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Review article

The production of monocyte chemoattractant protein-1 (MCP-1)/CCL2 in tumor microenvironments

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ABSTRACT

Infiltration of leukocytes is one of the hallmarks of the inflammatory response. Among the leukocyte populations, neutrophils are the first to infiltrate, followed by monocytes and lymphocytes, suggesting the presence of mediators that specifically recruit these cell types. Cytokine-like chemoattractants with monocyte chemotactic activity, such as lymphocyte-derived chemotactic factor (LDCF) or tumor-derived chemotactic factor (TDCF), were reported as molecules that could play a critical role in the recruitment of monocytes into sites of immune responses or tumors; however, their identities remained unclear. In the 1980s, researchers began to test the hypothesis that leukocyte chemotactic activity is a part of the wider activities exhibited by cytokines, such as interleukin-1 (IL-1). In 1987, we demonstrated, for the first time, the presence of a cytokine like chemoattractant with cell type-specificity (now known as the chemokine interleukin-8 or CXC chemokine ligand 8) that was different from IL-1. This led us to the purification of the second such molecule with monocyte chemotactic activity. This monocyte chemoattractant was found identical to the previously described LDCF or TDCF, and termed monocyte chemoattractant protein-1 (MCP-1). Isolation of MCP-1 created a revolution in not only inflammation but also cancer research that continues today, and MCP-1 has become a molecular target to treat patients with many diseases. In this review, I will first describe a history associated with the discovery of MCP-1 and then discuss complex mechanisms regulating MCP-1 production in tumor microenvironments.

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1. Introduction

One of the mechanisms that lead to the infiltration of leukocytes into sites of inflammatory responses or cancer is the production of chemotactic molecules that diffuse out from the site of

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release and form concentration gradient to which leukocytes respond and migrate. In 1987, we purified the first cytokine-like chemoattractant, monocyte-derived neutrophil chemotactic factor (MDNCF, also known as the chemokine interleukin-8 or CXCL8) [1]. In 1989, we and others reported the purification of the second chemokine monocyte chemoattractant protein-1 (MCP-1)/macrophages chemotactic and activating factor (MCAF)/monocyte chemotactic protein (MCP) [2–5]. This chemoattractant is now widely known as MCP-1 or CC chemokine ligand 2 (CCL2) [6]. The identification of MCP-1 and its receptor CCR2 [7] greatly contributed to the studies to examine the mechanisms of monocyte trafficking and the role of monocytes/macrophages during inflammatory responses or cancer development.

Several reviews concerning the role of MCP-1 in the pathogenesis of many inflammatory diseases and cancer are already available elsewhere [8–10]. In this review, I will first introduce earlier studies that led us to the purification of MCP-1 and then discuss the results of our recent studies analyzing the complex mechanisms by which MCP-1 production is up-regulated in tumor microenvironments.

2. Roads leading to the purification of MCP-1

Macrophages play important roles in host defense by presenting Ag to lymphocytes or by participating in efferent limb immune responses as effector cells or secreting cytokines. Macrophages infiltrating sites of inflammation are derived from blood monocytes, which are attracted by chemotactic factors produced at inflammatory sites. We were interested in monocyte chemoattractants that accounts for the predominant infiltration by monocytes in most delayed hypersensitivity reactions [11–13]. It was of historical interest that a focus on the cellular motility and accumulation of nonsensitized inflammatory cells in DTH led to the first description of a lymphokine - migration inhibitory factor (MIF) [14,15]. This was followed by a series of reports in the early 1970s that chemotactic activity for macrophages or monocytes (lymphocyte-derived chemotactic factor; LDCF) was elaborated by antigen-stimulated sensitized lymphocytes or by mitogen-stimulated non-sensitized lymphocytes [16]. However, neither MIF nor LDCF had been purified to homogeneity.

