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Review article

Recruited bone marrow derived cells, local stromal cells and IL-17 at the front line of resistance development to anti-VEGF targeted therapies

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ABSTRACT

Although anti-angiogenic agents targeting VEGF have shown affordable beneficial outcomes in several human cancer types, in most pre-clinical and clinical studies, these effects are transient and followed by rapid relapse and tumor regrowth. Recently, it has been suggested that recruited bone marrow derived cells (BMDCs) to the tumor-microenvironment together with stromal cells play an important role in development of resistance to anti-VEGF therapies. Additionally, acquired resistance to anti-VEGF therapies has shown to be mediated partly through overexpression of different pro-angiogenic cytokines and growth factors including G-CSF, IL-6, IL-8, VEGF and FGF by these cells. Alongside, IL-17, a pro-inflammatory cytokine, mostly secreted by infiltrated $CD4^+$ T helper cells, has shown to mediate resistance to anti-VEGF therapies, through recruiting BMDCs and modulating stromal cells activities including endothelial cells, tumor associated macrophages and cancer associated fibroblasts. Here, we examined the role of BMDCs, tumor stromal cells, IL-17 and their negotiation in development of resistance to anti-VEGF targeted therapies.

1. Introduction

The well-established proposal that chronic angiogenesis is one of the main characteristics of tumors has now been widely accepted due to several reports, suggesting that disturbance in genetical and pharmacological parameters of different components of vascular regulatory system is responsible in development of cancer. Today, the “angiogenic switch” theory is considered as the rate limiting secondary event in different types of human cancers [1]. The validity of the concept has been confirmed by promising results achieved through administration of different angiogenesis inhibiting agents, most importantly among them the pro-angiogenic vascular endothelial growth factor (VEGF) signaling pathway inhibitors [2]. Bevacizumab (Avastin), a monoclonal ligand-trapping antibody was the initial anti-angiogenic agent approved by US Food and Drug Administration (FDA) in treatment of late stage breast cancer, colon cancer and non-small cell lung cancer (NSCLC) in concurrent administration with conventional chemotherapeutic agents [3]. However, despite an initial successful and promising response to therapy, in most cases the treatment is followed by diminished response, recurrence of disease and development of resistance to primary successful therapeutic regimen. The enthusiasm regarding the anti-angiogenic therapies soon become hampered due to the modest beneficial effects of these agents on the overall survival of the patients [4]. Continuance of bevacizumab failure in achieving desired beneficial outcomes in different clinical trials finally convinced FDA to remove bevacizumab approval in the case of metastatic breast cancer treatment in the late 2011 [5].

Until recently, lack of tumor cells continuous sensitivity to specific therapeutic regimen was mostly attributed to the mechanisms including enhancement in drug efflux pumps, alteration in targets affected by drugs, increased drug metabolism and evasion from apoptosis which have been thoroughly reviewed in different papers [6–8]. Alongside, the ability of tumor cells in expressing and secreting different proangiogenic growth factors which could result in development of alternative vascularization pathways including vessel co-option and vascular mimicry also attracted much attention [9–11]. However, it has now been clearly established that most of the extrinsic mechanisms involved in development of resistance to anti-angiogenic agents, if not all, reside in tumors microenvironment [12]. These reports were initiated by the novel work of Teicher and colleagues, linking the process of development of in vivo resistance to the interactions presented in host's normal tissues [13]. Tumors are considered as complex tissues

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since they are not only composed of genomic instable malignant cells, but also from different stable stromal cells including endothelial cells, fibroblasts and different types of immune involved cells which can also significantly affect and regulate tumorigenesis [14].

Getting exposed to anti-cancer VEGF targeted therapies, tumor microenvironment demonstrates a multifaceted reaction. For instance, upregulation in secretion of PDGF-C by tumor associated fibroblasts (CAFs) occurs in response to administration of anti- VEGF therapies [15] or pericytes maintain vascular functionality following disruption of endothelial cells through regulation of endothelial cells proliferation [9,16,17] and/or taking the role of a scaffold for accelerated revascularization immediately after cessation of therapy [18]. Additionally, different types of bone marrow derived cells (BMDCs) can be recruited to the tumor site and induce resistance to anti-VEGF targeted agents through enhancing production of multiple pro-angiogenic agents [19,20]. As an example Gr1+ CD11b+ myeloid suppressor type cells can promote secretion of Bv8 (also referred as prokineticin) and G-CSF in response to anti-angiogenic therapies [21]. Furthermore, TIE2- and tumor associated macrophages can upregulate expression of angiopoietin 2 (Ang2) and Bv8 in response to anti-VEGF targeting agents respectively [22,23]. Overall, these orchestrated mechanisms either mediated by tumor cells or the ones recruited to the microenvironment result in weakening of anti-angiogenic agents' response even though therapeutic regimen is continued.

