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Interferon- γ as a Potential Link between Diabetes Mellitus and Dementia

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Review of Taylor et al.

Diabetes mellitus is a chronic disease characterized by sustained hyperglycemia, and it affects >400 million people worldwide (World Health Organization, 2018). There are two types of diabetes, characterized by their etiology, as follows: type 1 diabetes, an autoimmune disease that leads to defective insulin production; and type 2 diabetes, characterized by impaired insulin signaling.

The main complication among diabetic patients is vascular damage. This damage is a consequence of prolonged hyperglycemia, which leads to glycation of proteins and lipids, thus producing advanced glycation end-products (AGEs). AGEs lead to endothelial dysfunction by activating AGE receptors and stimulating ROS production, causing oxidative stress and inflammation (Domingueti et al., 2016).

Vascular damage normally activates microglia, recruiting them to the injury site by a mechanism involving ATP release

by damaged endothelial cells and the binding of ATP to P2Y₁₂R in microglia (Fig. 1A). When microglia reach the damaged vessel, they extend their processes to reconnect the severed ends. In diabetes, however, hyperglycemia and chronic inflammation alter the balance between proinflammatory and anti-inflammatory cytokines in the brain, thus shifting microglia toward a so-called M1-like, proinflammatory profile and away from the M2-like anti-inflammatory phenotype crucial for tissue repair (Fig. 1A; Hu et al., 2015). This prolonged M1-like activation reduces the efficiency of vascular repair (Fig. 1B; Okizaki et al., 2015).

Because microglia play a key role in blood–brain barrier (BBB) repair, their dysfunction contributes to BBB instability and microvascular leakage. In fact, microglial depletion leads to vessel damage and BBB disruption after microvascular lesions (Szalay et al., 2016). Importantly, microglial responses to vascular injury are altered in diabetic animal models and patients (Kondo et al., 2001; Li et al., 2011). Nevertheless, the exact mechanism by which diabetes alters microglial response to cerebral microbleeds has not yet been addressed.

In a recent issue of *The Journal of Neuroscience*, Taylor et al. (2018) investigated the microglial response to microvessel rupture in a mouse model of type 1 diabetes. Specifically, they injected streptozoto-

cin, a toxin that destroys insulin-producing pancreatic β -cells, leading to reduced insulin release and, as a result, hyperglycemia. To investigate the microglial response to cerebral microbleeds, Taylor et al. (2018) performed microvessel laser ablation. Compared with control brains, they found fewer microglial processes at distant sites to microbleeds and an increase in secondary plasma leakage in diabetic mice, suggesting a deficient microglial response to injury. Because they did not observe any differences in the growth rate of microglial processes, it is likely that dysfunction in the microglial response in diabetic mice reflects a chemotaxis impairment.

To investigate whether the impaired microglial response was triggered by immune system activation, Taylor et al. (2018) treated mice with immunosuppressant dexamethasone (DEX) for 5 d before microvessel damage. As hypothesized, DEX restored microglial processes and repair function, assayed by the leakage levels of a fluorescent dye. Because DEX also reversed increases in the level of the proinflammatory cytokine interferon- γ (IFN- γ) in diabetic mice, the authors tested whether treatment with an IFN- γ -neutralizing antibody had the same effects as the immunosuppressant. Indeed, blocking IFN- γ in diabetic mice restored microglial process polarity toward the microbleeds and reduced secondary leakage.

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Figure 1. Differences in microglial activation in response to vascular injury in normal and diabetic mice. **A**, Cerebral microbleeds trigger ATP release in brain parenchyma, resulting in the activation of microglial P2Y12 receptors. The M2-like microglia migrate to the injured vessel and repair the lesion. **B**, In diabetic/hyperglycemic mice, IFN- γ triggers a shift in microglia to a proinflammatory M1-like phenotype, which expresses lower levels of P2Y12R. Thus, microglial cells are no longer able to repair vascular lesions; this leads to secondary vascular leakage. These events might increase the risk of the development of dementia later in life. **C**, Blocking IFN- γ signaling restores P2Y12R expression levels, M2-like microglial response, and vascular repair. This approach might also decrease the risk of vascular dementia and Alzheimer's disease.

These findings indicate that hyperglycemia-induced brain inflammation impairs the microglial response to vascular injury through IFN- γ signaling.

The inability to repair injured vessels also aggravates the disruptive effect that permeable blood vessels have on local synaptic structure and function, thereby compromising synaptic plasticity and memory (Zhang and Murphy, 2007; Cianchetti et al., 2013; Reeson et al., 2015; Taylor et al., 2015). Indeed, vascular damage has been associated with cognitive impairment and risk of dementia (Seo et al., 2007; Hilal et al., 2014; Valenti et al., 2016). In addition, patients with diabetes have a higher risk of the development of dementia, and diabetes is more prevalent among patients with dementia (Ott et al., 1996; Biessels et al., 2006). Therefore, vascular complications might be a link in the relationship between these disorders.

