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Interleukin-6: An angiogenic target in solid tumours

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Contents

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.

Keywords: IL-6; Angiogenesis; VEGF; STAT3; HIF-1α; Bevacizumab; Sunitinib; Siltuximab

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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 differentiation 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 results 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 vasculogenesis [23]. It consists of a family of five structurally related molecules; namely VEGF-A,-B,-C, -D and placental growth factor (PlGF) 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