Chapter 27
Monocytes as Targets for Cancer Therapies

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ABSTRACT

The importance of monocytes in modulating the lymphocyte dependent tumor necrosis is a target for cancer therapeutics. Monocytes produce a plethora of chemokine receptors. Lymphocyte to monocyte ratio is one of the negative factors in cancer patients. It is being targeted for treatment of abnormal lymphocytopenia and monocytosis in untreatable metastatic cancer patients. The aim of the chapter is to throw light on the circadian and psychological factors that modulate the progression of cancer and identify novel targets for controlling transformation of preneoplasms to neoplasms, invasiveness, and metastasis.

INTRODUCTION

They are the largest type of cells in the peripheral blood under normal conditions. Their cytoplasm has azurophillic granules which stain purple to dark blue. They originate from the myeloid or progenitor cells in the bone marrow both during homeostasis as well as inflammation and migrate into blood. The works by (Dunay et al., 2008) and Serbina et al(2006) have thrown some light on the mechanism by which the monocytes leave bone marrow. They have shown that these cells egress from the bone marrow under the influence from CCR2 expressed by Gr-1hi monocytes in mouse (Dunay et al., 2008 and Serbina et al., 2006). The circulating TLR –Ligands can induce the production major monocyte chemoattractant MCP-1 by the bone marrow mesenchymal and progenitor cells (Shi et al., 2011). MCP-1 binds to CCR2 and promotes their egress from the bone marrow. In humans the exact mechanism is still not known. Further the exact mechanism of functioning of Gr1 low (mouse) monocyte subsets is yet to be ascertained. Apart from the bone marrow the spleen has a large reservoir of these cells.

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ROLE

The monocytes exit spleen and migrate to the site of injury (Reiss 1999), infection (Dunay et al., 2008, Dunay 2010, Voisine et al., 2010; Shi et al., 2011; Kim et al., 2011) or inflammation (Karlmark et al., 2012). It is in these sites of injury or inflammation that these monocytes will differentiate into various types of macrophages and dendritic cells. There are three types in humans based on the cell surface marker expressed i.e., classical $CD14^{++}$ $CD16^{-}$, non classical $CD14^{+}$ $CD16^{++}$and intermediate $CD14^{++}$ $CD16^{+}$. The mechanisms involved by the macrophages deploy to kill pathogens is phagocyting them to etosis. Monocytes produce a plethora of chemokine receptors. The interaction of chemokine receptors with the corresponding ligand governs the fate and function of monocytes. Upon infection or injury first line of defense comes from neutrophils followed by the monocytes which take over by producing the cytokines like IL-1Beta, IL6, TNF-ALPHA to modulate inflammation The Monocyte chemoattractant protein 1 (MCP1) is the major ligand for CCR2. The cytokine receptors SDF1-CXCR4 interactions are important for the homing of leukocytes in the bone marrow. Hence the importance of monocytes in modulating the lymphocyte dependent tumor necrosis is a target for cancer therapeutics. Mutations in the CXCR4 may cause WHIM (Swirski et al., 2009; Hernandez, et al., 2003; Gorlin, et al., 2000). Monocyte subsets with chemokine receptors with their corresponding ligands are as follows: Classical monocytes Mouse: Gr-1hi Human: CD14++CD16– CCR1 CCR2 CXCR2 MCP-2, MIP-1α (CCL3), RANTES (CCL5) MCP-1 (CCL2), MCP-3 (CCL7), MCP-5 CXCL1 (GROα), CXCL2 (GROβ), CXCL3 (GROγ) Non-classical monocytes Mouse: Gr-1low Human: CD14+ CD16+ CX3CR1 CCR5 CCR6 CX3CL1 (Fractalkine) CCL3 (MIP-1α), CCL4 (MIP-1β), CCL5 (RANTES) CCL20 (MIP-3α). Mouse models have been extensively used to discover the molecular mechanisms involved in monocyte mediated control of infections. Using mouse models, it has been shown that the monocytes Gr-1hi CCR2+ differentiate into TipDCs under certain microbial infection and produce TNF-a and iNOS as a strategy to control the infection (Gorlin, et al., 2000; Geissmann, Jung, & Littman, 2003 Serbina et al. 2003 and Serbina et al. 2009). Further these cells promote adaptive immune response by acting as antigen presenting cells to lymphocytes. It has also been shown in case of experimental muscle injury that these cells phagocytize the apoptotic cells followed by a phenotype switching where these cells become anti-inflammatory from proinflammatory and start producing IL10 and TGF-B1, for regeneration of muscles (Aldridge et. al., 2009). It has also been shown that during the inflammation of the skin and lungs they differentiate into Langerhans cells and CD103+ pulmonary dendritic cells. In a hepatic injury model, the monocytes have been shown to modulate disease progression by either producing iNOS or Arginase in response to the TH1/TH2 environment (Shi et al., 2011). Immunosuppression caused by monocyte macrophage system can be assessed by PB monocyte count. The degree of monocyte macrophage system regulates T lymphocytes via cytokines (Dunay et al., 2016). Leukocytosis has also been found to be correlated with depression. Further, both monocytosis and neutrophilia are associated with depression. The effects of depression may be caused by an underlying inflammatory process. Such effects are most profound in the cases of major depression whereas those suffering from minor depression have intermediate effects as compared to the normal controls (Serbina et.al., 2012). Hence the additional effects of depression on progression of disease are evident. Monocytosis may be induced by several factors from infections to neoplasms as well as therapies for treatment. Infections caused by viruses like HIV, Epstein Barr virus etc and bacteria like mycobacterium tuberculosis, Treponema pallidum, etc., protozoans such as Leishmania, Trypanosoma, Typhus etc., Neoplastic disorders like hairy cell leukemia, acute myeloid leukemiA, lymphomas etc., Monocytosis in patients with vascular disorders has been correlated with increased risk