Cancer Treatment Reviews 60 (2017) 24–31

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Tumour Review

Interleukin-8 in cancer pathogenesis, treatment and follow-up

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ARTICLE INFO

Article history:
Received 20 June 2017
Received in revised form 11 August 2017
Accepted 13 August 2017

Keywords:
IL-8 (CXCL8)
CXCR1/2
Pharmacodynamic biomarker
Myeloid-derived suppressor cells
Cancer therapeutic agents
Immunotherapy

ABSTRACT

Interleukin-8 (CXCL8) was originally described as a chemokine whose main function is the attraction of a polymorphonuclear inflammatory leukocyte infiltrate acting on CXCR1/2. Recently, it has been found that tumors very frequently coopt the production of this chemokine, which in this malignant context exerts different pro-tumoral functions. Reportedly, these include angiogenesis, survival signaling for cancer stem cells and attraction of myeloid cells endowed with the ability to immunosuppress and locally provide growth factors. Given the fact that in cancer patients IL-8 is mainly produced by tumor cells themselves, its serum concentration has been shown to correlate with tumor burden. Thus, IL-8 serum concentrations have been shown to be useful as a pharmacodynamic biomarker to early detect response to immunotherapy. Finally, because of the roles that IL-8 plays in favoring tumor progression, several therapeutic strategies are being developed to interfere with its functions. Such interventions hold promise, especially for therapeutic combinations in the field of cancer immunotherapy.

CXCR1 and CXCR2 functions in immunity

Immune responses are characterized by the activation of leukocytes and migration of hematopoietic cells to secondary lymphoid organs or to the site of inflammation [1]. Under inflammatory conditions, the expression of specific chemokines, a class of soluble small proteins with potent chemotactic activity, is markedly upregulated [2]. Chemokines constitute a large family of structurally related polypeptide signaling molecules characterized by their ability to promote the directed chemotaxis of leukocytes. They were originally discovered due to their role in inflammation, but they are now known to play important roles in cancer [3–6] and the steady-state traffic of immune system cells. Chemokines mediate diverse biological and biochemical activities, including endothelial adhesion, directed migration, and activation of cytotoxic activities such as respiratory burst and exocytosis [1,2,7]. Chemokines are structurally classified into four categories based on the position of conserved cysteine residues, namely the CCL, CXCL, XCL and CX3CL-families [8]. Some act constitutively and some only under inflammatory conditions. The CXCL family encompasses two subfamilies depending on the presence of the ELR motif. ELR-containing CXCL chemokines are mainly involved in acute inflammatory responses [9].

Chemokine receptors conform a family of transmembrane coiled proteins with 7 transmembrane domains [8]. Most chemokines activate more than one chemokine receptor, and many chemokine receptors are activated by multiple chemokines [3]. The CXCL family comprises some of the main chemokines that are involved in neutrophil migration, including CXCL1 (GRO-α), CXCL2 (GRO-β), CXCL3 (GRO-γ), CXCL5 (ENA-78), CXCL6 (GCP-2), CXCL7 (NAP-2) and CXCL8 (IL-8). These chemokines can be produced both by immune cells (including neutrophils, macrophages and T cells) and non-leukocytes (including epithelial and endothelial cells) in response to injury and infection [3,4,8].

In contrast to the multiple CXC chemokines, only two CXC chemokine receptors, CXCR1 and CXCR2 (also known as IL-8RA and IL-8RB), have been shown to mediate the responses to ELR+ CXC chemokines in polymorphonuclear leukocytes [10] (Table 1). These two receptors have different ligand binding affinities. CXCR1 binds with high affinity to IL-8, but binds with low affinity to CXCL1, CXCL2, CXCL3, CXCL5 and CXCL7. In contrast, CXCR2 binds to these CXC chemokines with higher affinity [11,12]. Upon chemokine

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http://dx.doi.org/10.1016/j.ctrv.2017.08.004
0305-7372/

Table 1
This table summarizes the CXCR1/2 chemokine receptors and their known ligands and illustrates the fact that some ligands (CXCL6 and CXCL8) bind both receptors.

Systematic name	Human ligand (alternative name)	Chemokine receptor
CXCL1	GROα, NAP-3, MGSA-α	CXCR2
CXCL2	GROβ, MIP-2α	CXCR2
CXCL3	GROγ, MIP-2β	CXCR2
CXCL5	ENA-78	CXCR2
CXCL6	GCP-2	CXCR1/CXCR2
CXCL7	NAP-2	CXCR2
CXCL8	IL-8, NAP-1	CXCR1/CXCR2

binding, heterotrimeric small G protein downstream signaling promotes activation of phosphatidyl-inositol-3-kinase (PI3K), giving rise to the activation of Akt, PKC, calcium mobilization and/or MAPK signaling cascades [11]. CXCR1 (but not CXCR2) also activates phospholipase C and induces respiratory NAPDH oxidase-mediated burst, suggesting that the two receptors may play different physiological roles [10,11,13]. Like most G protein-coupled receptors, both receptors become phosphorylated, desensitized, and internalized upon exposure to CXC chemokines. CXCR2 internalization occurs at a faster rate and at lower ligand concentrations than CXCR1. CXCR2 is also recycled back to the surface at a much slower rate than CXCR1 [10,11,13].

The role of CXCR1 and CXCR2 in the pathogenesis of inflammatory responses has been demonstrated in a number of rabbit models [14–18]. For instance, neutralization of IL-8 by a monoclonal antibody resulted in the suppression of lung inflammation, delayed type hypersensitivity reactions or ischemia/reperfusion injury [14–18]. As we will discuss, CXCR1 and CXCR2 play an important role in cancer progression and metastasis [19–21].

