Interleukin-6: An angiogenic target in solid tumours

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Abstract

During the past decade, incorporating anti-angiogenic agents into the therapeutic management of a myriad of malignancies has in certain cases made a significant impact on survival. However, the development of resistance to these drugs is inevitable and swift disease progression on their cessation often ensues. Hence, there is a drive to devise strategies that aim to enhance response to anti-angiogenic therapies by combining them with other targeted agents that facilitate evasion from resistance. The pleiotropic cytokine, interleukin-6 (IL-6), exerts pro-angiogenic effects in the tumour microenvironment of several solid malignancies and there is emerging evidence that reveals significant relationships between IL-6 signalling and treatment failure with antibodies directed against vascular endothelial growth factor (VEGF). This review summarises the role of IL-6 in pivotal angiogenic processes and preclinical/clinical research to support the future introduction of anti-IL-6 therapies to be utilised either in combination with other anti-angiogenic drugs or as a salvage therapy for patients with diseases that become refractory to these approaches.

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1. **Introduction**

Over 40 years since Folkman’s seminal work on tumour angiogenesis [1], the era of targeted therapy has witnessed the successful incorporation of anti-angiogenic agents into treatment algorithms for a plethora of malignancies. Although their impact on survival in numerous tumour types has been significant, several issues relating to deleterious side effects, development of resistance, establishment of optimal duration of treatment and predictive biomarkers have yet to be adequately addressed. Consequently, there is an urge to discover alternative angiogenic targets which serve as a solution to these problems and ultimately enhance response to the myriad of therapeutic agents that inhibit angiogenesis. One such factor is the pleiotropic cytokine, interleukin-6 (IL-6); a potent pro-angiogenic mediator that is omnipresent in the inflammatory microenvironment of most solid tumours [2].

IL-6 has a broad spectrum of biological activity relating to regulation of inflammation, cell proliferation, immunomodulation, haematopoiesis and tumourigenesis. Human IL-6 consists of 184 amino acids and was initially identified as an antigen-nonspecific B-cell differentiating factor that induced B-cell production of immunoglobulins. IL-6 acts through the formation of a high-affinity complex with a receptor that consists of an 80-kDa IL-6 binding glycoprotein gp80 (α-chain, IL-6Rα) and the 130-kDa signal transducer gp130 (β-chain). Both gp80 and gp130 exist in transmembranous and soluble (sgp80 and sgp130) forms. The transmembrane domain of gp80 consists of a short intracytoplasmic region that associates with gp130 as a consequence of IL-6 binding. This result in gp130 homodimerisation and signal transduction that characterises classic signalling; the predominant mode through which IL-6 orchestrates its homeostatic functions [3]. Both sgp80 and sgp130 are formed either by cleavage from the cell membrane by transmembrane metalloproteinases or translated from alternate mRNA splicing [4–7]. Whilst gp80 expression is restricted to certain cell types (monocytes, T cells, B cells, neutrophils, hepatocytes and tumour cells) [7], gp130 expression is ubiquitous. However, as with viral IL-6, human IL-6 signalling transduction can remain in cells lacking transmembrane gp80 by forming a complex with sgp80 and membrane bound gp130 to initiate downstream events. This is known as trans-signalling and is critically involved in inflammatory diseases (e.g. inflammatory bowel disease and rheumatoid arthritis) and is the principal mode for IL-6 tumour promoting activity; which is particularly evident in colorectal cancer. [3,8,9]. Trans-signalling is tightly modulated by sgp130 which can neutralise IL-6-sgp80 complexes, and sgp80 that enhances the antagonistic activity of sgp130 [10]. Although previously thought not to impede classic signalling, recent reports confirm that sgp130 can indeed inhibit this pathway in addition to trans-signalling [11]. Gp130 behaves promiscuously in that it acts as a common signal transducer for other cytokines along with IL-6, namely IL-11, IL-27, ciliary neurotrophic factor (CNTF), cardiotropin-1 (CT-1), oncostatin M (OSM), neurotrophin-1 and leukaemia inhibitory factor (LIF) [3,12]; each of which have defined physiological roles. This group of cytokines are collectively known as the IL-6 cytokine superfamily [13] and all, with the exclusion of LIF and OSM, interact with their specific binding receptor leading to gp130 heterodimerisation. Intracellular signalling is then initiated through activation of gp130 associated cytoplasmic tyrosine kinases, namely the Janus-activated kinases 1 and 2 (JAK1 and JAK2) which phosphorylate signal transducers and activators of transcription (STAT) proteins, Ras/MEK/ERK and PI3K/Akt [14]. These downstream IL-6 signalling pathways efficiently facilitate tumour proliferation, migration [2,15], survival [2,16] and chemoresistance [2] which all contribute to poor outcomes in patients with a broad spectrum of malignancies [2,17]. Through these pathways and in particular STAT3, IL-6 provides a fertile environment for angiogenic processes to flourish through the induction of factors that are currently well recognised targets for a host of anti-angiogenic therapies.

