EDITORIAL COMMENT

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Type-I interferons in Parkinson's disease: innate inflammatory response drives fate of neurons in model of degenerative brain disorder

An editorial comment on 'Type-I interferons mediate the neuroinflammatory response and neurotoxicity induced by rotenone'

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The type I interferons (IFN-Is) are a family of pleiotropic, essential cytokines that regulate the innate immune response and have various immunomodulatory functions (Deczkowska *et al.* 2016; Goldmann *et al.* 2016). In humans, the IFN-Is are encoded by 14 genes; the most studied protein products of which are IFN-α and IFN-β. The actions of the IFN-I signaling system have been relatively well described in the periphery, and in recent years, researchers have began to understand more about their role in the central nervous system (CNS) under both physiological and pathological conditions. It is now known that a central CNS function of the pathway is protecting the brain against infection, and that its dysregulation causes human neurological disease. However, IFN-Is are also expressed and secreted at low levels under normal physiological conditions.

Activation of the IFN-I system is tightly regulated and occurs rapidly upon inflammatory insult (McGlasson *et al.* 2015). Although the brain lacks professional IFN-I producing cells, both neurons and glia have the ability to mount the IFN-I response, and the IFN-I receptor is present on virtually all cell types. In particular, microglia, the CNS-resident immune competent myeloid cells, respond robustly to IFN-I (Goldmann *et al.* 2016). The IFN-Is act primarily through the classical Janus kinase and two signal transducer and activator of transcription protein pathway, leading to the transcription of interferon-stimulated genes, of which there are hundreds. Classical pro-inflammatory genes induced by IFN-I include tumor necrosis factor-α, interleukin-6 and interleukin-1 1β.

Conditional deletion of the IFN-I receptor (IFNAR) in the brain causes increased susceptibility to fatal viral infection (Weber *et al.* 2014), while constitutive activation of the pathway causes chronic inflammation (Ivashkiv and Donlin 2014), that is also exemplified by the genetically determined inflammatory encephalopathy Aicardi–Goutières syndrome, which is linked to chronically elevated IFN-α production in the CNS. Recently, dysregulation of the INF-I pathway has been implicated in the pathogenesis of a widening spectrum of neuroinflammatory conditions.

Ablation of IFN-I signaling is neuroprotective not only in chronic neurodegenerative disorders including Parkinson's disease (PD) and Alzheimer's disease (Minter *et al.* 2016), but also in traumatic brain injury (Karve *et al.* 2016). However, studying the cell-specific actions and consequences of IFN-I signaling in the context of neurodegenerative diseases has yielded somewhat contradictory results

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(Deczkowska *et al.* 2016). For example, lack of IFN-β signaling specifically in neurons has been reported to cause a cascade of events that mimics neurodegeneration observed in human PD (Ejlerskov *et al.* 2015). It should be noted that the specific pathological context affects the signaling mediated by IFN-I, and the effects may be different in different cell types. Furthermore, it is well established that the various IFN-I subtypes have varying effects. Intriguingly, IFN-β is a common treatment for individuals with multiple sclerosis, although its mechanism of action remains poorly understood and neurological side effects are commonly observed (Annibali *et al.* 2015).

In the current issue of *Journal of Neurochemistry*, Main *et al.* (2017) show that the IFN-I pathway has a central role in toxicity of rotenone, a compound commonly used to model PD through its neurotoxic activity toward dopaminergic neurons. Rotenone is a mitochondrial respiratory chain Complex I inhibitor, and induces oxidative stress from elevated mitochondrial reactive oxygen species. However, recent studies also demonstrate that rotenone induces a strong pro-inflammatory response (Ye *et al.* 2016). This study by Main *et al.* (2017) demonstrates that rotenone induces up-regulation of IFN-I-dependent pro-inflammatory responses in cultured rodent primary neurons and mixed glia. The current work provides a major advance beyond previous research on IFN-I responses in the brain by this group and other researchers. Through the elegant use of CNS cultures derived from IFNAR1$^{-/-}$ mice, Main *et al.* (2017) were able to demonstrate for the first time, the sequence of IFN-I pro-inflammatory changes in response to rotenone. Specifically, they demonstrated a glial cell-mediated pro-inflammatory response that drives subsequent neuronal death. Rotenone drives early up-regulation of IFN-I signaling. This results in an M1-like (elevated expression of CD11b, CD16 and CD86) pro-inflammatory response in glial cells and downstream glia-dependent neurotoxicity, possibly through increased neurotoxic cytokines including interleukin-6 and tumor necrosis factor-α.

