Monocyte-Derived Cells of the Brain and Malignant Gliomas: The Double Face of Janus

Q11 Q12 *Sergiy V. Kushchayev[1], Yevgeniya S. Kushchayeva[2], Philip C. Wiener[1], Behnam Badie[3], Mark C. Preul[1]*

Key words
- Dendritic cells
- Glioblastoma
- Macrophages
- Microglia
- Monocytes

Abbreviations and Acronyms
APC: Antigen-presenting cell
CCL: C-C chemokine ligand
CNS: Central nervous system
COX: Cyclooxygenase
CpG: Carbon nanotubes with oligodeoxynucleotides
CXCR: Chemokine C-X-C motif ligand receptor
DC: Dendritic cell
GBM: Glioblastoma multiforme
gMD: Granulocytic myeloid derived
GM-CSF: Granulocyte macrophage colony-stimulating factor
HIF: Hypoxia-inducible factor
HLA: Human leukocyte antigen
IL: Interleukin
M-CSF: Macrophage colony-stimulating factor
MCP: Monocyte chemotactic protein
MDCB: Monocyte-derived cells of the brain
MD: Myeloid derived
MHC: Major histocompatibility complex
mMD: Monocytic myeloid derived
MMP: Matrix metalloproteinase
PGE_2: Prostaglandin E_2
ROS: Reactive oxygen species
STAT: Signal transducer and activator of transcription
TEM: Tie2-expressing monocytes
T_{reg}: Regulatory T cell
TGF: Transforming growth factor
TNF: Tumor necrotic factor
VEGF: Vascular endothelial growth factor

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OBJECTIVE: **Monocyte-derived cells of the brain (MDCB) are a diverse group of functional immune cells that are also highly abundant in gliomas. There is growing evidence that MDCB play essential roles in the pathogenesis of gliomas. The aim of this review was to collate and systematize contemporary knowledge about these cells as they relate to glioma progression and anti-glioblastoma therapeutic modalities with a view toward improved effectiveness of therapy.**

METHODS: **We reviewed relevant studies to construct a summary of different MDCB subpopulations in steady state and in malignant gliomas and discuss their role in the development of malignant gliomas and potential future therapies.**

RESULTS: **Current studies suggest that MDCB subsets display different phenotypes and differentiation potentials depending on their milieu in the brain and exposure to tumoral influences. MDCB possess specific and unique functions, including those that are protumoral and those that are antitumoral.**

CONCLUSIONS: **Elucidating the role of mononuclear-derived cells associated with gliomas is crucial in designing novel immunotherapy strategies. Much progress is needed to characterize markers to identify cell subsets and their specific regulatory roles. Investigation of MDCB can be clinically relevant. Specific MDCB populations potentially can be used for glioma therapy as a target or as cell vehicles that might deliver cytotoxic substances or processes to the glioma microenvironment.**

INTRODUCTION

Surgical resection of a malignant glioma can remove much of the visible tumor mass; however, it cannot eradicate invasive and migratory cells. This challenge underscores the need for novel strategies to improve the outcome of patients with glioblastoma multiforme (GBM). Much attention has recently focused on the tumor cells, but up to a third of the GBM tumor mass can consist of glioma-associated monocyte-derived cells of the brain (MDCB). The role of these cells in glioma development and progression is perhaps as fundamental to the understanding of the biology of a glioma as the tumor cells themselves (65, 122). Identifying, classifying, and describing their roles and relationships, even in the steady state is challenging, notwithstanding their even more complex interactions with a malignant glioma. Recent research on inflammation, including the increasingly important roles of immune cells, was included as one of the *Insights of the Decade* by *Science* (1). New insights into chronic inflammation and inflammatory cells have revealed implications with various illnesses such as cancer, diabetes, obesity, and Alzheimer disease.

There is growing evidence that MDCB play essential roles in the pathogenesis of gliomas. A recent review proposed that tumor-associated macrophages (i.e., macrophages and microglia) may undergo neoplastic conversion in GBM, just as other monocytes do in other cancers (Huysentruyt et al.). Q1 Understanding these processes will be critical to improve existing treatments and to create new therapeutic approaches for malignant gliomas. This review concerns the systems of MDCB cell populations with gliomas as a basis for the neurosurgeon and neuro-oncologist to understand their complex relationships and interaction. This review concentrates and synthesizes the

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research data on MDCB in relation to glioma pathogenesis with therapeutic implications; however, a complete review of various MDCB-based therapies involved against gliomas is beyond the scope of this article. Before treatment strategies can be assessed, we suggest that neurosurgeons would benefit from an understanding of the fundamental organization of the MDCB system, including information on prominent cytokines, chemokines, and receptors that appear to be involved. We traced the process of MDCD transformation starting from their appearance in blood as monocytes to their migration and selective existence in the brain and within the tumor milieu. MDCB are a hetogeneous population of cells, thus our review describes these specific populations in steady-state conditions (i.e., normal conditions) and in gliomas. We also analyzed current approaches using MDCB as a therapeutic tool.

