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The chemokine system, and its CCR5 and CXCR4 receptors, as potential targets for personalized therapy in cancer

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ABSTRACT

Chemokines and their receptors regulate the trafficking of leukocytes in hematopoiesis and inflammation, and thus are fundamental to the immune integrity of the host. In parallel, members of the chemokine system exert a large variety of functions that dictate processes of cancer development and progression. Chemokines can act as pro-tumoral or anti-tumoral regulators of malignancy by affecting cells of the tumor microenvironment (leukocytes, endothelial cells, fibroblasts) and the tumor cells themselves (migration, invasion, proliferation, resistance to chemotherapy). Several of the chemokines are generally skewed towards the cancer-promoting direction, including primarily the CCR5–CCL5 (RANTES) and the CXCR4–CXCL12 (SDF-1) axes. This review provides a general view of chemokines and chemokine receptors as regulators of malignancy, describing their multi-faceted activities in cancer. The tumor-promoting activities of the CCR5–CCL5 and CXCR4–CXCL12 pathways are enlightened, emphasizing their potential use as targets for personalized therapy. Indeed, novel blockers of chemokines and their receptors are constantly emerging, and two chemokine receptor inhibitors were recently approved for clinical use: Maraviroc for CCR5 and Plerixafor for CXCR4. The review addresses ongoing pre-clinical and clinical trials using these modalities and others in cancer. Then, challenges and opportunities of personalized therapy directed against chemokines and their receptors in malignancy are discussed, demonstrating that such novel personalized cancer therapies hold many challenges, but also offer hope for cancer patients.

1. Introduction

Chemokines and their receptors are key regulators of immune activities. In parallel, they have many diverse and at times conflicting roles in malignancy. The aim of this review is to discuss the potential use of members of the chemokine family as therapeutic targets in cancer, primarily in those cases where they have mainly a pro-malignancy phenotype, and to allude to future prospects of using them for personalized treatment in neoplasia.

To put these issues in perspective, the review will first provide brief overview of chemokines and chemokine receptors (Section 2), which will be followed by a general description of the roles played by these elements in cancer (Section 3). Then, the review will focus on two key pathways that are involved in cancer and have high relevance to targeted and personalized therapy in malignancy, namely the CCR5–CCL5 axis and the CXCR4–CXCL12 pair. The roles of these two pathways in cancer will be described in more detail in Section 4; information on inhibitory modalities against the CCR5–CCL5 and CXCR4–CXCL12 pathways that have been introduced in cancer will be provided in Section 5. The future scope for developing additional strategies that would block members of the chemokine family in cancer will be discussed in Section 6, and in Section 7 the review will address challenges and opportunities in inhibiting chemokines and their receptors, and their implications in personalized treatment of cancer. A concluding summary of this intriguing and promising field will be given in Section 8.

2. Overview: chemokines and chemokine receptors

The family of chemokines is composed of about 50 low-molecular weight proteins, sharing the main function of regulating leukocyte trafficking in physiological and pathological conditions. All chemokines bind to seven-membrane spanning G protein-coupled receptors (GPCRs) that are expressed predominantly by leukocytes. One of the major characteristics of the "chemokine world" is that many chemokines bind more than one receptor, and in parallel, most of the chemokine receptors have several high affinity ligands [1–5].

Chemokines are divided to sub-groups according to structural and functional criteria. Structurally, the categorization is based on the number and location of cysteine residues in the N' terminus of the molecules, dividing the chemokines to four major

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sub-groups: CXC, CC, C and CX_3C, the larger ones being CXC and CC. After years of confounding terminology, and many cases when a single chemokine was given several names, a new nomenclature was established by Zlotnik and Yoshie [6], which relies on this structural classification. In parallel, functionally, chemokines are roughly divided to two major sub-groups, homeostatic and inflammatory. Homeostatic chemokines are constitutively expressed, mainly in lymphoid organs (such as bone marrow and lymph nodes), and mediate leukocyte trafficking to these sites during immune homeostasis. In contrast, inflammatory chemokines are inducibly expressed at infected/damaged tissues, and thereby recruit leukocytes to sites that have been exposed to an inflammatory insult [1–5]. Chemokines are presented to circulating leukocytes by endothelial cells *via* glycoseaminoglycans (GAGs), facilitating leukocyte arrest, which is followed by extravasation to the tissue [7].

Intact and timely functions of chemokines and their receptors are essential for the immune integrity of the host. Homeostatic chemokines are central for proper hematopoiesis, while inflammatory chemokines play key roles in eliciting immune responses against pathogens. In parallel, growing number of reports attribute more roles to both groups, as chemokines and their receptors were found to be involved in inflammatory/autoimmune diseases [8,9], HIV-1 cell entry [10,11], development and reproduction [12,13], bone remodeling [14] and malignancy (specific reviews are provided below).