Alzheimer's disease (AD) and vascular dementia (VaD) are the most prevalent forms of dementia among patients with diabetes (Biessels et al., 2006; Ninomiya, 2014; Biessels and Despa, 2018). Notably, the presence of cerebral microbleeds also correlates with decreased amyloid- β peptide levels in CSF, as in patients with AD (Noguchi-Shinohara et al., 2017; Sparacia et al., 2017). In addition, IFN- γ levels are increased in the sera of patients with VaD (Schmitz et al., 2015) and AD (Lai et al., 2017). Moreover, a study in a small cohort showed that peripheral IFN- γ levels are higher in patients with mild to severe AD, compared with control subjects (Belkhef et al., 2014). Transgenic mouse models of AD also display increased levels of IFN- γ , and treatment with an anti-IFN- γ antibody attenuates microglial activation and memory deficits (Browne et al., 2013). Finally, recent work indicated that cerebrovascular damage can be an

early biomarker of dementia in patients with AD (Nation et al., 2019). Together, these results suggest that increased IFN- γ levels observed in patients with diabetes might increase the risk of dementia.

Conversely, vascular lesions and BBB instability have also been reported in patients with VaD and AD (Janelidze et al., 2017), leading to microglial dysfunction and increased proinflammatory cytokine secretion (Zuliani et al., 2007). In aged AD model mice, BBB stability is compromised, and microglia are abnormally activated, along with high IFN- γ levels (Minogue et al., 2014). Thus, the anti-IFN- γ therapy proposed by Taylor et al. (2018) may also ameliorate the cognitive symptoms in VaD and AD. It is possible that anti-IFN- γ therapy for diabetes may also prevent dementia later in life by decreasing the proinflammatory state and vessel damage.

How do increases in IFN- γ impair microglial function? Taylor et al. (2018) suggest that microglial dysfunction is caused by chemotaxis impairment. The P2Y12R, which has an important role in mediating microglial chemotaxis to BBB repair (Haynes et al., 2006), was downregulated in diabetic mice (Taylor et al., 2018). Notably, both DEX and anti-IFN- γ treatments rescued P2Y12R expression levels (Taylor et al., 2018). Together, these results indicate that microglial recognition and migration to the damaged vessel is impaired in response to insulin depletion, and that P2Y12R and IFN- γ are key regulators of microglial dysfunction.

Impairments in microglial chemotaxis and P2Y12R levels have also been described in systemic inflammation and aging (Damani et al., 2011; Hickman et al., 2013; Gyoneva et al., 2014; Rawji et al., 2016). While microglial cells from patients with AD have lower levels of

P2Y12R (Mildner et al., 2017), the up-regulation of this receptor has been linked to a neuroprotective M2-like phenotype (Moore et al., 2015). P2Y12R levels are also decreased in AD model mice, relative to controls (Jay et al., 2015). Given that vascular damage is a key player in the progression of dementia and that P2Y12R has a key role in microglial-dependent repair, P2Y12R might be a potential target to modulate microglial responses in VaD and AD (Haynes et al., 2006).

Whether P2Y12R reciprocally regulates IFN- γ signaling remains to be elucidated. It has been shown that the related purinergic receptor P2Y11R regulates IFN- γ -induced IL-6 production (Ishimaru et al., 2013). This evidence suggests that microglial P2Y12R might also regulate IFN- γ production. But Taylor et al. (2018) showed that blocking IFN- γ restores P2Y12R expression levels. IFN- γ is produced by both leukocytes and microglia, so future work should assess which cells are responsible for the increase in IFN- γ in hyperglycemic mice. Given the BBB dysfunction, it is possible that peripheral IFN- γ permeates into the brain (Pan et al., 1997; Filiano et al., 2016; Bialas et al., 2017), thereby activating adaptive immune responses and increasing microglial IFN- γ production.

In conclusion, the microglial response to cerebral microbleeds is impaired in hyperglycemic mice. Increased levels of IFN- γ are likely crucial for this dysfunction, activating microglia into an M1-like state. In turn, P2Y12R is downregulated and microglial chemotaxis is deficient. Notably, inflammation and vascular damage have been widely associated with neurodegenerative disorders, such as VaD and AD (Fig. 1B). Data from the study by Taylor et al. (2018), along with previous findings on vessel damage and dementia,

encourage future studies on IFN- γ as a therapeutic target for both diabetes and dementia (Fig. 1C), and set the grounds for further steps toward preclinical and clinical trials.

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