Aberrant expression of pro-angiogenic cytokines and growth factors including VEGF subtypes, granulocyte colony stimulating factor (G-CSF), IL-17, IL-6, IL-8, fibroblast growth factor (FGF) and their complex interrelated network, also play a pivotal role in linking the refractoriness to the anti-angiogenic targeted therapies to the components of the tumor microenvironment [24,25]. Among mentioned cytokines, expression of IL-17 by specific group of recruited CD4+ T cells, namely T helper 17 (T_H17) cells in response to anti-angiogenic therapies, play the most important role in development of resistance to anti-VEGF therapies [26]. IL-17, initially cloned by subtractive hybridization from an activated T-cell library (named cytotoxic T-lymphocyte–associated antigen 8), consists of different homologous proteins which may possess different biologic profiles [27] and its role in development of resistance to anti-angiogenic targeted therapies is currently under investigation.

In present review, we tried to illustrate the role of recruited BMDC and tumor stromal cells in development of resistance to anti-VEGF targeted therapies, as well as clarifying the crucial role of IL-17 in development of resistance both directly through activation of VEGF independent angiogenic mechanisms and indirectly through recruiting BMDCs and affecting tumor stromal cells.

2. Currently approved anti-VEGF targeted therapies in clinic

The first anti-VEGF targeted therapy approved by FDA and several other regulatory authorities for application in cancer therapy was bevacizumab. This agent is currently approved for treatment of glioblastoma, non-small cell lung, colorectal and renal cell cancers. Except for glioblastoma, in all other indications, bevacizumab approval has been granted in combination with chemotherapy. Sunitinib, belonging to the family of multikinase inhibitors, capable of inhibiting VEGFR1, 2, 3, c-Kit and PDGFR is currently approved for treatment of gastrointestinal stromal tumors (GISTs) and renal cancer cell. Sorafenib is a similar agent, approved for treatment of renal cell cancer and hepatocellular carcinoma (hepatoma). Pazopanib is another multikinase inhibitor, also approved for treatment of renal cell cancer. All three mentioned multikinase inhibitors have been approved as monotherapies in treatment of cancer. Unfortunately, development of resistance to anti-VEGF targeted therapies has been reported both in the form of monotherapy and combination therapy [28]. When discussing development of resistance to these group of agents, considering the tumor type as well as the mode of therapy (i.e. monotherapy or in combination with chemotherapeutic agents) is of utmost importance. In the case of monotherapy (e.g. in hepatoma or renal cell cancers) resistance is primarily connected to the VEGF pathway. Nevertheless, in the case of colorectal, breast and non-small cell lung cancer which anti-VEGF targeted therapy is together with chemotherapy, the resistance mechanism seems to be more complex [29].

3. The role of local stromal cells and BMDCs in development of resistance to anti-VEGF therapy

3.1. BMDCs in development of resistance to anti-VEGF therapy

So far, many studies have reported the tumorigenic and angiogenic effects of infiltrated bone marrow derived cells (BMDCs) including macrophages, endothelial progenitor cells (EPCs) and myeloid derived suppressor cells (MDSC) [30–32]. It has been shown that secretion of pro-angiogenic factors in response to anti-VEGF therapies including Placental growth factor (PIGF), VEGF, FGF and Angiopoietin 1 (Ang1) together with cytokines like IL-8, G-CSF and Stromal cell-derived factor 1 (SDF-1) significantly induce recruitment of these cells to the tumor microenvironment which in turn, results in development of resistance to anti-angiogenic agents. MDSCs also referred as $Gr1^+$ $CD11b^+$ myeloid cells mostly compose of neutrophils which possess both immunosuppressive and tumor promoting abilities [33,34]. Based on the study performed by Shojaei et al., it was demonstrated that the population of MDSCs in tumors refractory to anti-VEGF therapies was significantly higher compared to the treatment sensitive ones [35]. Also, the functionality of these cells was different from the ones in treatment sensitive tumors. These cells were able to maintain tumor growth even in the presence of anti-VEGF antibodies [35]. Same group explained the reason to be related to the overexpression of G-CSF, which in turn, induces production of Bv8 from bone marrow, promoting differentiation and also survival of myeloid progenitor cells. Bv8 itself can also promote mobilization of progenitor cells to the tumor microenvironment [33,35,36]. Furthermore, it has been shown that neutrophils presented in tumors were capable of producing Bv8 and VEGF [33,37,38] which in turn, could accelerate tumor angiogenesis even in the presence of anti-VEGF pathway blocking agents [39]. Additionally, it has been shown that Th17 induced recruitment of MDSC cells to the tumor microenvironment can also result in development of resistance to anti-VEGF targeted agents [26].

