● PERSPECTIVE

Role of formyl peptide receptor 2 (FPR2) in the normal brain and in neurological conditions

There is much recent interest in the role of the anti-inflammatory molecules and their receptors in the normal brain and in neurological disorders. The formyl peptide receptor (FPR) subfamily of G protein-coupled receptors play important roles in these processes. Binding to specific peptides triggers activation of FPRs, leading to signalling events that regulate inflammatory responses. One member of this subfamily of receptors is FPR2, also known as ALX (the lipoxin A4 (LXA4) receptor). FPR2 is specifically activated by LXA4 and resolvin D1 (RvD1) (Pirault and Bäck, 2018). LXA4 is an anti-inflammatory molecule produced by the action of lipoxygenases on arachidonic acid, while RvD1 is produced by the action of lipoxygenases on docosahexaenoic acid, a component of fish oil. Activation of FPR2 by LXA4 or RvD1 triggers downstream signalling cascades, *e.g.*, inhibition of calcium-calmodulin dependent protein kinase and p38 mitogen-activated protein kinase phosphorylation, leading to a reduction in inflammatory responses. Annexin A1 (ANXA1) is another molecule which could interact with FPR2. A Ca^{2+}-dependent phospholipid-binding protein, ANXA1 suppresses phospholipase A_2 activity to reduce arachidonic acid and eicosanoid production and decrease leukocyte inflammatory events such as cell migration, chemotaxis, phagocytosis and respiratory burst. While many studies have shown that binding to FPR2 is a chemotactic signal to attract macrophages to the site of tissue injury, other studies have highlighted that it is part of an anti-inflammatory process. For example, from some of the studies detailed below (summarized in **Figure 1**), it seems that activation of this receptor does not itself cause further production of pro-inflammatory mediators by macrophages. Instead, FPR2 appears to attract macrophages and other immune cells to the site of tissue injury to initiate a "quiet mopping-up process" to resolve inflammation.

In recent years, the FPR2 signaling pathway has also been shown to be utilized by the brain for a range of normal activities (**Figure 1**). Interestingly, FPR1 and FPR2 are expressed in neural stem cells and are involved in promoting their migration and differentiation into neurons (Wang et al., 2016). FPR2 is expressed in many parts of the adult rat central nervous system. The cerebral neocortex is moderately immunolabelled for FPR2, while dentate granule neurons and their axons (mossy fibres) in the hippocampus, the deep cerebellar nuclei, inferior olivary nucleus, vestibular nuclei, spinal trigeminal nucleus and dorsal horn of the spinal cord are densely labeled. FPR2 immunolabelled processes have the appearance of immature processes under electron microscopy, and inhibition of FPR2 results in reduced length of axons and dendrites in cultured hippocampal neurons (Ho et al., 2018). Moreover, $FPR2^+$ neuronal processes were found to have features of growth cones (Korimová et al., 2018). The neurite-promoting function of anti-inflammatory molecules and their receptors such as FPR2 may be important for the day-to-day functions of the central nervous system, such as synaptic plasticity, learning and memory. This system may be overwhelmed during conditions of neuroinflammation, leading to loss of neuronal functions.

In this context, it is interesting to note that there is much interest in the role of FPR2 in Alzheimer's disease. Early studies have shown a high level of expression of FPR2 in amyloid plaques of Alzheimer's disease patients and that the amyloid β peptide (Aβ) is a chemotactic agonist for FPR2 receptor. Aβ binding to FPR2 is followed by internalization of Aβ/FPR2 complexes and leads to the accumulation and activation of mononuclear phagocytes (monocytes and microglia) (Cui et al., 2002). Other studies have highlighted the beneficial effects of triggering early minor activation of microglia to mediate soluble Aβ clearance and resolution of neuroinflammation. For example, ANXA1, acting *via* FPR2 receptors, reduces Aβ levels by enhancing its degradation by neprilysin in N2a cells and stimulating Aβ phagocytosis by microglia. Moreover, ANXA1 prevents Aβ-induced secretion of microglial inflammatory mediators

