Cytokine & Growth Factor Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cytokine & Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Mini review

Chemokine binding proteins: An immunomodulatory strategy going viral

Víctor González-Motos, Kai A. Kropp, Abel Viejo-Borbolla*

Institute of Virology, Hannover Medical School, Carl-Neuberg Strasse 1, 30625 Hannover, Germany

ARTICLE INFO

Article history:
Received 22 February 2016
Accepted 27 February 2016
Available online xxx

Keywords:
Chemokine
Glycosaminoglycan
Herpesvirus
Poxvirus
vCKBP
Immune evasion

ABSTRACT

Chemokines are chemotactic cytokines whose main function is to direct cell migration. The chemokine network is highly complex and its deregulation is linked to several diseases including immunopathology, cancer and chronic pain. Chemokines also play essential roles in the antiviral immune response. Viruses have therefore developed several counter strategies to modulate chemokine activity. One of these is the expression of type I transmembrane or secreted proteins with the ability to bind chemokines and modulate their activity. These proteins, termed viral chemokine binding proteins (vCKBP), do not share sequence homology with host proteins and are immunomodulatory *in vivo*. In this review we describe the discovery and characterization of vCKBP, explain their role in the context of infection *in vivo* and discuss relevant novel findings.

1. Introduction

1.1. Chemokines

Chemokines are small, basic cytokines that orchestrate the migration of leukocytes during development, homeostasis, tissue damage and infection [1]. Deregulation of chemokine function plays a key role in cancer development, immunopathologies and induction of pain [2,3]. Chemokines are secreted, with the exception of CXCL16 and CX3CL1, which are transmembrane proteins and can be shed following cleavage (reviewed in [4]). Interaction with glycosaminoglycans (GAGs) on the cell surface is required for chemokine retention on the endothelium, presentation to the chemokine receptor and thereby activity *in vivo* [5,6]. Binding of the chemokine to its receptor at the leukocyte plasma membrane triggers signalling cascades leading to a coordinated reorganization of the cytoskeleton, activation of adhesion molecules and leukocyte extravasation [7] (Fig. 1). Chemokines can interact with both GAGs and the chemokine receptor simultaneously through distinct domains, although for some chemokines these domains may overlap [8,9]. Chemokine receptors are 7 transmembrane G protein-coupled receptors (GPCR) that signal through heterotrimeric G proteins, normally of the Gαi-type. There are, however, atypical chemokine receptors that act as chemokine scavengers and do not induce G protein signalling [10]. For a detailed description of the nature and nomenclature of atypical chemokine receptors see the report by Bachelerie and colleagues [11].

Chemokines form the largest family of cytokines, with approximately 50 chemokines and 20 chemokine receptors discovered to date [10]. Most receptors interact with more than one chemokine and most chemokines use more than one receptor [10]. This peculiarity led to the assertion that there is a high level of redundancy in the chemokine network. This notion is partially supported by failure of therapeutic strategies aimed at blocking single chemokine activity and by the use of knock out and transgenic mouse models. However, several sets of data indicate that there is a certain degree of selectivity in the chemokine network. This selectivity seems to be achieved by (i) biased signalling; (ii) differential interaction with GAGs; (iii) effect of GAG binding on chemokine oligomerization and (iv) chemokine–chemokine interactions [5,12–15].

Chemokines are classified as homeostatic, inflammatory or dual function according to their main functional activity and as CXC, CC, C, and CX3C according to structural criteria based on the relative position of their N-terminal cysteines [13,16]. Inflammatory chemokines are essential in controlling the recruitment of leukocytes during inflammation whereas homeostatic chemokines are involved in directing the migration of leukocytes during development, adaptive immune response, and in peripheral healthy tissues [13]. Homeostatic chemokines seem to be less promiscuous and more conserved between species than

* Corresponding author.
E-mail addresses: Gonzalezmotos.victor@mh-hannover.de (V. González-Motos), Kropp.kai@mh-hannover.de (K.A. Kropp), Viejo-borbolla.abel@mh-hannover.de (A. Viejo-Borbolla).