3. Overview: chemokines and chemokine receptors in malignancy

The involvement of members of the chemokine family in cancer is very complex, multi-faceted and has broad effects through chemokine activities on leukocytes, as well as on stroma cells and on the malignant cells themselves. Under specific conditions, primarily those in which chemokines induce the recruitment of leukocytes with anti-cancerous activities to tumors, chemokines can exert tumor-inhibitory effects. However, in many other conditions, a large number of chemokines – both inflammatory and homeostatic – have powerful pro-malignancy impacts (see Fig. 1).

The research area concerning the roles of the chemokine system in cancer is very dynamic, diverse aspects have been extensively studied, and much is yet to be revealed. This current review will provide a brief overview of the most influential roles of the chemokine family in cancer, but due to page and scope limits will not cover all aspects. Many reviews have summarized different angles of this intricate subject, and thus cover aspects that are not addressed in depth in the current manuscript. Representative reviews will be cited along the current manuscript, with our apologies to all those excellent reviews that were not included.

In this present section, the review will delineate the complexity of the field, and will provide the information required for further understanding of the aspects related to personalized therapies that are directed against chemokines and their receptors in cancer, to be discussed in the following sections of this manuscript.

3.1. The chemokine system in malignancy: dictating leukocyte landscape

As a result of their strong chemotactic properties towards leukocytes, members of the chemokine family exert predominant roles in dictating the content of different subsets of lymphoid and myeloid cells in tumors, and eventually they also control the way lymphocytes undergo activation towards different functional directions. The landscape of different leukocytes residing in tumors has an important fate-decision impact, determining to large extent whether tumor cells will succumb to immune surveillance and die, or alternatively would propagate and metastasize, partly as a result of leukocyte-driven tumor-promoting events, including of the inflammatory phenotype [15–22]. The forthcoming sub-sections provide examples representing the large diversity of immune and inflammatory cells that regulate malignancy. These selected examples demonstrate the variable effects that chemokines, which are major leukocyte chemoattractants, can have on the immune/inflammatory contexture in malignancy.

When lymphocytes and activation of acquired immunity are concerned, the following aspects arise (several selected reviews on related subjects that are discussed below, are provided: [17–19,23–26]): To what extent are the tumors infiltrated by Th1 cells, CD8+ cytotoxic T lymphocytes (CTLs) and/or natural killer (NK) cells, whose presence in tumors generally leads to beneficial consequences through tumor cell eradication? Would T regulatory cells (Tregs) suppress potential anti-tumor immune activities, or maybe they would prevent the development of chronic inflammation that in general is tumor-supporting? Would Th2 cells and B cells have anti-tumor protective roles mediated by antibodies recognizing tumor antigens, or would Th2 cells rather shift the balance towards the production of cytokines like IL-10 that are immune-suppressive? Would B cells lead through other mechanisms to pro-inflammatory conditions? What is the role of Th17 cells? Can dendritic cells exhibit potent antigen-presenting capabilities? Would the activation of toll-like receptors by remnants of necrotic cells lead to tumor-promoting consequences, as has been recently described?

In parallel to the very large diversity of lymphocyte subsets that act at the tumor microenvironment, a major role has been attributed to myeloid cells. Here, high degree of plasticity is recognized, leading to many different sub-populations that control all stages of the malignancy process. The myeloid infiltrates can come in many different flavors (several selected reviews: [20–22,27–35]): Macrophages exhibiting the M1 classically-activated phenotype, that have assumed anti-tumor activities (but can also induce tumor cell initiation); Tumor-associated macrophages (TAMs) that usually have the phenotype of alternatively-activated M2 macrophages, with typical pro-cancerous activities; Myeloid-derived suppressor cells (MDSC) from the granulocyte and monocyte subsets; Tie-2-expressing macrophages (TEMs) that contribute to angiogenesis; and the recently addressed N1 and N2 neutrophils that are speculated to have anti-tumoral or pro-tumoral activities, respectively.

Eventually, the immune/inflammatory contexture and summation of activities exerted by lymphoid and myeloid sub-populations, as well as their amounts and exact localization in the tumors, will have a large impact on the clinical outcome. This is the exact place in which chemokines come into play, by recruiting different leukocyte sub-populations that express their cognate receptors. Many tumors contain chemokines of different types that can be expressed by the cancer cells, by leukocytes and by stroma cells, each chemokine having its own expression pattern. Each of these chemokines also has its own specific array of target cells, and many of the chemokines attract more than one leukocyte subtype. Thus, the composition of chemokines will have a major role in dictating the content of leukocytes in tumors [5,19,36–42].

Inflammatory and homeostatic chemokines alike regulate the content of immune/inflammatory leukocytes in tumors; however, often these are the inflammatory chemokines that play a major role in this respect, as can be demonstrated by several examples: The non-ELR expressing, CXCR3-binding chemokines CXCL9, CXCL10 and CXCL11 recruit Th1 and NK cells, and induce anti-tumor activities [38,43–46]; CCL5 recruits Th1 and CTLs but also monocytes that differentiate to TAMs [39,47–51]; CCL2 that has been shown in the recent study by Pollard and his team to promote metastasis in breast cancer through the recruitment of

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