3.1.1. Macrophages

Macrophages are the other group of myeloid cells involved in development of resistance which have been shown to be recruited to the microenvironment through secretion of different cytokines including monocyte chemotactic protein 1 (MCP-1), VEGF and macrophage colony stimulating factor (M-CSF) [40,41]. Tumor associated macrophages are capable of secreting several pro-angiogenic factors including VEGF-A, VEGF-C, EGF, TGFβ, IL-8 and thymidine phosphorylase [42–45]. Furthermore, secretion of matrix metalloproteinases (MMPs) which induce degradation of extracellular matrix and secretion of matrix-sequestered growth factors, capable of promoting tumor growth and angiogenesis, is mostly accelerated by macrophages [46]. Also, acting as “bridging cells” between two separate tip cells, macrophages can mostly accelerate vascular sprouting [44,45]. Although in several murine tumor models anti-VEGF therapy has shown to decrease macrophage infiltration, as different growth factors are involved in recruiting macrophages, it is mostly expected that these effects are transient [47–49]. Furthermore, observed effects might also depend on the specific subclass of macrophages. For instance, TIE2-expressing macrophages are a distinct subclass of macrophages which are mostly recruited to the tumor site by means of hypoxia inducible and tumor secreted chemokines [50]. Also, TIE2-macrophages can both secret multiple pro-angiogenic factors including VEGF and associate with tumor levels (Fig. 1) [51].

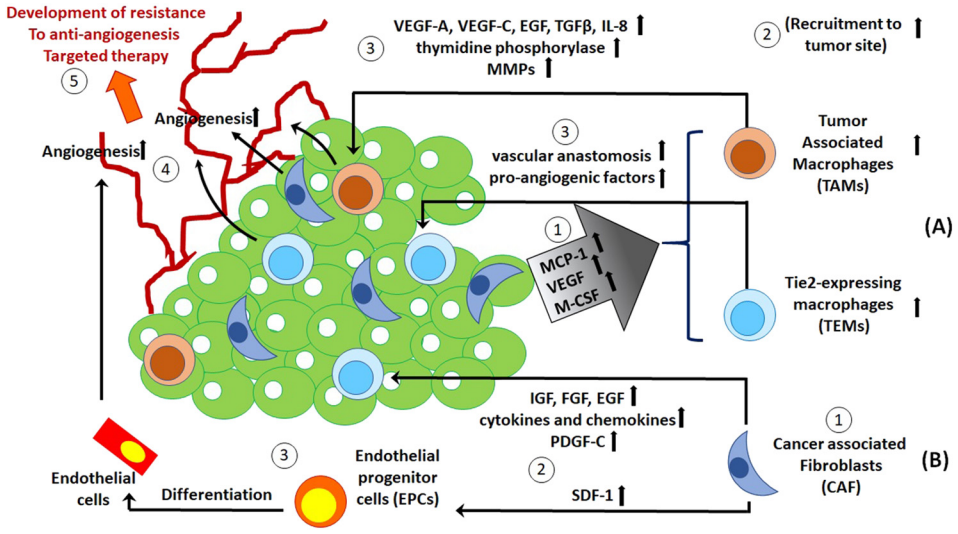

Fig. 1. The role of local stromal cells in development of resistance to anti-VEGF therapy. **(A)** secretion of different cytokines including monocyte chemotactic protein 1 (MCP-1), VEGF and macrophage colony stimulating factor (M-CSF) recruit tumor associated macrophages (TAMs) and Tie2- expressing macrophages (TEMs) to the tumor microenvironment. TAMs result in development of resistance to anti-angiogenic therapies through the secretion of several pro-angiogenic factors including VEGF-A, VEGF-C, EGF, TGFβ and IL-8, thymidine phosphorylase and matrix metalloproteinases (MMPs) while TEMs promote vascular anastomosis and secret different proangiogenic factors. **(B)** cancer associated fibroblasts (CAFs) develop resistance to anti-angiogenic therapies by two ways: (1) through secreting a number of pro-angiogenic mediators including IGF, FGF, EGF, cytokines and chemokines and PDGF-C; and (2) through secretion of SDF-1 which in turn, recruits endothelial progenitor cells (EPCs) to the tumor site.

