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Comment on ''Paroxetine Prevents Loss of Nigrostriatal Dopaminergic Neurons by Inhibiting Brain Inflammation and Oxidative Stress in an Experimental Model of Parkinson's Disease''

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Letters to the Editor

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Comment on "Cutting Edge: FcR-Like 6 Is an MHC Class II Receptor"

The article published by Schreeder et al. (1) in the July 1, 2010 issue of *The Journal of Immunology* identifies MHC class II molecules as ligands for FcRL-6, an Ig-like molecule belonging to the FcR-like (FcRL) family. The function of FcRL molecules remains elusive because they share many features with classical FcR molecules, but they do not bind Igs [during the revision process, Wilson et al. (2) reported an intracellular association of FcRL-A and Igs]. Identification of MHC class II as a ligand for FcRL-6 renders this molecule strikingly similar to another member of the Ig superfamily, CD223. CD223 is not part of the FcRL family because of its distinct chromosomal localization and weak sequence homology, but it is a receptor for MHC class II (3). FcRL-6 and CD223 show a restricted cellular expression on NK, γδ, and Ag-experienced αβ T cells, mostly $CD8^+$ (4–6). In addition, a situation of chronic T cell activation, such as HIV infection (5, 7) and tumor development (6, 8), increases expression of these molecules. CD223 is an immunosuppressive molecule (9, 10), and it is likely that FcRL-6 also negatively regulates cell activation due to its ITIM present in the intracytoplasmic tail. Hence, several inhibitory receptors specific for MHC class II molecules may be present on the surface of NK and activated T cells. The function of these receptors is not easy to understand on NK cells, but CD223 and FcRL-6 may contribute to the exhaustion phenomenon frequently observed in chronically stimulated T cells.

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Response to Comment on "Cutting Edge: FcR-Like 6 Is an MHC Class II Receptor"

We thank Dr. Huard for his letter and appreciate the opportunity to comment on the interesting parallels between FcR-like 6 (FCRL6) and the CD223 receptor, lymphocyte activation gene 3. Indeed, both proteins bind MHC class II molecules (1, 2) and are expressed by cytotoxic NK and effector T cell subsets (3–5), but these receptors also possess several distinct features. Whereas FCRL6 is related to the classical FcRs for IgG and IgE and the more recently identified FCRL1–5 family that all derive from human chromosome 1q (6), the gene encoding CD223 is a *CD4* paralog positioned in tandem on chromosome 12 (7). That FCRL6 and CD223, at least in humans, have evolved independently as T and NK cell surface receptors for MHC class II indicates the importance of these interactions in immunobiology. Interestingly, the *Fcrl6* ortholog in mice, which occupies a syntenic genomic location, has differences in its protein structure and expression, suggesting that its function may differ from its human counterpart (3, 8 and W.J. Won, R.P. Stephan, and R.S. Davis, unpublished observations). Another distinction is their modulation in response to cytokine stimulation. Whereas CD223 is induced following exposure to activating signals, such as IL-12 and IL-2 (9), FCRL6 is downregulated under similar conditions (3). This indicates that these molecules are regulated differently and implies that they may vary temporally in their interactions with MHC class II. Finally, although FCRL6 has a consensus ITIM and can recruit Src homology region 2 domain-containing phosphatase-2 (3), whether it functions as a bona fide inhibitory molecule and/or plays a role in T cell exhaustion similar to CD223 (10) are subjects of ongoing investigation.

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Comment on "Paroxetine Prevents Loss of Nigrostriatal Dopaminergic Neurons by Inhibiting Brain Inflammation and Oxidative Stress in an Experimental Model of Parkinson's Disease"

I read with interest the article by Chung et al. (1) describing how pretreatment with the serotonin reuptake inhibitor paroxetine (10 mg/d for 6 d) prevented 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced neuroinflammation (increased production of reactive oxygen species and proinflammatory cytokines by glial cells) and neuronal cell death in the substantia nigra in mice. The mechanism by which paroxetine inhibits inflammation is unknown. We have data from humans ($n = 9$) receiving i.v. LPS (0.8 ng/kg) that pretreatment with the serotonin reuptake inhibitor citalopram (20 mg/d for 5 d) did not reduce the innate immune response to LPS compared with placebo pretreatment. For instance, LPS administration caused IL-6 serum levels to increase from 1.3 ± 0.4 to 197.8 ± 47.9 pg/ml in subjects who received placebo pretreatment and from 0.9 ± 0.2 to 215.9 ± 54.2 in subjects who received citalopram pretreatment. Similarly, TNF levels increased from 2.0 ± 0.6 to 45.2 ± 10.8 in placebo-pretreated subjects and from 1.4 ± 0.3 to 38.3 ± 6.2 in citalopram-pretreated individuals. All p values were >0.8 for pairwise t tests. Our data indicate that the selective serotonin reuptake inhibitor citalopram does not have an anti-inflammatory effect in peripheral innate immune cells. This may suggest that the anti-inflammatory effects of paroxetine observed by Chung et al. (1) is either specific to neuroinflammation (i.e., paroxetine has a differential effect on microglia compared with peripheral innate immune cells) or that the anti-inflammatory effect of paroxetine is mediated by increases in synaptic serotonin in the brain.

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We have evidence from 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice ($n = 3$) that citalopram (5 mg/kg/d for 6 d) did not inhibit microglial activation as evidenced by Mac-1 immunocytochemical staining. However, another serotonin uptake inhibitor (fluoxetine; 5 mg/kg/d for 6 d) inhibited MPTP-activated glial activation as assessed by Mac-1 and GFAP immunostaining. Fluoxetine was also found to prevent MPTP-induced neuroinflammation (increases in reactive oxygen species and proinflammatory cytokines, such as TNF-α, IL-1β, and inducible NO synthase). In the LPS-injected rat substantia nigra, fluoxetine (10 mg/kg/twice a d for 6 d) dramatically reduced neuroinflammation (reactive oxygen species and proinflammatory cytokines). This is in line with recent findings that fluoxetine inhibits the expression of proinflammatory cytokines, such as TNF-α, and IL-1β in the rat cerebral ischemia model of middle cerebral artery occlusion (1) and kainaic acid-treated mouse hippocampus (2). Contrary to citalopram, Taler and his colleagues (3, 4) reported that paroxetine and sertraline, another serotonin uptake inhibitor, reduced secretion of TNF-α in human T lymphocytes and rat splenocytes. It is therefore likely that anti-inflammtory actions of paroxetine may not be specific to neuroinflammation, and not all of serotonin uptake inhibitors possess anti-inflammtory properties.

Striatal serotonin levels were measured in MPTP-treated mice to determine the relationship between anti-inflammatory effects of the fluoxetine and serotonin system. Results (MPTP:

14.6 ± 2.5 μg/mg protein, $n = 6$; MPTP + fluoxetine: 15.3 ± 1.3 μg/mg protein, $n = 6$) show that, whereas fluoxetine prevented MPTP-induced neuroinflammation, it failed to increase serotonin levels in the striatum. These results carefully suggest that the anti-inflammatory effect of paroxetine is not mediated by increases in synaptic serotonin, although serotonin levels are not provided.

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