1.1. **IL-6 and angiogenic processes**

The phenomena of tumour neo-angiogenesis (characterised by vessel sprouting and incorporation of bone-marrow derived endothelial precursors) and co-opting of existing blood vasculature is paramount to the growth of tumours beyond 100–200 μm. This is governed by the balance of pro- and anti-angiogenic factors and the weighting of these determine the ‘angiogenic switch’ state [18]. It follows that a preponderance of pro-angiogenic molecules over anti-angiogenic molecules will turn on this switch and signals such as genetic mutations alongside hypoxia and inflammation within the tumour microenvironment can assist this process [19–21]. Subsequently, tumours can develop their own vasculature through expansion of existing blood vessels characterised by endothelial tip sprouting and insertion of interstitial tissue columns into the lumen of these vessels (i.e. intussusceptions) [20,22]. The prominent feature of this sprouting phase is tumour vessel dilatation, increased permeability and leaking due to the effects of vascular endothelial growth factor (VEGF). VEGF, a 45 kDa glycoprotein, was the first vascular-specific growth factor to be characterised and is widely accepted to be the essential driver for vascularisation [23]. It consists of a family of five structurally related molecules; namely VEGF-A, B, C, D and placental growth factor (PIGF) and signals through three receptor tyrosine kinases namely VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1) and VEGFR-3 (Flt-4) [24]. Most of the aforementioned properties of VEGF are mediated through VEGFR-2 and conversely VEGFR-1 exhibits antagonistic effects by blunting signalling through VEGFR-2 [23]. Furthermore, although VEGFR-1 has a higher affinity for VEGF than VEGFR-2, it only possesses a weak capacity for signal transduction [24,25]. Interestingly, there are additional co-receptors that exhibit a high affinity for particular VEGF isoforms; namely the neuropilins, which include neuropilin-1 (NRP-1) and
neuropilin-2 (NRP-2). NRP-1 is able to bind VEGF$_{165}$ (the predominant exon splice variant of VEGF) and present this ligand to VEGFR2 which results in both increased signal transduction through VEGFR2 and enhanced VEGF$_{165}$ related chemotaxis [23,26].

The influence of hypoxia on VEGF induction is particularly highlighted by the intimate relationship between the Von Hippel Lindau (VHL) tumour suppressor gene and hypoxia inducible factor-1α (HIF-1α). Under normoxic conditions, VHL induces the hydroxylation and subsequent ubiquitin mediated degradation of HIF-1α which in turn modulates the expression of VEGF mRNA [27,28]. Conversely, under hypoxic conditions, this process is reversed and hence promotes angiogenesis. More specifically, in malignancies such as renal cell carcinomas characterised by VHL mutations, HIF-1α is constitutively activated [29] and aberrant angiogenesis is a prominent feature.

As inflammation is one of several conditions that results in HIF-1α and VEGF upregulation, it stands to reason that considerable interplay exists between these factors and inflammatory mediators within the tumour microenvironment. Amongst the plethora of such mediators, IL-6 in particular exhibits an intimacy with HIF-1α and VEGF which is predominantly driven by STAT3 signalling [30]. For example, using chromatin immunoprecipitation assays, Niu et al. confirmed that STAT3 binds directly to the VEGF promoter and an activated STAT3 mutant (STAT3C) could effectively upregulate VEGF and tumour angiogenesis [31]. Moreover, treatment of various epithelial cell lines with IL-6 for 6–48 h can significantly induce VEGF mRNA to a level comparable to the effects of hypoxia or cobalt chloride, an activator of hypoxia-induced genes [32]. Furthermore close correlations have been identified between IL-6 and hypoxia inducible factors (both HIF-1α and HIF-2α), which suggest an alternative link between this pleiotropic cytokine and VEGF regulation [33].