3.1.2. Tumor associated macrophages (TAMs)

As mentioned earlier, BMDCs play a crucial role in development of resistance to VEGF targeted therapies. The most well-known example of this mechanism is development of resistance to vatalanib in glioblastoma. It has been proposed that therapies with capability of depleting the number of BMDCs in tumor site may resensitize refractory tumors to vatalanib [19,52,53]. In this case, hypoxia regulated neuropilin 1 (NRP1) by controlling TAMs infiltration in hypoxic areas of tumor may control angiogenesis and tumor growth. Therefore, future studies on NRP1 may identify whether this biomolecule is also involved in development of resistance to targeted anti-VEGF therapies or not. Furthermore, it has been shown that proliferation of differentiated macrophages as well as their polarization play an important role in recruitment of TAMs into the xenograft resistant to bevacizumab [54]. Furthermore, bevacizumab therapy has shown to result in down-regulation of macrophage inhibitory factor (MIF) expression at tumor edges which can promote proliferation of TAMs and their reprograming to proangiogenic macrophages regardless of continuation of therapy with this agent [54]. These types of macrophages are important as they can secret VEGFA, TNFα and IL-2 which in turn can promote tumor growth, metastasis and development of acquired resistance to bevacizumab.

3.1.3. Tie2-expressing macrophages (TEMs)

As a subpopulation of TAMs, TEMs cross talk with other stromal cells may significantly contribute to development of resistance to anti-VEGF therapies. For instance, the negotiation between TEMs and Ang2/Tie2 tip cells may increase vascular anastomosis and Ang2/Tie pathway blockade can significantly impair angiogenesis process [55,56]. Furthermore, inhibiting VEGFR2 results in upregulation of Ang2 which in turn, promotes TEM infiltration in RIP-Tag2 pancreatic tumor model. In this case, administration of concurrent inhibitors of Ang2 and VEGF decreases TEM, vascular permeability and promotes pericyte coverage. Ang2, mainly produced by endothelial cells, is one of the main mediators of endothelial and myeloid cells interaction. Therefore, it is not surprising to observe a better vascular normalization and shift to TAM phenotype compare to monotherapy [57]. Despite this, application of trebananib, an Ang1,2 inhibitor together with bevacizumab couldn't significantly improve outcome of therapy in comparison to bevacizumab monotherapy in glioblastoma.

3.1.4. Myeloid-derived suppressor cells (MDSCs)

MDSCs have shown to be involved in multiple steps of tumor progression including tumor cell survival, invasion, metastasis and angiogenesis [58,59]. Nevertheless, it was the pioneering works of Shojaei and coworkers which introduced the role of MDSCs in development of tumor resistance to anti-VEGF therapies [35,36]. To facts have been established regarding the role of MDSCs in development of resistance to anti-VEGF therapies. First, enhanced recruitment of MDSCs to the tumor site has been observed in tumors refractory to anti-angiogenic therapies. Second, through secreting Bv8 and VEGF, MDSCs result in promotion of tumor growth regardless of administration of anti-VEGF targeted agents [35,39]. Continuous residence of MDSCs in tumors has been observed in sunitinib resistant mouse models. This phenomenon has been partly explained by the local expression of GM-CSF and activation of STAT-5. Despite this, detailed mechanism of resistance development to anti-VEGF targeted therapies due to MDSCs has not been fully established yet (Fig. 2).

3.1.5. Endothelial progenitor cells (EPCs)

EPCs are other group of BMDCs which are mostly recruited to the tumor site through secretion of VEGF and SDF-1 by endothelial and tumor associated cells [34,60]. Being stimulated by SDF-1, EPCs begin to secret different pro-angiogenic factors and accelerate angiogenesis [61,62]. Furthermore, these signaling pathways have shown to modulate recruitment and homing of mononuclear cells involved in multiple myeloma associated angiogenesis [63]. More importantly, EPCs can differentiate in to endothelial cells and further take part in newly forming blood vasculatures (Fig. 2) [64]. During hypoxia, tumor cells activated by secreted HIF-1α, initiate to secret VEGF and SDF-1 which in turn, significantly promote recruitment of EPCs in to the tumors microenvironment [65].

