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Editorial

Microglia: a novel treatment target in gliomas

Microglial cells have not received much attention in neuro-oncology over the past decades, despite the fact that they may be the most abundant cell in glioma tissue. Accordingly, *Neuro-Oncology* has now devoted a major review article to the changing concepts of what microglial cells do or do not do, both in the normal and diseased brain, with a focus on the biology of gliomas (1).

Traditionally, microglial cells have been considered part of the immune system, but to what extent these cells are capable of antigen presentation and participation in immune responses has remained controversial. Their origin, local resident brain cell *versus* bone marrow derived, has been one focus of microglia research for years, and it now seems clear that the microglial cell population, especially in the disease state, is likely derived from both cellular sources.

Currently, microglial cells are seen not as an efficient arm of the immune system but rather as a misguided host cell population, abused by the growing glioma for its own advantage. Microglial cells are attracted to the site of tumor growth and expand locally through signaling molecules, such as monocyte chemoattractant protein 1, macrophage colony-stimulating factor, vascular endothelial growth factor, and placental growth factor. These factors are not only released by glioma cells but presumably also by the microenvironment that is constantly shaped by these tumors. Thus, microglial cells are now thought to support invasiveness by releasing matrix metalloproteases, angiogenesis by releasing proangiogenic factors, and immunosuppression. The latter is mediated by converting microglial cells or macrophages recruited from the periphery, into the M2 macrophage phenotype, which is characterized by the release of immunosuppressive (e.g., interleukin 10) rather than immunostimulatory cytokines, (e.g., tumor necrosis factor-α or interferon-γ), less nitric oxide production, and poor antigen presentation. These changes in the microglia/macrophage phenotype, in turn, are thought to be controlled by soluble factors such as transforming growth factor-β, which interact with their respective receptors expressed on microglial cells.

Together, these considerations may lead to new treatment approaches for glioblastoma that not only focus on glioma cells but also on trying to contain glioma growth by modulating its microenvironment, notably its permissiveness for immune responses against the tumor. Thus, any immunotherapy will work better if the M2 phenotype of microglial cells and macrophages can be (re)converted to a M1 phenotype.

Finally, if microglial cells are indeed partly bone marrow derived and exhibit efficient homing to the brain, cellular therapy strategies may adopt some of the pathways mediating this specific cellular trafficking between the peripheral and central nervous systems to deliver therapeutic payloads to the intracranial tumor sites or even use engineered, reprogrammed microglial cells for such purposes.

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Reference

1. Li W, Gräber M. The molecular profile of microglia under the influence of glioma. *Neuro-Oncology*. 2012;14(8):958–978.