IL-6 also has notable effects on other angiogenic processes such as promoting endothelial progenitor cell migration and proliferation [34,35], regulation of basic fibroblast growth factor (bFGF) [36], stimulation of vascular smooth muscle cell (VSMC) migration [37] and induction of platelet derived growth factor (PDGF) mediated VSMC proliferation [38]. However, the relationship between IL-6 signalling and its influence on PDGF-mediated pericyte recruitment warrants further investigation. IL-6 also has the potential to manipulate factors responsible for either inhibiting or stabilising angiogenic switching. Loganadane et al. have previously demonstrated that secretion of the endogenous angiogenesis inhibitor thrombospondin-1 (TSP-1) into the subendothelial matrix can be modulated by IL-6; however, this effect was predominantly influenced by increased cell density [39]. Although, the angiostatic factor, endostatin (a 20 kDa carboxy-terminal fragment of collagen XVIII) has been shown to effectively reduce IL-6 in human umbilical vein endothelial cells (HUVECs) [40], further studies are required to verify the extent of its regulation by IL-6.

IL-6 has also been implicated in other angiogenic signalling pathways. Activation of the evolutionary conserved Notch signalling pathway by its ligands jagged-1 and Delta-like 4 ligand (DLL4) regulate numerous aspects of the tumour angiogenesis spectrum including endothelial tip cell sprouting and vascular maturation [41]. Sansone et al. noted that IL-6 can stimulate Notch3 dependent upregulation of jagged-1 (Fig. 1) and this promoted growth of breast cancer cells and maintained their aggressive phenotype [42]. More recently, targeting IL-6 has been shown to impede jagged-1 expression alongside decreased tumour vasculature in ovarian cancer in vivo models [43].

With such compelling evidence highlighting the angiogenicity of IL-6, it would intuitively appear to be an attractive target in numerous tumour types; especially in view of the recent success witnessed with other anti-angiogenic regimens [44–48]. This review will summarise the evidence linking this pleiotropic cytokine with angiogenic processes (Fig. 1) in a host of solid malignancies and point towards the possible future therapeutic implications alongside other novel agents and as a salvage strategy for patients developing resistance to these therapies.

2. IL-6 and angiogenesis in solid tumours

2.1. Colorectal cancer

Over the past few years, there has been increasing evidence linking IL-6 to the development and progression of colorectal cancers [49]. Elevated expression in serum and tumour cells have been reported alongside correlations with advancing stage and poor survival [50–52]. Furthermore, in colitis associated cancer (CAC) in vivo models, IL-6 can enhance proliferation of tumour initiating cells, increase tumour burden at late stages of disease and protect both normal and malignant intestinal epithelial cells from apoptosis in a STAT3 dependent fashion [53]. Significantly, reduction in tumour size and number has also been observed in CAC models with IL-6 ablation via stable knockdown or IL-6R monoclonal antibodies [53,54]. With respect to the influence of IL-6 on angiogenesis in this disease, the evidence unsurprisingly leans towards its relationship with VEGF. Eldesoky et al. measured preoperative serum VEGF and IL-6 in 35 colorectal cancer patients and 30 controls. Colorectal cancer patients had significantly higher IL-6 and VEGF levels and were elevated further in those with advanced pathological tumour stage and metastatic disease [55]. Interestingly, in the quest to define biomarkers predicting response to anti-angiogenic therapy in CRC, IL-6 is also emerging as a potential candidate. A Phase II study with bevacizumab combined with chemoradiation in rectal cancer patients noted that elevated IL-6 and circulating endothelial cells levels were associated with poorer outcomes [56].
IL-6 and tumour angiogenesis. IL-6 exerts pro-angiogenic activity predominantly through STAT3 signalling leading to VEGF transcription, endothelial cell proliferation and migration. IL-6 may potentially orchestrate resistance to anti-angiogenic agents through induction of CXCL12 and influencing the phenotyping of immune cells which also secrete numerous angiogenic factors.
2.2. Gastric cancer

