Interleukin 4-induced neuroprotection and regulation of microglia activation as a therapeutic approach in the MPTP model of Parkinson’s disease

Parkinson’s disease (PD) has been described as one of the most common neurodegenerative diseases affecting up to 2% of the worldwide population over 60 years of age. The hallmarks of PD are progressive loss of midbrain dopaminergic (mDA) neurons and a decrease in striatal dopamine levels, which result in typical clinical motor symptoms such as akinesia, resting tremor, rigidity, and gait impairments. Although the causes for PD are only partially understood and seem to be very heterogeneous, one of the common phenomena observed in toxin-based animal models of PD as well as PD patients is a microglia-driven neuroinflammatory response, which is at least in part responsible for exacerbation of neuronal loss and worsening of clinical symptoms (Machado et al., 2016). As recently summarized by these authors, degeneration of mDA neurons results in reduced neuron-microglia communication and the release of intracellular components from dying neurons further triggers the activation of microglia located in close proximity to challenged mDA neurons. Upon activation, microglia increase expression and release of several inflammatory factors that subsequently compromise stressed mDA neurons, thus, fostering the progressive nature of PD (Figure 1). Next to microglia-mediated neurotoxicity, aging is one of the major risk factors to develop PD. Interestingly, aging further affects microglia as well as their functional states and the impact of age-dependent microglia changes on neurodegeneration is currently extensively studied. Microglia in the aged central nervous system (CNS) have been described to express higher levels of inflammatory markers such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) or interleukin 6 (IL-6) and have been further shown to react to inflammatory stimuli with a stronger and prolonged response. This phenomenon is referred to as microglia priming and recent studies have demonstrated that aged and primed microglia promote enhanced neurotoxic effects in animal models of PD (Spittau, 2017). However, depending on the activating stimuli, microglia reactions are also able to promote neuroprotection and neuroregeneration. Among the factors inducing a protective microglia activation phenotype, interleukin 4 (IL-4) has been demonstrated to shift microglia activation towards a regenerative and anti-inflammatory phenotype in vitro and in vivo (Zhou et al., 2012; Casella et al., 2016).

In a recent study, we addressed the question whether endogenous IL-4 is involved in 1-methyl-2-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced degeneration of mDA neurons in mice. We demonstrated that exogenous IL-4 was able to protect mDA neurons from 1-methyl-4-phenylpyridinium (MPP⁺)-induced neurodegeneration in mixed neuron-glial cultures. Moreover, neutralization of endogenous microglia-derived IL-4 in these cultures augmented the MPP⁺-induced loss of mDA neurons. The protective effect of IL-4 was at least in part mediated by increased expression and release of insulin-like growth factor 1 (IGF-1), a potent neurotrophic factor for mDA neurons. However, intraperitoneal injections of MPTP in IL-4-deficient mice did not result in increased loss of mDA neurons and enhanced decrease in striatal dopamine levels compared to wild type controls. Noteworthy, in contrast to in vitro conditions, increased expression of IL-4 could not be detected in the in vivo MPTP model, indicating that endogenous IL-4 does not play a major role during MPTP-induced mDA neurodegeneration (Hühner et al., 2017). IL-4 has recently been shown to promote protection of injured CNS neurons after optic nerve crush injury and in model for spinal cord contusion injury. The authors further demonstrated that IL-4-producing CD4^+ T cells accumulated at the injury sites and induced recovery of injured neurons (Walsh et al., 2015). One of the major differences between the abovementioned studies is the level of blood-brain barrier (BBB) integrity. Whereas the BBB leakage is very pronounced in contusion models, allowing peripheral immune cells to invade the CNS, the systemic application of MPTP only has a minor impact on BBB integrity. However, a distinct BBB impairment after MPTP intoxication of mice has been described and resulted in accumulation of blood-borne monocytes/macrophages and CD25^+ T cells in the nigrostriatal system (Depboylu et al., 2012). Interestingly, CD4^⁺CD25^⁺ regulatory T cells (Tregs) have been described to regulate microglial inflammatory responses and protect mDA neurons from MPTP-induced degeneration as demonstrated after adoptive transfer of Tregs. Furthermore, transferred Tregs increased expression of glial cell line-derived neurotrophic factor (GDNF) and the potent immunosuppressive factor transforming growth factor (TGF)-β (Reynolds et al., 2007). Of note, TGF-β is a cytokine that has been shown to inhibit interferon γ (IFNγ)-induced microglia activation and subsequent degeneration of mDA neurons (Zhou et al., 2015) and further enhances IL-4-induced activation of a regenerative microglia phenotype (Zhou et al., 2012). Regulatory T cells, Th2 cells as well microglia itself are supposed to be the source for endogenous IL-4, but especially Th cell-derived IL-4 effects are difficult to explain in the presence of an intact BBB (Gadani et al., 2012), therefore, a loss of BBB integrity might be a prerequisite for neuroprotective effects of endogenous IL-4 and recent studies support this hypothesis indicating that endogenous IL-4 is important in models with pronounced impairments of the BBB (Figure 1). However, Zhao et al. (2015) used an IL-4 reporter mouse to demonstrate that IL-4 is also expressed by neurons. In a model of cerebral ischemia, the authors observed that neurons in the penumbra region surrounding the ischemic core are predominantly expressing IL-4 to modulate microglia activation states. Although endogenous IL-4 does not seem to be involved in the regulation of microglia activation in the MPTP mouse model of PD, exogenous IL-4 has been demonstrated to efficiently protect mDA neurons in vitro, which further underlines the therapeutic potential of IL-4 administration in PD models (Hühner et al., 2017). Moreover, the systemic injections of MPTP and the relative mild impairment of the BBB in this toxin-based model of PD might explain why endogenous IL-4 did not influence the extent of mDA neurodegeneration. In the 6-OHDA model of PD, the toxin is directly injected into the striatum, the substantia nigra or the medial forebrain bundle, indicating a direct lesion of the CNS parenchyma and a subsequent impairment of the BBB integrity. However, it remains to be elucidated whether endogenous IL-4 protects mDA neurons in this toxin-based PD model. It has to be taken into consideration that administration of exogenous IL-4 via intracerebral injection/infusion or via viral gene transfer might be promising approaches to regulate microglia-mediated neurodegeneration in animal models of PD, especially, in the models where the integrity of the BBB is not impaired or less affected. Interestingly, Kiyota et al. (2010) have demonstrated that overexpression of IL-4 in the CNS of APP/PS1 transgenic mice attenuated Alzheimer’s disease-like pathologies and reduced microglia-mediated
neuroinflammation. This study indicates that CNS delivery of IL-4 is a potent therapeutic approach to reduce neuronal damage induced by microglia-induced inflammatory responses in the most common neurodegenerative disorder. It has to be further evaluated whether IL-4 plays a role in different toxin-based PD models in vivo, such as the abovementioned 6-OHDA mouse model and whether IL-4 supports mDA neuron survival in transgenic mouse models of PD. Finally, the contribution of IL-4 in regulating microglia activation states and facilitating neuroprotection in human PD cases has to be addressed in order to validate the observations made in animal models of PD and in vitro studies where IL-4 induced glia-driven neuroprotective effects on mDA neurons. Taken together, the data observed after IL-4 administration in animal models of PD and other neurodegenerative diseases suggest that IL-4 bears a strong therapeutic potential by shaping microglia activation towards a neuroprotective and regenerative phenotype. However, treatment with single factors alone might not be sufficient to promote proper protection of mDA neurons and, thus, therapeutic approaches including combinations of neuroprotective and immunomodulatory factors are likely to be most promising.

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