Chapter 2

CHEMOKINES AND CANCER

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1. INTRODUCTION

Chemokines represent a large family of cytokines that play a fundamental role in controlling the directional migration of leukocytes to sites of infection and inflammation. The chemokine superfamily can be subdivided into four groups, based on the relative positioning of the first two cysteine residues. All chemokines exert their activities through the engagement of specific seven-transmembrane G protein-coupled receptors (Table 1, at the end of the chapter). Distinct from other cytokines, most chemokines can bind to and activate more than one cognate receptor, leading to a complex network of biological outcomes.

Originally identified for their chemo-attractant properties, there is accumulating evidence that chemokines play a critical role in a number of pathological conditions, including cancer. Many, if not all cancers can be characterized by abnormal chemokine production, or aberrant expression and signaling through chemokine receptors. Chemokine receptors belong to a group of seven-transmembrane domain G-protein-coupled receptors. Chemokine binding to the extracellular domain of the chemokine receptor leads to a cascade of intracellular events mediated, in part, by G-protein-coupled signal transduction. These events include the activation of phospholipases, the hydrolysis of phosphatidylinositol (4,5)-bisphosphate, the formation of inositol trisphosphate and diacylglycerol, changes in intracellular calcium concentration, the activation of protein kinase C, and the activation of mitogen-activated protein kinases [1]. Additionally,
chemokine receptor activation of protein tyrosine kinase signaling intermediates has been identified [2].

Through their interactions with chemokine receptors on target cells, tumor-associated chemokines can promote tumor growth directly by mediating the infiltration of leukocytes to the tumor microenvironment and stimulating the release of growth factors, or indirectly, by initiating angiogenesis. The intent of this chapter is to highlight the key roles chemokines play in cancer biology including the control of leukocyte infiltration into tumors, tumorigenesis, initiation of primary tumor growth and survival, regulation of angiogenesis, and the control of tumor cell adhesion, invasion and migration (Figure 1). Understanding the complex role chemokines play at each stage of disease progression will assist with defining potential therapeutic strategies. We review recent advances made in the field of cancer therapy involving the manipulation of the chemokine system.

2. CHEMOKINES AND LEUKOCYTE TUMOR INFILTRATION

Infiltrating leukocytes are found in most solid tumors, comprised of monocytes/macrophages, T cells, dendritic cells, and mast cells. The infiltration of immune cells into solid tumors was initially believed to reflect the anti-tumor immune response. However, there is increasing evidence that tumor-derived chemokines attract leukocytes to the tumor microenvironment, thereby promoting tumor growth, angiogenesis and metastasis.

Over two decades ago, Bottazzi et al. showed that CCL2 (MCP-1) is expressed and secreted by most tumor cell lines [3, 4]. Specific monocyte/macrophage recruitment has been linked to local production of CCL2 by tumors and stromal cells, and is implicated in breast, ovarian, bladder, and lung cancer. [1, 3, 4] CCL2 production was also detected in tumor-infiltrating macrophages, indicating the existence of an amplification loop for their recruitment. Interestingly, tumor-associated macrophages from ovarian cancer patients displayed defective expression of CCR2 and did not migrate in response to CCL2, suggesting a possible mechanism for macrophage retention within the tumor microenvironment [5]. Other CC chemokines that bind CCR2, CCL8 (MCP-2) and CCL7 (MCP-3), have also been shown to be produced by tumors and to recruit monocytes [6]. Furthermore, CCL2 expression seems to be a phenotype of tumor aggressiveness. In bladder and breast cancer, CCL2 expression levels