3.2. Local stromal cells in development of resistance to anti-VEGF therapy

3.2.1. Endothelial cells

Endothelial cells, considered as group of cells lining the luminal layer of blood vessels, are the main target of developed anti-angiogenic agents so far. This mainly comes from two reasons: first, they are easily accessible for the compounds presented in blood stream and second, they are the key cells involved in blood vessels growth [66,67]. Based on different genetical experiments and morphological studies, it is now clear that a significant heterogeneity dose exist in endothelial cells both in healthy and disease-associated tissues [68]. Genomic material transferring between endothelial cells and tumor associated cells has proposed to be the main reason of genetical abnormalities observed in

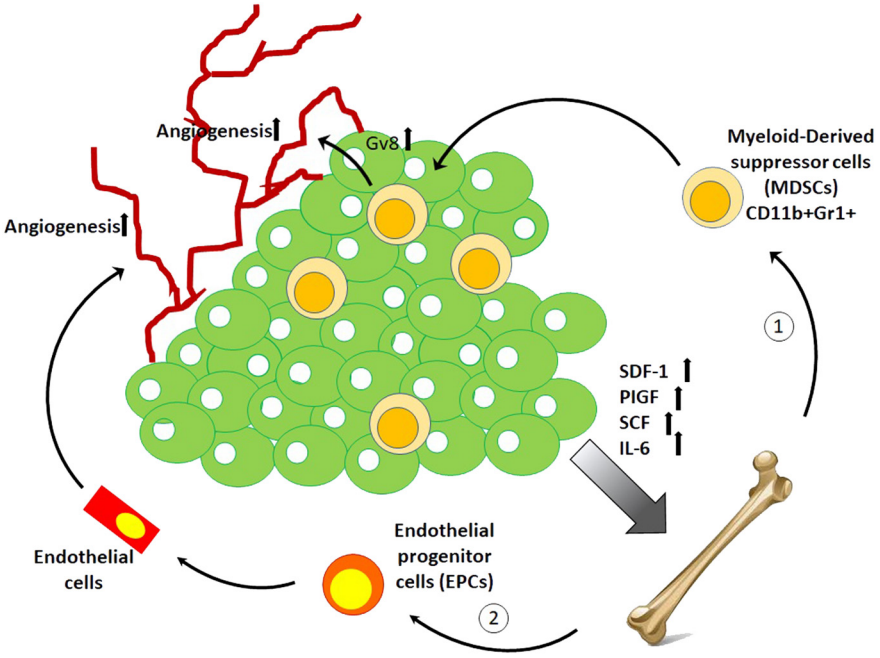

Fig. 2. The role of BMDCs in development of resistance to anti-VEGF therapy. Secretion of pro-angiogenic factors in response to anti-VEGF therapies including Placental growth factor (PIGF), Stromal cell-derived factor 1 (SDF-1), together with cytokines like IL-6 and 8 significantly induce recruitment of BMDCs. (1) Recruited myeloid-derived suppressor cells (MDSCs) in tumor microenvironment initiate secretion of Bv8 which in turn, enhances angiogenesis and development of resistance. (2) Recruited endothelial progenitor cells (EPCs) can differentiate in to endothelial cells and further take part in newly forming blood vasculatures.