The discovery of potent and selective antagonists [22,23], neutralizing monoclonal antibodies to these receptors and their ligands [24,25], the availability of CXCR2 knockout mice [26,27] and the identification of polymorphisms and genetic mutations [28] have contributed a great deal to improve our physiopathological knowledge of these tissue inflammatory mediators.

Cancer functional cooption of the CXCR1/CXCR2 chemokine axis

Tumor cells can gain the expression of various cytokines and their receptors to exploit these molecules for their own benefit [3–6]. Cytokines secreted by tumor cells act on the surrounding stroma, recruiting non-malignant cells to support growth, survival, and spread of the tumor [3–6]. Tumor cells may also benefit directly from cytokine stimulation when gaining expression of cognate cytokine receptors, thereby allowing them to respond to lower cytokine concentration levels [3,5,6].

Malignant cells express and secrete various CXC chemokines acting on CXCR1 and CXCR2 receptors, including CXCL1, CXCL2, CXCL3 (GRO family chemokines), CXCL5, CXCL7 and CXCL8. These molecules conceivably set up a protumorigenic tissue microenvironment and facilitate progression and metastatic dissemination of cancer via autocrine and paracrine loops [29–32].

One such important cytokine/receptor pair is IL-8/IL-8R. Cooption of the IL-8/IL-8R axis is known to be an established occurrence in human cancer, and has been shown to promote tumor progression by multiple means [20,21,33]. Acquisition of IL-8 and/or its receptors CXCR1 and CXCR2 is known to be a relatively common occurrence during tumor progression [20,21,33].

Intriguingly, IL-8 is absent from the mouse genome, albeit mouse CXCR1 responds to human IL-8 [34]. This fact has hampered faster research progression in the field because of the lack of proper genetically-targeted mouse models.

Functional studies have revealed that tumor-derived IL-8 can function in a paracrine manner to alter the composition of immune infiltrates in the tumor microenvironment and to induce angiogenesis (Fig. 1). In an autocrine fashion IL-8 facilitates oncogenic signaling and pro-metastatic features such as invasion and resistance to chemotherapy [19,21,35,36]. Indeed, this cytokine axis can substantially alter leukocyte infiltration into the tumor, resulting in the accumulation of immunosuppressive and protumorigenic immune cells [20,37].

Emerging research suggests that signaling by tumor-derived IL-8 can bias the tumor microenvironment towards an immunosuppressive state by the trafficking of neutrophils and myeloid-derived suppressor cells (MDSCs), which have the ability to locally dampen anti-tumor immune responses [20,38,39].

Chemokines produced by tissues in eventual destination sites for metastasis are reported to be important in establishing the metastatic niche through the recruitment of bone marrow-derived progenitor stem cells [40–42]. Expression of such chemokines leads to a myeloid and suppressor lymphoid infiltrate being recruited into the metastasis-shedding tumor, thus providing a microenvironment that is supportive of dissemination [41,42].

Tumor vasculature delivers essential nutrients and oxygen to the tumor cells that permit the uncontrolled growth and invasion of tumor cells [43,44]. For example, upon IL-8 stimulation, endothelial cells begin angiogenic processes characterized by secretion of matrix metalloproteinases (MMPs) to break-down the extracellular matrix, with proliferation and formation of new vessels [45,46] (Fig. 1).

Furthermore, the involvement of CXCR1/2 in tumor progression and angiogenesis is further demonstrated by several in vivo cancer models [47,48]. A series of experiments showed that neutralization of chemokines and/or their receptors significantly reduced tumor growth in association with decreased microvessel density [49,50]. For example, CXCR2 knockout mice implanted with Lewis lung carcinoma (LLC) exhibit reduced tumor growth, more spontaneous metastases and less vascular density upon orthotopic engraftment as compared to wild-type mice [27].

In lymphoma, IL-8 production by the tumors attracts neutrophils that enhance lymphoma cell survival via APRIL production [51]. Other disease-specific protumor mechanisms of IL-8 are likely to be discovered in the future.

All in all, these reports collectively suggest that the IL-8-CXCR1/2 signaling pathway plays significant roles in tumor progression and metastasis [52]. Importantly, IL-8 activity on endothelial cells has been extensively reported to mediate tumor escape and resistance to antiangiogenic agents targeting VEGF or their receptors [53].

The role of IL-8 in regulating inflammatory angiogenesis has been probably underestimated in the general belief that VEGFs are the dominant mediators. In fact, there is a much underexplored crosstalk between VEGFRs and IL-8 in angiogenesis. In this regard, a loop in endothelial cells have been described according to which IL-8 induces VEGF-A production by endothelial cells and increases the expression of VEGFR2 to respond to it in an autocrine fashion [54]. The role of IL-8 in angiogenesis is readily observed in multiple types of *in vivo* assays including 3D tumor organoids [55] and IL-8 upregulates survival/proliferation and metalloprotease expression in endothelial cells [45]. It remains to be seen if other CXC chemokines can substitute these pathogenic functions of IL-8. Again, the absence of an IL-8 gene in mice precludes direct evaluation of the likely importance of this chemokine in the hierarchy of proangiogenic factors involved in various cancer types [56–58]. As mentioned, most of the research attention has been paid to the role of IL-8 to the resistance to VEGF/VEGFR antagonists [59,60]. Indeed, IL-8 has been clearly shown to at least partially underlie