Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Targeting Alzheimer's Pathology through PPARγ Signaling: Modulation of Microglial Function

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Review of Yamanaka et al

Memory impairment and progressive cognitive decline are the main symptoms of Alzheimer's disease (AD), a neurodegenerative disorder with rising incidence among elderly people. Although knowledge on how this disease develops and triggers brain damage has substantially increased in recent years, novel drugs/mechanisms that help counteract neurodegeneration are still urgently required.

The most obvious pathological feature of AD is the accumulation of amyloid-β (Aβ) peptides in the brain, and these peptides are thought to underlie synaptic pathology and cognitive impairment. Aβ peptide is a cleavage product of the amyloid precursor protein (APP) and it has been proposed to accumulate in AD brains as a result of both excessive production and impaired clearance. Therefore, reducing Aβ accumulation in the brain may be critical for preventing and/or reversing AD-related dysfunction (Selkoe, 2011).

A possible strategy to reducing Aβ accumulation is to modulate microglial function. In a recent paper in *The Journal of Neuroscience*, Yamanaka et al. (2012) reported that stimulating PPARγ signaling increases Aβ uptake by microglia and restores cognition in mice. They initially found that PPARγ activation by either pioglitazone or DSP-8658 significantly enhances microglial uptake of a fluorescently labeled Aβ peptide *in vitro*. The increase in uptake did not take place when PPARγ was knocked down. These findings are also supported by another recent study that demonstrated effective reversal of amyloid burden and cognitive impairment by pioglitazone (Mandrekar-Colucci et al., 2012).

Yamanaka et al. (2012) further found that enhancement of microglial Aβ uptake by PPARγ agonists required *de novo* transcription and translation. Based on previous reports showing that expression of the scavenger receptor CD36 is regulated by PPARγ, Yamanaka et al. (2012) hypothesized that CD36 mediates increased uptake induced by PPARγ agonists. First, they confirmed that CD36 mRNA and protein levels were increased in the presence of PPARγ agonists. Using either a selective CD36 antibody or RNAi knockdown, the authors then demonstrated that CD36 is indeed required for PPARγ effects on Aβ uptake.

Upon ligand binding, PPARγ directly binds to and dimerizes with retinoid X receptors (RXR) to promote transcriptional reprogramming. It is thus possible that RXR proteins contribute to increased microglial function. In support of this hypothesis, Yamanaka et al. (2012) showed that pharmacologically stimulating both PPARγ and retinoid signaling had an additive effect on Aβ uptake by microglia. This is particularly interesting because activation of RXRs by bexarotene has recently been shown to drive Aβ clearance and memory improvement in a mouse model of AD (Cramer et al., 2012).

It is also important to note that rosiglitazone, another specific PPARγ agonist, regulates hippocampal expression of PPAR-target genes and restores ERK/MAPK signaling in AD transgenic mice (Denner et al., 2012). The signaling mechanisms involving increased ERK signaling and expression of metabolism-related genes may also facilitate Aβ uptake by microglia.

Finally, Yamanaka et al. (2012) tested the relevance of their findings *in vivo*. For this purpose, they used APP/PS1 mice, which carry two AD-related transgenes and exhibit brain amyloid plaque deposition and early behavioral deficits. DSP-8658 significantly increased microglial recruitment to plaques and CD36 expression in the brains of such mice. Importantly, DSP-8658 reduced cortical and hippocampal Aβ burden and improved cognitive performance in APP/PS1 mice tested in the Morris water maze.

The results presented by Yamanaka et al. (2012) and others shed light on neuroprotective mechanisms leading to Aβ clearance and memory improvement triggered by PPARγ activation in animal models. Previous studies, however, have shown modest or no cognitive benefit of PPARγ agonists in AD patients, so the therapeutic potential of these drugs remains in doubt (Sakurai, 2011). Never-

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theless, the recent findings in animals encourage additional clinical trials aimed to maximize the efficacy of this strategy. For example, the combination of a PPARγ stimulator (e.g., rosiglitazone or DSP-8658) and an RXR agonist (bexarotene) may improve cognition. Both strategies have already been used for therapeutic intervention in humans and seem to reach the brain.

The beneficial action of PPARγ has typically been attributed to increased insulin sensitivity and reduced inflammation. However, the findings by Yamanaka et al. (2012) suggest that increased microglial function is an additional beneficial mechanism triggered by PPARγ signaling. Microglia are the main mediators of inflammation in the CNS, and they function as specialized scavengers that eliminate pathogens and supply neurons with trophic factors (Kettenmann et al., 2013). On the other hand, microglial overactivation may lead to exacerbated generation of neurotoxic molecules, such as reactive oxygen species and pro-inflammatory cytokines (Saijo and Glass, 2011). Moderate build up of cytokines is likely to be helpful, however. Therefore it is crucial that therapeutic approaches maintain the proper balance of these molecules. This is a challenge because our understanding of how microglia work in health and disease is still incomplete. As an emerging field in cellular neurobiology, understanding how inflammation develops in AD will provide important clues to help modulate microglial action in diseased brains.

In summary, the study by Yamanaka et al. (2012), in combination with other recent reports, has provided novel insights into how PPARγ signaling counteracts amyloid toxicity and cognitive impairment in animal models of AD. Moreover, the notion that stimulating both PPARγ and retinoid pathways might have synergistic effects against neurodegeneration unveils novel targets for drug development and opens still unexplored roads toward much-needed AD therapeutics.

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