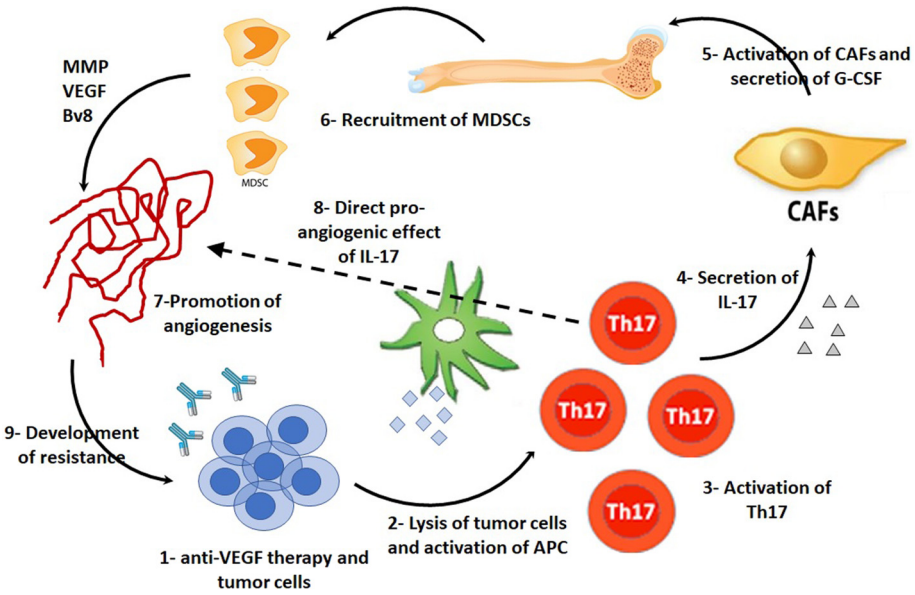

Fig. 3. The negotiation between T_H17 and IL-17 with stromal cells and BMDCs in development of resistance to anti-VEGF targeted therapies. (1) Administration of anti-VEGF targeted therapies results in ablation of tumor cells and release of antigens. (2, 3) Released antigens are up taken by antigen presenting cells which in turn, activate T_H17 cells. (4, 5) T_H17 cells secret IL-17 which in next place, triggers secretion of pro-inflammatory cytokines including G-CSF by CAFs in tumor microenvironment. (6) G-CSF enhances mobilization and recruitment of immunosuppressive myeloid cells (MDSCs). (7) Secretion of proangiogenic factors including MMPs and Bv8 from MDSCs results in progression of VEGF-independent tumor angiogenesis. (8) IL-8 also directly induces angiogenesis. (9) The consequence of this overall process is development of resistance to anti-VEGF targeted therapy.

tumor associated endothelial cells [69,70]. Whatever the reason, genetical instability may result in development of resistance to therapies although overexpression of p-glycoprotein and breast cancer resistance proteins are currently considered as the main reasons for development of resistance in endothelial cells [71,72]. Recently, altered glycosylation of VEGFR2 has also been proposed as a mechanism beyond the overexpression of growth factors in development of resistance to anti-angiogenic agents in endothelial cells [73].

3.2.2. Cancer associated fibroblasts (CAFs)

Although still unknown in origin, CAFs entail a large percentage of resident cells in tumor microenvironment, with a well-known accelerating effect on tumor progression, invasion, angiogenesis and development of resistance to different anti-angiogenic agents have been clearly stablished in different studies [74,75]. CAFs secret a number of pro-angiogenic mediators including IGF, FGF, EGF, cytokines and chemokines, all of which have shown to be upregulated in tumors refractory to anti-angiogenic therapies [76,77]. Based on Orimo and colleagues, these cells are also capable of secreting SDF-1 which in turn, recruits endothelial progenitor cells (EPCs) to the tumor site [78,79]. Based on the study performed by Crawford and coworkers, isolated CAFs from resistant tumors to anti-VEGF targeted therapies could promote growth of tumors sensitive to anti-VEGF targeted therapies even during administration of anti-VEGF therapies in the mouse tumor model. This capability is strongly linked to the increased secretion of PDGF-C rather than SDF-1 by CAFs [15]. Kinugasa et al. have recently demonstrated that CAFs grown in hypoxic and avascular areas can express CD44, a marker for cancer stem cells in different tumor types. Interestingly, treatment of tumors with anti-angiogenic agents significantly increases CD44 expression by CAFs. As expression of CD44 has shown to be together with increased tumor cells resistance, CAFs can develop resistance to different therapeutic regimens. These data suggest CAFs as a promising target for overcoming both resistance to anti-angiogenic agents and other therapeutic regimens (Fig. 1) [80].