The aetiological origins of gastric cancer (GC) are clearly linked to Helicobacter pylori infestation and chronic gastritis and inevitably the GC microenvironment is rich in inflammatory mediators promoting disease progression [57,58]. Specifically, elevated IL-6 expression relates to poor surgical outcome, increased invasive and metastatic potential in GC [59–62]. As with colorectal cancer, the correlations between increased IL-6 and VEGF in GC compared to healthy subjects also contribute to its pathogenesis [58]. Additionally, gastric cancer cells can produce significant amounts of VEGF with increasing dose and duration of IL-6 stimulation via JAK-STAT signalling [63]. In parallel with this, IL-6 induces VEGF to promote HUVEC cell proliferation and tube formation in vitro and Matrigel plug vascularisation in vivo [63].

2.3. Pancreatic and hepatocellular carcinomas

As with a host of malignancies, circulating levels of IL-6 are increased in pancreatic cancer patients and higher levels have been shown to correlate with worse survival [64]. In vitro, pancreatic cell lines can express higher levels of IL-6 than normal human pancreatic duct epithelium and there are various reports of IL-6 induced expression of phosphorylated STAT3 (pSTAT3), HIF-1α, VEGF and the VEGFR-2 co-receptor, NRP-1 in these cells [65,66]. Furthermore, more recently, the hypoxia induced aggressive phenotypic nature of pancreatic cancer has been partly attributed to both VEGF and IL-6 [67]. However, in view of the avascular nature of pancreatic cancer and lack of clinical efficacy in targeting VEGF-A with bevacizumab, it is unlikely that any potential benefits exerted by anti-IL-6 therapeutics will be as a consequence of ameliorating angiogenesis in this unrelenting tumour type.

With respect to hepatocellular carcinoma (HCC), IL-6 is significantly linked to both its pathogenesis and poor prognosis [68,69]. In addition, IL-6 knockdown in HCC in vivo models can abrogate cell proliferation, migration and invasion [70]. Although its pro-tumorigenic activity appears to be principally mediated through STAT3 signalling [71], its specific influence on angiogenesis in HCC requires further exploration. Nevertheless, higher levels of IL-6 alongside soluble c-Kit and CXCL12 (stromal derived factor-1α; SDF-1α) were documented by Zhu et al. throughout a course of sunitinib (VEGFR2, c-kit and PDGFR tyrosine kinase inhibitor) treatment in HCC patients who rapidly progressed [72]; another example of the potential role of IL-6 in the development of anti-angiogenic refractory disease.

2.4. Cervical cancer

IL-6 is certainly omnipresent in the inflammatory milieu of gynaecological cancers and is central to a host of tumorigenic processes in this group of diseases [73]. Again, within the spectre of angiogenesis, its role is mediated through VEGF induction. In FIGO stage IB-IIA cervical cancer patients, Wei et al. reported consistently higher levels of IL-6 and VEGF in cancerous tissues than in adjacent non-malignant tissues in early-stage cervical cancer patients [74]. Furthermore, they confirmed that the addition of recombinant human IL-6 induced VEGF in a time- and dose-dependent manner in vitro. Moreover, impeding autocrine IL-6 signalling with anti-IL-6 or anti-IL-6R antibodies reduced the expression of VEGF at the transcriptional level [74]. In parallel with this observation, an in vivo model using a Matrigel plug assay has shown that IL-6 increases angiogenic activity via upregulation of VEGF in a STAT3 dependent manner (Fig. 1) [75].

2.5. Ovarian cancer

The pleiotropic nature of IL-6 is lucidly exemplified in ovarian cancer by its extensive influence on cell survival, migration and chemoresistance through JAK/STAT signalling and the observation that elevated circulating levels are associated with poor prognosis [73]. It also facilitates the development and progression of malignant ascites by enhancing tumour endothelial cell migration; a process mediated through trans-signalling [76]. Similarly, Nilsson et al. have demonstrated that this process is directed by STAT3 in vitro and elegantly demonstrated significant increases in microvascular density in vivo as a consequence of exogenous IL-6 stimulation [77].