BLOOD MONOCYTES

Blood Monocytes in the Steady State and Glioblastoma

Monocytes originate in the bone marrow from the colony-forming unit. The macrophage colony-stimulating factor (M-CSF) interacts with its cell surface receptor (CD115) and promotes growth and differentiation of monocytes and monocyte-derived cells (24). Most of the monocytes circulate in the bloodstream for 48 hours; only a small fraction (15%) remains for up to 168 hours. After this period circulating monocytes undergo spontaneous apoptosis. Monocytes can escape their apoptotic fate by migrating to different organs and differentiating into tissue macrophages (41). In the steady state, blood monocytes are also a heterogeneous population of cells.

Inflammatory and Resident Monocytes. Inflammatory and resident monocytes represent two major populations. Inflammatory monocytes (cell surface receptor profile $Gr1^{+}$/Ly-$6C^{high}$) give rise to macrophages that can activate and inhibit the immune response, depending on local or systemic cues and the nature of the encountered pathogen (39). Resident monocytes (historically designated $Gr1^{-}$/Ly-$6C^{low}$) do not express monocyte chemotactic protein-1 (MCP-1 also C-C chemokine ligand 2 [CCL-2]) and L-selectin, thus are less available for recruitment and have a higher expression of the chemokine receptor chemokine C-X-C motif ligand receptor 1 (CX3CR1), which plays major role in the survival of monocytes (39). In humans, most monocytes are designated by their surface receptor profile $CD14^{+}CD16^{-}$ and are referred to as classic monocytes. In contrast, $CD14^{+}CD16^{+}$ cells are referred to as nonclassic monocytes and are resident cells that migrate into tissues to renew macrophage populations (38, 113). In the steady state, mature monocytes probably seed tissues and differentiate into specific populations of resident macrophages. Peripherally circulating monocytes in patients with GBM are altered phenotypically and their functional capacity to differentiate into mature antigen-presenting cells (APCs) is reduced (86). Monocytes of patients with GBM exhibit reduced expression of human leukocyte antigen (HLA)-DR molecules (46). HLA-DR^{low} monocytes are associated with high expression of the immunosuppressive cytokines interleukin (IL)-10 and transforming growth factor-β (TGF- β). In addition HLA-DR^{low} monocytes mature less effectively into functional dendritic cells (DCs) and macrophages that are capable of antigen presentation (123).

Myeloid-Derived Suppressor Cells. In murine studies, myeloid-derived (MD) suppressor cells (cell surface receptor marker designation Gr-$1^{+}CD11b^{+}$) have been identified as another class of MD cells with immunosuppressive properties (22). They do not represent a single cell population but are composed of immature myeloid cells at different stages of cell differentiation (132). In healthy humans, these cells are generated in the bone marrow and quickly differentiate into mature granulocytes, macrophages, or DCs. In cancer, the differentiation of immature myeloid cells into mature cells is partially blocked, resulting in expansion or accumulation of MD suppressor cells in pathologic tissue (108). These suppressor cells have a potent ability to suppress immune responses, especially T-cell proliferation and cytokine production (6, 7, 78, 120, 131). In mice and humans, MD suppressor cells can be subdivided into two major groups: granulocytic MD suppressor cells (gMD suppressor cells) and monocytic MD suppressor cells (mMD suppressor cells) (131). In mice, gMD suppressor cells display a $CD11b^{+}$Ly-$6G^{+}$Ly-$6C^{low}$ cell surface receptor phenotype, whereas mMD suppressor cells show a phenotype of $CD11b^{+}$Ly-$6G^{-}$Ly-$6C^{high}$ (75, 132). In humans, the phenotype of these cells is less clearly defined; however, CD15 and CD66b are implicated as additional cell surface markers allowing detection of gMD suppressor cells and mMD suppressor cells (61, 102). gMD suppressor cells and mMD suppressor cells differ not only in the morphology and phenotype but also in the mechanisms by which they suppress immune function. mMD suppressor cells are more potent at immunosuppressive activity than gMD suppressor cells (131).

Tie2-Expressing Monocytes. Tie2-expressing monocytes (TEMs) are another class of MD cells. They express angiopoietin receptor Tie2 and account for 2%–7% of blood mononuclear cells in healthy donors (121). TEMs are already preprogrammed in the circulation to be angiogenic and to express high levels of such proangiogenic genes (e.g., matrix metalloproteinase 9 [MMP9], vascular endothelial growth factor [VEGF], cyclooxygenase 2 [COX-2], and wingless-type MMTV integration site family, member 5A) than Tie2-negative monocyte population (16). The surface marker profile of mouse and human TEMs is similar to that of resident monocytes (79). The role of Tie2 expressing the cell population is not established in glioma, but it likely contributes significantly to angiogenic aspects of gliomas. Selective depletion of TEM in nonglioma tumor-bearing mice inhibits tumor angiogenesis and growth, suggesting that these monocytes might regulate angiogenic processes in tumors by providing paracrine support to nascent blood vessels (20).

Dendritic Cells. DCs that leave the bone marrow are in an immature form. They have high levels of major histocompatibility complex (MHC) II messenger RNA and protein in the cytoplasm but only low levels of MHC II expression at the cell surface. Immature DCs have little or no expression of costimulatory molecules that participate in DC–T-cell interaction—such as CD40, CD80, and CD86—at the cell surface, and they produce little or no IL-12, which is required to support T-cell proliferation. Contact of DCs in tissues with antigens activates DCs, maturing them, resulting in up-regulation of the cell surface expression of MHC II, CD40, CD80, and CD86;

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