Rotenone induced an increased expression of IFN-α and IFN-β mRNA in treated wild-type glia, resulting in elevated release of these cytokines as demonstrated with a sensitive cell reporter assay. Similar treatment of IFNAR1$^{-/-}$ glia resulted in substantially impaired IFNα/β release. As up-regulation of IFN-Is preceded other pro-inflammatory responses and cell death, these findings now clearly establish the IFN-I pathway as an early response to rotenone action. While the study itself did not specifically identify the mechanism of neuronal cell death, the results are consistent with a previous report from Dedoni *et al.* (2010) who demonstrated that IFN-Is were able to block neuronal brain-derived neurotrophic factor action through inhibition of the neuronal brain-derived neurotrophic factor TrkB receptor activation, and this led to neuronal impairment and reduced survival. It remains to be determined if the same mechanism is occurring in rotenone-treated neuronal cultures.

It is interesting to note that IFN-Is also possess protective activity, for example, Gesuete *et al.* (2012) have shown that IFN-Is can promote neuroprotection through pre-conditioning in a model of ischemia. Moreover, IFN-β is therapeutic in multiple sclerosis. Such pleotropic effects highlight the complexity of the IFN-I pathway in disease and especially the CNS. To address this complexity, future studies should focus on IFN-I action in human induced pluripotent stem cell-derived neurons and glia, including from PD patients (Imaizumi and Okano 2014). As reported by the authors, it will be intriguing to understand the role of IFN-Is in specific forms of PD, driven by different gene mutations, and whether the level of IFN-I pathway activation correlates with disease severity, α-synuclein changes, and/or disease time course? Another intriguing aspect to investigate would be the role of the master regulator of antioxidant and inflammatory pathways, the transcription factor Nrf2. This key regulator has an important role in PD and other neurodegenerative disorders and is also regulated in response to rotenone (Abdelsalam and Safar 2015). Whether IFN-Is are associated with Nrf2 in PD remains to be investigated.

This important study by Main *et al.* (2017) builds on recent work by the same authors that demonstrated a key role for IFN-I pathway in the toxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice, another compound used to model PD. Main *et al.* (2016) showed that IFNAR1$^{-/-}$ animals were substantially resistant to the pro-inflammatory and neurotoxic action of MPTP, resulting in improved survival of dopaminergic neurons. Interestingly, the authors also demonstrated an IFN-I-mediated up-regulation of the M1-like pro-inflammatory response to MPTP, analogous to that described in response to rotenone here, however, the present study has been able to map the pro-inflammatory pathway from rotenone-induced IFN-I up-regulation, leading to cytotoxic cytokine release by glia, and subsequent neuronal death. Previously, the authors also demonstrated that IFN-Is were elevated in PD brain (Main *et al.* 2016), as well as in Alzheimer's brain and an amyloid precursor protein/PS1 model of Alzheimer's disease (Minter *et al.* 2016). Together with the present study, these findings provide strong evidence that the Type-I interferon pathway has an important early role in the neuroinflammatory response in major neurodegenerative diseases, a process that warrants a great deal of further investigation.

This study is especially significant in the face of ongoing failures to successfully treat neurodegeneration using approaches aimed at inhibiting protein aggregation. Many researchers are now looking once again at new targets that involve modulation of the neuroinflammatory response in neurodegeneration. While traditionally this has focused on more classical neuroinflammatory pathways, the work by Main *et al.* highlight the need to extend these studies to

alternative inflammatory processes in the CNS such as IFN-Is. Interestingly, an IFNAR1 blocking monoclonal antibody also inhibited the inflammatory and neurotoxic action of rotenone (and MPTP), suggesting that therapeutic outcomes could be modeled on a similar approach. As the authors understand, it will also be essential to determine how such approaches affect CNS IFN-I signaling compared to peripheral regulation of the same pathway.

In conclusion, the detailed studies by Main *et al.* (2017) provide exciting new insights into the role of IFN-Is in the early stage events of neurodegeneration and open up new opportunities to slow or reverse the cognitive impairment central to disorders such as PD and Alzheimer's.

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