Conversely, by using IL-6 producing intraperitoneal IGROV-1 and TOV21G xenograft models, Coward et al. have shown that a high affinity anti-IL-6 monoclonal antibody, siltuximab, can significantly reduce neovascularisation on confocal imaging of tumour sections and decrease expression of jagged-1 [43]; also known to have angiogenic effects in advanced epithelial ovarian cancer [78]. Furthermore, in a phase II clinical trial of siltuximab in 18 patients with platinum resistant ovarian cancer, VEGF and IL-8 plasma concentrations decreased markedly in platinum resistant patients treated with siltuximab monotherapy for 6 months [43]. The authors also concluded that IL-6 co-regulates TNF-α, IL-1β, CCL2, CXCL12 and VEGF; resulting in paracrine promotion of angiogenesis within the tumour microenvironment [43]. IL-6 may also pose as an attractive angiogenic target in sub-types which are inherently chemoresistant. Anglesio et al. reported upregulation of IL-6-STAT3-HIF-1α signalling in ovarian clear cell carcinomas and some modest response to the anti-angiogenic agent, sunitinib [33]. The pro-angiogenic repertoire of IL-6 also extends to its influence on tumour immunity, where it enables skewing of macrophages to the M2 (i.e. tumour associated macrophage; TAM) phenotype which themselves secrete a host of angiogenic mediators (including VEGF, PDGF, bFGF and IL-8) and, in conjunction with TGF-β1, drives T cell differentiation towards the Th17 lineage; a subset of immune cells also critical to angiogenesis (Fig. 1) [79–82].
2.6. Melanoma

IL-6 transcription and downstream signalling have significant roles in melanoma progression, especially in the context of angiogenesis. Karst et al. demonstrated that the NF-κB p50 subunit strongly induces IL-6 upregulation in melanoma cells at both transcriptional and translational levels and consequently enhanced the growth of endothelial cells in vitro [57]. In addition, knockdown of p50 expression using lentiviral-based shRNA abrogated cellular IL-6 expression, endothelial cell growth and blood vessel formation [57]. The induction of angiogenesis by IL-6 also relates to the relationship between the NF-κB p65 subunit and the integrin-linked kinase (ILK); whose overexpression strongly correlates with melanoma progression, invasion and the poor overall survival of melanoma patients [83]. Wani et al. demonstrated that ILK enhances IL-6 gene transcription by supporting the binding of NF-κB p65 to the IL-6 promoter [83]. Furthermore both STAT3 and VEGF levels were increased in ILK overexpressing melanoma cells and this was associated with enhanced tube forming capacity of endothelial cells in vitro and microvessel formation in vivo. [83]. Interestingly, these effects diminished with IL-6siRNA and resulted in declining VEGF levels, suggesting that the angiogenic effects are reliant on IL-6 signalling through STAT3 [83]. Li et al. have also confirmed an additional link to establish the importance of the NF-κB-IL-6 axis in angiogenesis within the melanoma tumour microenvironment. They discovered overexpression of the breast cancer metastasis suppressor 1 (BRMS1) gene inhibited endothelial cell growth and tube formation ability in vitro along with decreased microvasculature in vivo by suppressing NF-κB activity and IL-6 expression [84]. Subsequently, they also confirmed BRMS1 knockdown increased IL-6 expression and promoted these processes; indicating that the inhibitory effects of BRMS1 on IL-6 expression are dependent on NF-κB [84].

2.7. Prostate Cancer

Amongst the solid tumours highlighted in this review, the largest body of research highlighting the significance of IL-6 in tumourigenesis relates to prostate cancer. Several reports have consistently confirmed its role as an autocrine growth and survival factor, mediator of chemoresistance, metastasis and upregulator of androgen receptors [85–90]. With respect to angiogenesis, IL-6 has a further pivotal role. In hormone resistant prostate cancer cells, Wu et al. observed that IL-6 inhibition impeded recruitment of myeloid derived suppressor cells (MDSCs) in tumour- bearing mice, resulting in attenuated angiogenesis and abrogated tumour growth [91]. Furthermore, Jemaa et al. recently confirmed cross talk between IL-6 and bFGF through MAPK signalling and postulated that IL-6 could potentially enhance angiogenesis through this relationship [92]. Wang et al. have also shown that the angiogenic properties of the chemokine CXCL12 and its receptor, CXCR4 are mediated through IL-6 via ERK activation (Fig. 1) [93]. In addition, they confirmed that angiostatin levels inversely correlated with CXCR4 expression [93]; however, the influence of IL-6 on this phenomenon has yet to be determined. To date, two Phase I/II trials have investigated the efficacy of combining chemotherapy with siltuximab in castrate resistant prostate cancer [94,95]. However, the conflicting results from these studies highlight the need to further investigate the optimal scheduling of anti-IL-6 therapy in this disease.