3.3. IL-17 induced resistance to anti-VEGF targeted therapies in negotiation with recruited bone marrow derived cells and local stromal cells

As a pro-inflammatory cytokine, IL-17 has shown to significantly involve in acceleration of tumor growth, transformation of malignant cells and induction of metastasis. Affecting stromal cells and fibroblasts in tumor microenvironment, IL-17 results in expression of a number of angiogenic factors including VEGF. Furthermore, the micro vessel density of tumors is directly correlated with IL-17 producing $CD4^+$ T-cells [81]. Additionally, it has been shown that IL-17 can promote secretion of TGFβ which in turn can induce overexpression of VEGF receptors on endothelial cells and further enhance the response of these cells to VEGF [82]. Besides, IL-17A and IL-17F by affecting epithelial and endothelial cells and inducing production of chemokines can indirectly recruit neutrophils to the tumor microenvironment. Neutrophil's response may also be modulated by IL-17 through induction of TNF-α, IFNγ and GM-CSF secretion. It has been shown that IL-17 can promote expression of IL-6 both in malignant and stromal cells presented in tumor microenvironment by activating STAT3 pathway [83]. IL-17 is also an effective mediator in regulating secretion of several proangiogenic factors including VEGF, KC, MIP2, prostaglandins and nitric oxide (NO) from fibroblasts especially in tumors and inflammatory disorders [84].

Macrophages are also another member of either physiologically or pathologically immune involved cells in angiogenesis [85]. The proangiogenic factors secreted from macrophages include TNF-α, IL-8 and VEGF, which can affect different stages of angiogenesis by modifying the local extracellular matrix, promoting proliferation and migration of endothelial cells and inhibiting vascular growth through forming differentiated capillary [85]. Additionally, infiltrated $CD4^+$ T cells to the tumor tissue may influence tumor cells and fibroblasts, together with Tumor associated macrophages to orchestrate secretion of multiple proangiogenic factors including VEGF which in turn, can affect immune system through inhibiting dendritic cells, resulting in induction of tumor growth and angiogenesis [81]. Secretion of IL-17 by tumor infiltrating Th17 cells also results in expression of G-CSF which in turn, promotes recruitment of immature myeloid cells to the microenvironment and development of resistance to anti-VEGF targeted therapies via inducing synthesis of pro-angiogenic factor Bv8 from myeloid cells [26]. Although G-CSF doesn't have any promoting effect on proliferation of cancer cells in vitro, enhanced neovascularization results in accelerated tumor growth in vivo. It has also been reported that G-CSF may promote mobilization and differentiation of EPCs which have been incorporated in new blood vessels [86].

In the case of invasive ductal carcinoma, it was reported that IL-17 enhances tumor aggressiveness through inducing secretion of multiple angiogenic factors including IL-8 (CXCL8), VEGF, MMP2 and MMP9 [87,88]. Furthermore, secretion of recombinant IL-17 in a case of murine breast cancer model 4T1 was together with increased density of microvasculature which is a direct biomarker for induction of tumor angiogenesis [89]. Previous studies have also reported the stimulatory effect of IL-17 on induction of several angiogenic mediators secretion including IL-6, IL-8 and prostaglandin together with enhancing expression of intracellular adhesion molecule (ICAM-1) both in keratinocytes and fibroblasts [90–93]. Furthermore, secretion of TNF-α, IL-1β and stromelysin has also been reported by macrophages being affected by IL-17 [94]. Indirect angiogenic factors refer to a group of cytokines or growth factors which can effectively stimulate angiogenesis in vivo, however, fail to represent mitogenic activity for vascular endothelial cells in vitro. IL-17 is one of these indirect angiogenic factors similar to several other ones including platelet derived growth factor B (PDGFB) subunit homodimer and TGF-β [95].

Based on studies, a direct correlation exists between the expression levels of IL-17 and micro vessel density in different cancers including human ovarian cancer, NSCLC and hepatocellular carcinoma (HCC) [96–98]. Furthermore, the number of IL-17 producing cells has shown to be meaningfully increased in tumor tissues, peripheral blood and malignant ascites fluid [99–101]. Recently, it has been proposed that IL-17 may demonstrate direct angiogenic effects through interaction with IL-17 receptors presented on endothelial cells. Additionally, based on study performed by Liu et al., the most important angiogenic factor produced by IL-17 in colorectal carcinoma is VEGF [102]. In another study performed by Changchun et al. it was demonstrated that IL-17 pathway results in augmentation of TNF-α induced increment in expression of HIF-1α and inhibition of vasodilation stimulated phosphorylation [103]. Accelerated expression of HIF-1α results in further enhancement in expression of several angiogenic factors, some of them include expression of G-CSF, GM-CSF, KC, MIP-2, PGE2 and VEGF [104,105]. The proposed mechanism have been related to promoting stability of TNFα induced mRNA [106].