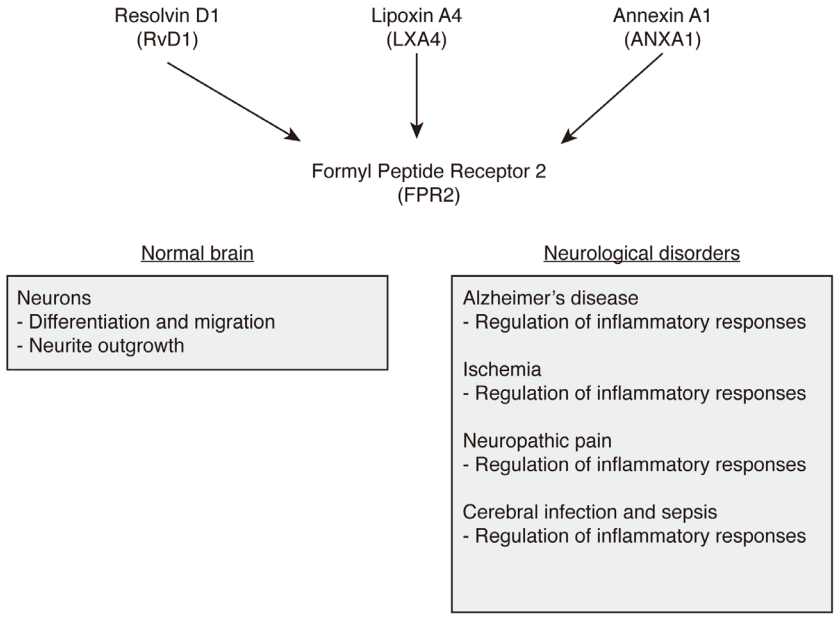

Figure 1 The involvement of formyl peptide receptor 2 signaling in normal brain function and during neurological disorders.

(Ries et al., 2016). Likewise, upregulation of FPR2 due to activation of Toll-like receptors leads to decreased Aβ deposits in the brain with concomitant improvements in spatial and working memory (Pourbadie et al., 2018). Interestingly, microglia in this instance are polarised towards an anti-inflammatory phenotype. Further studies are necessary to dissect FPR2-mediated effects on Alzheimer's disease progression in mouse models, for possible translation to the clinics.

FPR2 has been found to play a role in limiting inflammation and promoting neuroprotection during cerebral ischemia. The FPR2 agonist LXA4 decreases brain water content, reduces Evans blue extravasation, improves neurological functions and improves the learning and memory ability of rats after subarachnoid haemorrhage. These effects were abolished by small interfering RNA-mediated knockdown of FPR2 (Guo et al., 2016). Another study showed that *in vivo* administration of RvD1 promotes functional recovery and neuroprotection by reducing the activation of ionized calcium bindingadaptor molecule-1-positive microglia and glial fibrillary acidic protein-positive astrocytes, as well as by impairing inflammatory-induced neuronal cell death in remote regions. These effects were counteracted by intracerebroventricular neutralization of FPR2 (Bisicchia et al., 2018). The results suggest that therapies targeting the RvD1-FPR2 axis might be useful to reduce local and remote damage after cerebral ischemia.

The mechanism of FPR2 effect on microglia was investigated in a study on neuropathic pain after spinal cord injury. Here, LXA4 treatment significantly reduces the intensity of mechanical pain hypersensitivity as well as spinal expression levels of microglial markers and pro-inflammatory cytokines, compared to rodents receiving control vehicle injections. An FPR2 agonist reduces the expression of the microglial marker ionized calcium bindingadaptor molecule-1 and the pro-inflammatory cytokine tumor necrosis factor-α (Martini et al., 2016). Cortical microglial cultures express FPR2 and display anti-inflammatory responses upon challenge with LXA4 (Martini et al., 2016). The details of how this is achieved is of interest, and a topic for future study.

A role of FPR2 has been reported in endothelial cells, during cerebral infection and sepsis. Mice that received intraperitoneal injection of the endotoxin lipopolysaccharide show increased cerebrovascular permeability, brain myeloperoxidase activity and leucocyte adhesion to venules in wild type mice that was further exacerbated in ANXA1 null mice. These effects were reduced by administration of an ANXA1 mimetic, whose beneficial effects were in turn, abrogated by co-administration of a FPR2 antagonist or in FPR2/3 null mice. The results show an important role of the ANXA1/FPR2 system in limiting cerebral inflammation (Gavins et al., 2012).

Several agonists and antagonists of FPR2 have been developed (Tsai et al., 2016). In view of FPR2's involvement in Alzheimer's disease, stroke, brain sepsis and neuroregeneration as mentioned above, there could be many uses of the agonists in these conditions. Together, these developments highlight the emerging importance of FPR2 as a target for the treatment of various neurological conditions.

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