2.8. Renal cell carcinoma (RCC)

As previously mentioned, VHL mutations and consequent upregulation of the angiogenic mediators HIF-1α and VEGF are synonymous with RCC pathogenesis. In turn, the interplay of IL-6 with these factors certainly contributes to its role in orchestrating metastatic spread and consequent poor prognosis and survival [96,97]. Furthermore, prior to the current sunitinib era where immunotherapy with either IL-2 or interferon-α (IFN-α) was standard treatment, IL-6 also contributed to poor outcomes with this management [98,99]. This latter observation fuelled the development of a Phase I/II study with siltuximab which resulted in disease stabilisation in more than 50% of patients who had relapsed after numerous lines of immunotherapy [100]. In parallel with immunotherapy failure, a recent small study in 85 patients with advanced RCC has also implicated IL-6 in the development of resistance to sunitinib [101]. Porta et al. performed serum cytokine assays for angiogenic factors (IL-6, hepatocyte growth factor (HGF) and bFGF) and specifically excluded VEGF analysis. Significant increases (>1.5 times higher than baseline) in HGF, and in particular, IL-6 and bFGF preceded progression on sunitinib in approximately 30–44% of these patients [101].

2.9. Glioblastoma

The functional role of IL-6 in glioblastoma (GBM) development was demonstrated by Weissenberg et al. who noted failure of GBM development with IL-6 ablation in transgenic mice expressing the src oncogene in astrocytes [102]. In vitro, IL-6 also promotes GBM cell invasion and angiogenesis by enhancing vascular endothelial cell migration via STAT3 signalling [103]; a pathway also confirmed as a direct effector for the EGFRvIII mutant protein which has been linked to poor long term survival [104].

Despite this, anti-IL-6 monotherapy may not completely abrogate GBM invasiveness. IL-6 and VEGF are both produced by glioma cells and possibly act in union to facilitate tumour growth and survival through angiogenesis, cell proliferation and resistance to apoptosis. Data suggest that the combinatorial approach of IL-6 targeting alongside bevacizumab may be more efficient in dampening invasiveness and growth in malignant cell clusters [105]. Saidi et al. compared the effect of inhibiting IL6 and VEGF on U87-derived experimental glioma grown on the chick chorio-allantoic
membrane (CAM) or in the brain of xenografted mice. In vitro, IL-6 knockdown had no effect on proliferation but substantially enhanced invasion. In the CAM glioma model, IL-6 or VEGF knockdown equally reduced growth and vascularisation of the tumours, but paradoxically increased invasion of residual tumour cells. In contrast, combined IL6 and VEGF knockdown showed enhanced reduction of tumour growth, angiogenesis and also significantly impeded invasion. In mice, combining IL-6 knockdown and bevacizumab treatment completely inhibited tumour development and infiltration. Hence these results suggest that a combination of IL6 and VEGF inhibitors could induce a synergistic anti-tumoural effect [105]; a significant finding for the development of future trials with these agents in GBM and other malignancies.

In line with a selection of aforementioned tumour types, IL-6 has an inferred role in anti-angiogenic resistance in GBM. Jin et al. demonstrated that IFN regulatory factor 7 derived IL-6 had a pivotal role in maintaining GBM stem cell properties, increased tumour heterogeneity and formation through JAK/STAT activation of the jagged-Notch pathway (Fig. 1) [106]. Interestingly, alongside stem cell accumulation, myeloid infiltration and mesenchymal phenotype are associated with anti-VEGF therapy resistance in GBM [107]. Most significantly, all such processes can be governed by IL-6 within the tumour microenvironment [78,107,108]. Furthermore, recent reports have confirmed correlations between increased glioma cell pSTAT3 expression and patients failing bevacizumab therapy [109]. These findings have been recapitulated by Jahangiri et al., whose micro-array gene expression analysis comparing GBM primary tumours with bevacizumab resistant glioblastoma (BRG) has shown significant upregulation of c-Met expression in BRG specimens [110]. Subsequently, they demonstrated that the increased hypoxia (analysed via immunostaining for hypoxia marker, CA9) associated with BRG cells correlated with increased phosphorylation of STAT3, c-MET and c-MET activated focal adhesion kinase (FAK) [110]. Moreover, in BRG xenograft models, both intrinsic and acquired bevacizumab resistance could be ameliorated with the c-MET inhibitor; XL184 (Exelixis) [110].

