognostic factor [131, 136, 137]. According to a report, VEGF overexpression in surgically resected adenocarcinomatous lung tissue was indicative of earlier postoperative relapse [138]. Overall, patients with lower serum VEGF levels had longer survival compared to the patients with higher VEGF levels [135, 137, 139-141]. The measurement of serum VEGF has also been shown to be a marker for the response of patients to chemotherapy, as decreases in VEGF levels at week 12 after the initiation of chemotherapy was demonstrated to be correlated with response to therapy [135]. In a recent study, pre-treatment VEGF serum levels proved to be an independent prognostic factor in patients with metastatic NSCLC [141, 142]. VEGFR-1 expressions were shown in several tumor tissues. Decaussin et. al. showed that VEGF and its two receptors are expressed not only in tumor cells but also in fibroblasts and endothelial cells. In tumor cells, the levels of expression of VEGF and the VEGF-R1 in lung cancer were correlated, suggesting an autocrine function of VEGF on tumor cells via the VEGF-R1 receptor [134]. According to another report, high levels of serum VEGF and sVEGF-R1 before the treatment might give partial prognostic information in patients with various types of 42 lung cancer patients. They found that high levels of VEGF and sVEGF-R1 were observed when the stage of disease was high and the prognosis was worst [143]. Another study demonstrated that the pretreatment sVEGF-R1 levels were significantly lower in progressive disease [144]. Seto et al. also examined the prognostic value of the expression of VEGF and of the VEGF-Rs, fms-like tyrosine kinase receptor-1 (flt-1) and kinase insert domain-containing receptor (KDR) in NSCLC and their data suggested that expression of VEGF and VEGFRs are associated with a poor prognosis via paracrine and autocrine growth stimulation of cancerous cells (Figure 7). Moreover, tumors expressing both KDR and flt-1 may have greater metastatic potential and are associated with a poor prognosis [145]. Furthermore, the synergy between the VEGF-R1 and VEGF-R2 specific ligands, indicative of “cross-talk” between the receptors, allowing modulation of a variety of VEGF-R dependent signals is also reported [122].
Conclusion

Vascular endothelial growth factor receptors (VEGFRs) are critical for angiogenesis and lung cancer development as it is evident from growing body of literature and are considered among favourable targets for therapeutic intervention. VEGFR expression has been observed in all forms of non-small cell lung cancer (NSCLC), including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma and has invariably been correlated with all forms of cancers. However, the prognosis of cancer patients is most influenced by the type of cancer, stage of cancer, or extent of the disease. In addition to histological grading, presence of specific molecular markers can be helpful in establishing prognosis, as well as in determining personalised therapies for individuals. Despite advances in early detection and choice of treatment, non-small-cell lung cancer (NSCLC) is often diagnosed at late stages and has a poor prognosis. One of the prospective methodologies to better the outcome of treatment strategies would be to develop a comprehensive global VEGFR-Exome wide report based on the population division and smoking exposure criteria. For an effective therapeutic approaches and better understanding of the molecular origins of lung cancer, it is essential to develop the integrative molecular database comprising of details about validated molecular binders for the specific population and conditional regime (cigarette smoking and domestic smoking agents) based predictive diagnostic markers. This could lead us to devise precise personalized treatment strategy.

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