Microglial Response to Brain Injury: A Brief Synopsis

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ABSTRACT

In addition to astrocytes and oligodendrocytes, microglia represent the third major population of glial cells within the central nervous system (CNS). Microglia are distributed ubiquitously throughout the brain and spinal cord, and one of their main functions is to monitor and sustain neuronal health. Microglial cells are quite sensitive to even minor disturbances in CNS homeostasis, and they become readily activated during most neuropathologic conditions, including peripheral nerve injury, trauma and stroke, inflammatory disease, and neurotoxicant-induced neuronal injury. During activation, microglia display conspicuous functional plasticity, which involves changes in cell morphology, cell number, cell surface receptor expression, and production of growth factors and cytokines. The many changes occurring in activated cells reflect the altered functional states of microglia that are induced by signals arising from injured neurons. Thus, neuronal-microglial signaling plays a fundamental role in understanding how the CNS responds to injury. Reactive microgliosis should be viewed as a cellular effort to initiate ameliorative and reparative measures in the injured brain.

Keywords: Microgliation; neuropathology; reactive gliosis; neuronal injury; cell death; neurodegeneration; neuron-microglia interaction

INTRODUCTION

The microglial cell can be described as "the cell that came out of the closet" little more than a decade ago. The term "microglia" was coined in the 1920s by the Spanish neuroanatomist Pio del Rio-Hortega, who conducted the first detailed microscopic examination of this newly discovered cell type (3, 14, 17). Despite these exciting studies during the early part of this century, subsequent decades provided little follow-up on del Rio-Hortega's groundbreaking work. For reasons that are not entirely clear, interest in the study of microglial cells remained quite low among most neurobiologists and neuropathologists during that time. However, microglia research re-emerged during the 1980s, when for the first time it became possible to visualize these cells reliably and consistently using modern histologic techniques. The development of immunohistochemical and lectin histochemical methods for staining microglia in situ was paralleled by the development of in vitro systems that facilitated the study of primary microglial cell cultures. Together, these advances served to refocus attention on an almost-forgotten glial cell type that (as it turns out, after only a dozen or so years) is perhaps the single most important cellular entity for understanding disease processes that afflict the central nervous system (CNS).

WHAT IS THE FUNCTION OF MICROGLIAL CELLS?

With a renewed interest in microglia, a large number of histologic and cell-culture studies have been performed in recent years. It is beyond the scope of this manuscript to review these, and the interested reader is referred to several comprehensive reviews on the subject (1, 9, 10, 19). In vivo and in vitro investigations have portrayed microglial cell function from 2 opposing points of view. One school of thought, which is largely founded in in vitro studies, views microglia as neurotoxic immune effector cells that potentially endanger neuronal survival. The other point of view, which is derived primarily from in vivo studies, is apparently in diametric opposition to the first school of thought in that it claims a neurotrophic role for microglia. This presents the neurobiologist with a dilemma, as these are ostensibly conflicting cellular functions. However, as discussed in a recent review of the subject (19), it is possible to reconcile this conflict by postulating that microglia can, at least in principle, carry out both neurotrophic and neurotoxic functions in vivo. The determining factor for which function will come to bear is the type of signal emitted by a neuron in distress. If the nerve cell has been injured only slightly and can be rescued, the nature of the neuronal signal (presumably a chemical one) stimulates activated microglia cells to nurse the injured neuron back to health. On the other hand, if the injury sustained is sufficiently severe to be irreversible, the type of signal emitted by the dying neuron may signal microglia to become neurotoxic and to perform a merciful act of cellular euthanasia. This could occur via a number of potentially toxic mediator substances shown to be produced by microglia in vitro (2). While it may be an attractive idea conceptually, definitive experimental proof that these types of neuron-microglia interactions occur in the living brain is still missing. Undoubtedly, the nature of the interactions between neurons and microglia is going to be complex, and it likely involves many different and possibly still-unknown signaling molecules. A glimpse into these mechanisms has been provided by a recent study that has
suggested a role for chemokine signaling between microglia and injured neurons (8). Research into neuron-microglia interactions is considered to be important because these intercellular processes are at the heart of understanding the CNS response to injury. Without a doubt, this area holds great promise for future discoveries.

**Practical Issues Involved in Evaluating Reactive Microgliosis**

For the pathologist interested in identifying the site of a CNS lesion, reactive microgliosis can serve as most useful indicators. As mentioned, the cells are exquisitely sensitive to disturbances affecting neurons, and they do react promptly to neuronal distress via changes in morphology that are readily recognizable to the microscopist who analyzes immunohistochemical or lectin histochemical preparations. Cellular hypertrophy is the hallmark feature of microglial activation, and this can transform the finely branched, so-called resting microglial cells of the normal parenchyma into enlarged activated cells with short and stout processes (15, 16). Presumably, this morphologic transformation is reversible once the stimulus for activation has vanished. The extent and intensity of microglial activation is proportional to the extent and severity of the pathological insult, and often, gradients of microglial activation can be observed extending into brain regions away from the lesion epicenter. This is particularly conspicuous along myelinated white-matter tracts that are undergoing Wallerian degeneration (11, 13). However, it is important to bear in mind that the presence of activated microglia does not necessarily delineate areas of frank neurodegeneration. As indicated above, even subtle and nonlethal injuries can elicit microglial activation, which may then become a reflection of an ongoing rescue effort. When and if neuronal cell death does occur, microglia do undergo transformation into full-fledged brain macrophages, cells that are easily identifiable by their rounded shape and by the presence of phagocytic inclusions. However, the “decision” to become a brain macrophage is made only when required—that is, when tissue necrosis necessitates the removal of debris. Contrary to statements commonly found in the literature, microglia are not simply “the resident macrophages of the brain.” Their transformation into phagocytic cells is under strict control, and, as some of our recent experiments have shown, microglia in the normal brain parenchyma exist as facultative phagocytes (12). In terms of their functional state, the parenchymal microglia are to be differentiated from constitutive (or professional) macrophages of the CNS, also known as perivascular cells (6, 7). Unlike microglial cells, perivascular cells are not true components of the CNS parenchyma, since they reside underneath the vascular basement membrane as components of the vascular wall.

In histological preparations, necrotic foci within the CNS parenchyma can be readily identified by the presence of clusters of phagocytic microglia. Such clusters may contain 6 or more cells. Clustering of microglia together with other changes, such as rod-cell formation and cell fusion, also occurs with increasing frequency during normal aging (18). However, age-related clustering of microglia does not appear to be the result of acute tissue necrosis. Instead, it appears to be closely connected to gradually increasing extracellular deposition of insoluble, fibrillar β-amyloid protein over time (4, 18). Microglial rod cells are found in the aging cortex and hippocampus, and they represent activated microglia, which are lined up along the processes of pyramidal neurons (5). Rod cells usually form by longitudinal fusion of individual microglial cells. Thus, there is increasing microglial activation occurring with normal aging. Chronic pathological processes, such as Alzheimer’s disease, human immunodeficiency virus encephalopathy, or even systemic cardiovascular disease (18) could exacerbate age-related microgliosis to a point at which the balance between neurotrophic and neurotoxic functions becomes tipped such that microglia turn from friend to foe.

**Conclusions**

Considerable advances have been made in recent years regarding our understanding of the biology of microglial cells. One current view, which has been discussed in this paper, sees microglia as cellular elements that occupy a center-stage position in the mechanisms that govern neuronal regeneration and degeneration. Future research aimed at elucidating neuronal-microglial interactions could result in improved diagnostic and therapeutic strategies for the handling of CNS injury and disease.

**References**