Consequently, attention has now been drawn towards combinations with drugs targeting both the JAK/STAT pathway (AZD1480) and VEGF (cedirinib) which may potentially avert resistance to angiogenic inhibitors [109].

3. Conclusions

Arguably, the introduction of anti-angiogenic agents alongside chemotherapy represents one of the key advances in oncological practise over the past decade. However, as with all novel medical therapeutics, challenges swiftly emerge in developing robust biomarkers to assist appropriate stratification of patients most likely to gain significant benefit. Moreover, the inevitable development of resistance to these agents also puts the spotlight on creating effective strategies to avert processes underpinning this phenomenon. This review outlines considerable evidence to support the role of IL-6 in both tumour angiogenesis and treatment failure with anti-angiogenic drugs including bevacizumab and sunitinib; both of which best exemplify the recent success of this class of targeted agents in the current era of cancer therapeutics. Although they have brought varying increments in improved progression free survival in several malignancies, the impact on overall survival for certain tumour types has been negligible predominantly due to either intrinsic or adaptive resistance. This is driven by compensatory signalling pathways facilitating relapse and hence there is an urge to refresh current treatment algorithms with new strategies to prolong response to these therapies.

Interestingly, there is significant evidence supporting the integral role of inflammatory pathways in the development of evasive resistance to anti-angiogenic therapy. Hypoxic conditions that occur during vessel regression with anti-VEGF therapy can lead to compensatory increases in angiogenic mediators within tumours and also enhance recruitment of bone marrow derived-cells (BMDCs) which themselves potentiate neovascularisation [111]. Such pro-angiogenic BMDCs include vascular progenitors (i.e. endothelial and pericyte progenitor cells) and vascular modulatory cells [112,113]. The latter consist of TAM [114] and CD11b+ cells [115,116] which all express a myriad of pro-inflammatory cytokines and growth factors. Recruitment of BMDCs in areas of low oxygen tension is mediated through HIF-Iα and downstream effectors such as CXCL12 and VEGF [117–119]. Furthermore, compensatory mechanisms through IL-8 have been shown to maintain angiogenic potential in tumours that were otherwise impaired due to the absence of HIF-Iα [120]. Indeed, within the tumour microenvironment, IL-6 shares close relations with these pathways and processes as highlighted in recent clinical and preclinical studies with siltuximab; which has been shown to inhibit macrophage infiltration and angiogenic mediators such as CXCL12, jagged-1, IL-8 and VEGF [43]. Therefore it is feasible that targeting IL-6 could impede the development of resistance to anti-angiogenic agents. Indeed, in view of the myriad of other cytokines within the IL-6 superfamily that could also potentially enhance such resistance, therapeutic blockade of IL-6R may prove to be a more intuitive approach to prolong response to VEGF tyrosine kinase inhibitors.

In addition, increased circulating levels of IL-6 may also serve as a putative biomarker for poor response to sunitinib and bevacizumab as reported in HCC, RCC, glioblastoma and colorectal cancers [56,72,101,109]. Nevertheless, to date, most translational studies with anti-IL-6 therapies have been limited to patients with advanced disease and only modest benefits have been apparent [43,94,95,100]. In light of the evidence for the pro-angiogenic role of IL-6, any efforts to develop further clinical trials targeting this cytokine will need to focus on combinatorial (e.g. anti-IL-6/anti-IL-6R with MET inhibition) as opposed to monotherapeutic.
approaches. Additionally, its efficacy in adjuvant, maintenance and chemoresistant settings alongside other novel anti-angiogenic agents will require thorough exploration prior to being established as a viable treatment option.

Conflict of interest statement

None to declare.

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