Overall, based on theory proposed by Chung et al., ablation of tumor cells through administration of anti-VEGF targeted therapies may result in release of antigens which in turn, results in activation of T_H17 effector function mediated by antigen presenting cells. This process finally enhances secretion of IL-17 which in next place, triggers secretion of pro-inflammatory cytokines including G-CSF by CAFs in tumor microenvironment which enhances mobilization and infiltration of immunosuppressive myeloid cells (MDSCs). Alongside, IL-17 signaling also regulates secretion of proangiogenic factors including MMPs and Bv8 from immunosuppressive myeloid cells which results in progression of VEGF-independent tumor angiogenesis. Therefore, IL-17 directly potentiates angiogenesis in a VEGF independent manner [107].

4. The IL-17 signaling pathway promoting secretion of pro-angiogenic mediators inducing refractoriness to anti-VEGF targeted therapies

The IL-17 receptor (IL-17R) has shown to be made from IL-17RA and IL-RC, both of which possess an SEFIR domain. In addition to the IL-17RC domains, IL-17RA possesses two more domains namely TILL and Distal domains. Upon binding of IL-17, IL-17RA and IL-17RC create a heterodimer through which recruits AKT1 by interacting with the SEFIR domain. Through this, AKT binds with TRAF6 using its TRAF-binding domain and recruits it to the IL-17R complex. As an E3 ubiquitin ligase, AKT results in poly ubiquitination of TRAF6 which in turn may result in poly ubiquitination of TAK1, further activating IKK and NF-kB, a well-known transcription factor involved in angiogenesis and also development of resistance [108,109]. IL-17 mediated AKT complex also promotes activation of mitogen activating protein kinase (MAPK) and induces expression of C/EBP. Furthermore, IL-17 may also promote activation of JAK/PI3K signaling pathway. All these pathways in next step result in activation of AP1, NF-kB and C/EBPs further inducing expression of IL-6, IL-8, VEGF, MMPs and so on [110].

Secreted IL-8 by affecting phosphatidyl inositol 3 kinase (PI3K) promotes chemotaxis of neutrophils. Furthermore Activation of this lipid/protein kinase results in phosphorylation of PKB/AKT which its role in promotion of angiogenesis in different cancers has been well established. Additionally, IL-8 also involves in modulation of mitogen activated kinase (MAPK) signaling pathway further results in induction of specific signaling cascades including Raf1/MAP/ERK kinase1/ERK cascade. Activated MAPK promotes proliferation and survival in neutrophils, endothelial cells and cancer cell lines. Besides, IL-8 can activate phospholipase C which in turn cleaves the membrane associated lipids in to diacylglycerol and inositol 3-phosphate further activating protein kinase C (PKC). Which in neutrophils, promotes their secretory function and Mac-1-mediated adhesion. Tyrosine kinase receptor in endothelial and cancer cells is the other pathway affected by IL-8 pivotal in angiogenesis. Transactivation of EGFR in ovarian cancer endothelial cells results in further activation of MAPK. Additionally, it has been shown that IL-8 is capable of phosphorylating VEGFR2 in endothelial cells through which regulates the endothelial barrier permeability. Activation of specific transcription factors including NF-kB and

STAT3 which are greatly involved in modulation of angiogenesis are also mediated by IL-8 [111]. Other cytokines and growth factors expressed by IL-17 including IL-6, FGF, VEGF, IGF and EGF also demonstrate similar pro-angiogenic effects through activating PI3K and MAPK however by different receptors and activating different linking proteins in target cells (Fig. 3).

5. Future perspectives

Overall, as discussed in this paper, orchestrated mechanisms either mediated by BMDCs recruited to the tumor microenvironment or the stromal cells result in weakening of anti-angiogenic agent's response even though therapeutic regimen is continued. As IL-17 demonstrates a modulatory role on these cells and mediates resistance to anti-VEGF targeted therapies through inducing expression of complex network of pro-angiogenic agents, neutralizing IL-17 with specific monoclonal antibodies or the producing source of them, mainly Th17 cells appears to be an attractive opportunity for resensitizing refractory tumors to anti-VEGF targeted therapies. Plausible to this theory, administration of agents with the ability of blocking multiple signaling pathways appears to be another promising strategy for tackling resistance to anti-angiogenic agents. At the end, emphasizing this point seems necessary that angiogenesis is the consequence of interaction between multiple angiogenic factors and angio-stimulatory cells. Consequently, it is not surprising to observe rapid resistance in the case of single therapy with anti-VEGF targeted therapies.

Conflict of interest

The authors declare that there are no conflicts of interest.

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