http://dx.doi.org/10.1016/j.cytogfr.2016.02.007

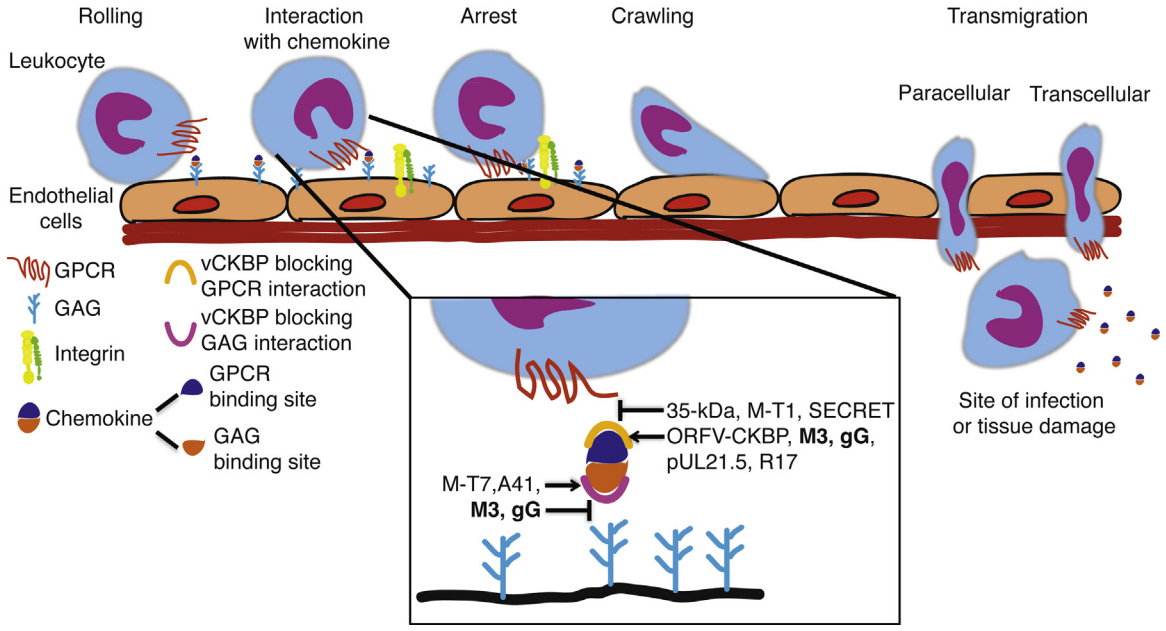

Fig. 1. Viral chemokine binding proteins (vCKBP) interfere with chemokine-mediated migration of leukocytes to the site of infection or tissue damage. Leukocytes rolling on the surface of endothelial cells detect GAG-bound chemokines. The interaction of the chemokine with the GPCR of the rolling leukocyte activates signalling cascades in the leukocyte. Arrest, crawling and transmigration depend also on adhesion molecules, mainly integrins and selectins. The process terminates with the para- or transcellular migration of the leukocyte to the site of injury or infection [7]. Inlet: vCKBP modulate chemokine activity through interacting with the GPCR-, GAG-binding domain of the chemokine or both (in bold). Examples for both types of vCKBP are indicated. Interaction with the GPCR-binding site results in inhibition of chemokine activity *in vitro* and *in vivo*. Binding to the GAG-binding site of the chemokine may affect chemokine retention at the cell surface and generation of a chemotactic gradient inhibiting chemokine activity *in vivo*. An exception to this rule is HSV gG, which interacts through the GAG-binding domain of the chemokine and enhances chemokine activity *in vitro* and *in vivo*.

inflammatory chemokines, probably reflecting the evolutionary pressure exerted on the latter by different types of pathogens [13]. Dual function chemokines include those that share functions of both inflammatory and homeostatic chemokines [16]. Chemokine receptors show a higher degree of conservation between mammals than their ligands and they are classified according to the chemokine group they interact with [17].

Despite differences in sequence, chemokines share some structural features: a long, flexible N-terminal loop followed by a three-stranded β sheet and a C-terminal α helix [18]. Recently, the structure of chemokines bound to their receptors was solved [19,20]. These studies reported the crystal structure of human CXCR4 complexed with the Kaposi's sarcoma-associated herpesvirus (KSHV) chemokine vMIP-II [20], and the structure of human cytomegalovirus (HCMV) chemokine receptor US28 bound to CX3CL1 [19]. In both cases the core of the chemokine interacts with the receptor N-terminus whereas the chemokine N-terminal residues bind to the transmembrane pocket of the receptor [19,20]. The predicted model suggests a two-step interaction of the chemokine with its receptor, triggering conformational changes in the latter leading to insertion of the N-terminal residues of the chemokine between the transmembrane helices [21].

1.2. Viral chemokine binding proteins (vCKBP)

Due to the essential role of chemokines in the antiviral response, some viruses express proteins that are able to interfere with the host chemokine network, modulating its activity and thereby interfering with leukocyte migration (Table 1). To do so they express viral chemokine receptors, viral chemokines and soluble receptors interfering with extracellular chemokines [22]. Viral chemokine receptors and viral chemokines share high degree of identity with host proteins suggesting that the virus has acquired them from the host and modified them in a process termed viral piracy (reviewed in Ref. [22]). However, in the case of the soluble receptors, also known as vCKBP, there is very little or no sequence identity with host proteins. Moreover, the amino acid homology between the distinct vCKBP in different viruses is very low or non-existent [23]. Despite this, the crystal structures of several vCKBP show common structural patterns [24,25], probably due to parallel evolution as suggested by Lubman and Fremont [24].

All known vCKBP have been so far discovered in members of the *Pox* and *Herpesviridae* families. Similar to chemokines, most vCKBP are secreted proteins but some are also structural proteins present at the viral envelope or at the plasma membrane of infected cells [26–29]. Also, like the chemokines, some vCKBP interact with GAGs and this seems to be relevant for their function [30–33]. While the majority of known vCKBP inhibits chemokine activity *in vitro* or *in vivo*, a vCKBP with the ability to potentiate chemokine function was found recently in herpes simplex virus type 1 and 2 (HSV-1 and HSV-2, respectively) [27]. In the following paragraphs we discuss the properties of the different vCKBP groups in more detail.

2. Discovery and characteristics of vCKBP

2.1. vCKBP that inhibit chemokine activity

All but one of the vCKBP described to date inhibit chemokine activity *in vitro* or *in vivo*. To inhibit chemokine activity, vCKBP bind to the chemokine through either its chemokine receptor- or its GAG-binding pocket or both, thereby impairing the interaction between the chemokine and its receptor or GAGs (Fig. 1). Impairment of GPCR binding can be functionally addressed *in vitro* by performing classical transwell assays. However, when the interaction takes place exclusively through the GAG-binding pocket of the chemokine, this type of assay may not provide information regarding the inhibitory properties of the vCKBP. Nevertheless, both types of binding impairment may result in inhibition of chemotaxis *in vivo*. The known vCKBP are described

Please cite this article in press as: V. González-Motos, et al., Chemokine binding proteins: An immunomodulatory strategy going viral, Cytokine Growth Factor Rev (2016), http://dx.doi.org/10.1016/j.cytogfr.2016.02.007