Editorial

The M1/M2 immune polarization concept in microglia: a fair transfer?

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Although macrophages were first described in 1882 by Ilya Ilyich Metchnikoff, it was 30 years before the first descriptions of monocytes, their relatives within the blood stream.[1,2] Initially described as a phagocytic cell mainly within the context of tissue inflammation, it took until the turn of the millennium to introduce the alternative myeloid cell (MØ) immune polarization concept, which was provided by Mills *et al*. in 2000.[3] This concept of differential M1-M2 polarization of MØ was deduced from the classical dichotomic activation program of lymphocytes.

However, it was an oversimplified idea to attribute MØ activation to the so-called Th1-lymphocytes producing interferon-γ while MØ inhibition was ascribed to Th2-lymphocytes secreting high levels of interleukin 10, among other cytokines. It was demonstrated that lymphocytes determine the activation state of MØ, and MØ strongly influences the differential activation state of lymphocytes.[4] Because it was shown that MØ stimulated by Th1-lymphocytes secreted high levels of nitric oxide, thereby leading to a reduced proliferative potential, the M1-M2 concept was quickly adapted to other paradigms, such as tumor-associated macrophages (TAM) or tissue repair mechanisms.[5] In general, M1-polarized TAMs were regarded as immune cells with tumor-suppressive capacity, whereas M2-polarized TAMs are tumor promoting.

The M1-M2 concept also quickly attracted the attention of many neuroscientists working in immunological research. Although there was a lack of substantial data, direct transfer of the immune polarization idea to microglial cells was frequently performed without further testing its applicability. More recent studies made it increasingly evident that microglial cells and blood-derived macrophages display considerably different phenotypes upon similar stimulation conditions.[6] In particular, M2 conditions, which typically induce CD163 and CD206 in macrophages, failed to result in a similar phenotype in microglial cells. Furthermore, in central nervous system (CNS) disorders, such as Alzheimer's disease, the immune polarization state of microglial cells is not solely dependent on the microenvironmental immune milieu, it is also strongly related to the amyloid beta deposit subtype (oligomeric or fibrillar forms).[7] A more recent study demonstrated that autopsy cases of Alzheimer's disease display M1-polarized MØs in very early stages, while more severe stages with increased levels of neuritic plaques (and often accompanied with extensive cerebrovascular pathology) displayed a M2a-polarized subtype.[8] Other findings in animal models of neurodegenerative disorders, such as the mutant superoxide dismutase model for amyotrophic lateral sclerosis, revealed that M2-polarized microglia were neuroprotective, but M1-polarized microglia were neurotoxic.[9] Notably, the first experimental treatment approaches revealed that chronic neurodegenerative changes related to microglial activation can be attenuated via minocycline, a substance inhibiting microglial activation, which leads to increased activation of the M2-polarized microglial phenotype.[10] However, there is also opposing data claiming that activated microglia do not specifically up-regulate molecules of either the M1- or M2-polarized phenotype; rather they show an increase on both axes.[11]

Nevertheless, many authors simply classify myeloid immune cells in the CNS under the combined term as

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"microglia/macrophages" without further distinction of their real origin, thereby gaining only a single phenotypic signature for distinct cell types.[12-16] The most recent experimental data from brain injury models even revealed that microglial cells did not transform to classical M1 or M2 phenotypes under circumstances in which their blood-borne-derived counterparts do, thereby suggesting another regulatory function subtype.[17] This study further pointed to a more protective role of microglia upon CNS injury, while blood-borne-derived myeloid cells seem to exert more cytotoxic properties. Because the pioneering authors of the M1-M2 concept in macrophages stated that their proposed views of classifying macrophages in either a M1 or M2 polarized state might be an oversimplification, a fortiori is its transfer to microglia cells.[3] In CNS pathologies, microglial cells are nonclonal and show a high-degree of plasticity, as well as intermixture with peripheral, blood-borne macrophages.

Deciphering the immunological properties of microglial cells under normal and pathological circumstances with regard to the M1/M2 concept requires more functional studies, which will need to take into account the distinct microglial gene expression signature.

More sophisticated scientific neuroimmunological and/or neuroinflammatory research approaches are necessary. Notably, sorting myeloid cell populations might pave the way for deeper insight into the applicability of the M1/M2 immune polarization concept for microglia, the resident immune cells of the CNS.[18] Such studies will impact and broaden the knowledge of basic research and influence further treatment strategies in traumatic, inflammatory, or neoplastic disorders of the CNS.

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