The infiltration of leukocytes into cancer tissues could also be a result of a host immune reaction against tumor-specific antigen. Many laboratories previously explored in vivo and in vitro aspects of this hypothesis. It was shown by experiments with transplantable tumors in inbred guinea pigs that at dermal sites of delayed hypersensitivity reactions to one tumor cell line, antigenically unrelated tumor cells were also destroyed [17]. This suggested that the response to the antigenically unrelated tumor cells was immunologically nonspecific, and was mediated by activated macrophages infiltrating the site. It was shown that macrophages were capable of destroying tumor cells in vitro, provided that they were activated [18,19]. The activated macrophages were therefore assigned a critical role in host destruction of tumors. On the other hand, there was evidence suggesting that tumor-associated macrophages might stimulate tumor growth or connective tissue development [20–23]. Thus, neither the role of tumor-associated macrophages (TAMs) nor the mechanism of TAM infiltration was clarified [23,24].

As a possible mechanism of macrophage infiltration into tumors, Meltzer et al. reported the presence of a macrophage chemotactic factor in the culture supernatants of five murine sarcoma cell lines whose molecular weight was different from that derived from activated murine lymphocytes [25]. After several quiet years, Bottazzi et al. reported the production of a different degree of monocyte/macrophage chemotactic activity by human and murine tumor cell lines. They also found a significant correlation between the amount of monocyte/macrophage chemotactic activity and tumor macrophage content. These findings strongly suggested that tumor-derived chemotactic factor (TDCF) plays a critical role in the recruitment of TAMs. Bottazzi et al. also detected monocyte chemotactic activity in the culture supernatants of human and murine embryo fibroblasts [22]; however, it was not clarified whether tumor cells and fibroblasts produced a same chemotactic molecule.

In 1987, we purified the first chemokine IL-8, based on its neutrophil chemotactic activity, from the culture supernatant of lipopolysaccharide (LPS)-activated human peripheral blood cells (PBMC) [1,26]. During the process, we also noted the presence of monocyte chemoattractant in the same supernatant. Since a similar monocyte chemoattractant was also present in the culture supernatant of mitogen-activated human PBMC, we speculated that the monocyte attractant found in the culture supernatant of LPS-activated PBMC might be identical to the previously described LDCF. We attempted to purify the molecule to homogeneity from culture supernatants of activated PBMC by using column chromatography; however, we were not successful due to the limited availability of PBMC culture supernatants. Our problem was soon solved when we found that human malignant glioma cell lines produced a low to high level of monocyte chemotactic activity that could not be distinguished from that produced by activated PBMC. Among the cell lines, U-105MG cells released the highest amount of monocyte chemotactic activity [27].

In 1988, we purified the monocyte chemoattractant from the culture supernatants of both U-105MG cells and mitogen-activated PBMC. When the N-terminal amino acid sequence of the protein was analyzed by Edman degradation, we found that the N-terminus was blocked. By a combination of Edman gradation and mass spectrometry and cDNA cloning, it was established that MCP-1 comprises 76 amino acid residues, beginning at the N-terminus with pyroglutamic acid. In 1989, we reported all these results in three papers [2,3,28,29], and replaced the names LDCF and GDCF with molecule monocyte chemoattractant protein-1 (MCP-1), anticipating later discovery of MCP-2, 3, and so on. Matsushima et al. simultaneously reported the purification of the identical molecule (macrophage activating and chemotactic factor; MCAF) using the culture supernatant of activated THP-1 human monocytic leukemia cells [4]. Van Damme et al. also purified MCP-1 from the culture supernatants of double stranded RNA-activated MG-63 osteosarcoma cell line and LPS-activated human monocytes [5], and later structurally related chemoattractants, MCP-2 and 3 [30].

When the amino acid sequence of human MCP-1 was compared with those in a database, we noted that it had a significant amino acid sequence similarity to the protein coded by the mouse JE gene that was inducible in fibroblasts by platelet-derived growth factor [31]. Subsequently, MCP-1 was found identical to the product of the human orthologue of the mouse JE gene [32]. Finally, Bottazzi et al. demonstrated the production of MCP-1 by tumor cell lines which they used for the detection of TDCF, and concluded that MCP-1 was identical to TDCF [33]. Thus, MCP-1 is produced by either non-tumor cells or tumor cells, and it contributes to the development of not only inflammatory diseases but also cancer by promoting the recruitment of monocytes.

3. MCP-1 production in tumor microenvironments

Tumor tissues contain a variety of non-tumor stromal cells, including fibroblasts, endothelial cells, myocytes and inflammatory cells, such as myeloid-derived suppressor cells, regulatory T cells, macrophages and dendritic cells. The interaction of tumor cells

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