NEUROIMMUNOLOGY

Estrogen receptor ligands suppress inflammatory responses in astrocytes and microglia

Research from the University of California, San Diego, USA has provided new insights into the role of estrogen receptor- β (ER β) in controlling brain inflammation. In collaboration with John Katzenellenbogen at the University of Illinois at Urbana-Champaign, Kaoru Saijo and colleagues showed that ER β ligands could prevent disease onset and relieve symptoms in an animal model of multiple sclerosis (MS). The team also found that ER β is a key component of a molecular pathway that leads to suppression of microglia-mediated inflammation.

Microglia and astrocytes are vital for immune surveillance in the CNS, but the inflammatory responses evoked in these cells following infection or injury, if left unchecked, can cause neuronal damage or even death. As part of an ongoing project to examine how nuclear receptors might inhibit inflammation in the CNS, Saijo and colleagues set out to identify molecular mechanisms through which such responses could be attenuated.

“We used lots of molecular and cellular biological techniques to understand the roles of ER β , including quantitative PCR, ELISA, luciferase assay, western blotting, and gas chromatography,” Saijo explains. “To test the roles of ER β *in vivo*, we chose experimental autoimmune encephalomyelitis (EAE), the animal model of MS.”

In mouse microglial cell cultures, the researchers showed that two synthetic ER β -specific ligands, Indazole-Br and Indazole-Cl, inhibited the production of cytokines that activate T helper 17 cells, which have been strongly implicated in the pathogenesis of MS and other autoimmune diseases. Further *in vitro* experiments revealed that these same ligands suppressed inflammatory responses in astrocytes.

In mice, Indazole-Cl was shown to prevent the onset of EAE, as well as partially resolving the symptoms in

Activated microglia. From Perry, V. H. et al. *Nat. Rev. Neurol.* 6, 193–201 (2010).

animals that had already developed the condition. In addition, ER $\beta^{-/-}$ mice developed severe disease in response to an immunization protocol that produced only mild symptoms in wild-type mice, indicating that ER β could have a protective function against EAE.

Unlike the synthetic ER β ligands, the endogenous ligand 17 β -estradiol did not attenuate inflammatory responses, leading the investigators to search for other endogenous ligands that might have anti-inflammatory properties. They decided to focus on 5-androsten-3 β ,17 β -diol (ADIOL), which is synthesized by microglia. The new study showed that this ER β ligand modulates inflammation in these cells.

“ADIOL induced transcriptional repressive activity by recruiting the transcriptional corepressor CtBP,” reports Saijo. “The level of ADIOL was regulated by inflammatory stimuli, and the ER β –ADIOL–CtBP pathway controlled the magnitude and duration of inflammation in microglia and astrocytes.”

17 β -estradiol—one of the main female sex hormones—has a higher affinity

for ER β than does ADIOL, and might antagonize the anti-inflammatory effects of the latter ligand. Further studies of the interplay between estrogen receptors and their ligands in the brain could help to clarify why women are more susceptible than men to conditions such as MS.

The new findings raise the possibility that ER β -specific ligands could be developed as therapeutic agents for neuroinflammatory disease. Asked how the team plans to take the work forward, Saijo says “we are trying to test whether ER β -mediated repression of inflammation can also apply to other neuroinflammatory diseases. We are also testing whether the level of ADIOL can be used as a biomarker for neuroinflammatory diseases.”

Heather Wood

Original article Saijo, K. et al. An ADIOL–ER β –CtBP transrepression pathway negatively regulates microglia-mediated inflammation. *Cell* 145, 584–595 (2011)

Further reading Jellinck, P. H. et al. Selective conversion by microglia of dehydroepiandrosterone to 5-androstenediol-A steroid with inherent estrogenic properties. *J. Steroid Biochem. Mol. Biol.* 107, 156–162 (2007)