p38beta MAPK not critical to brain inflammation, study finds

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(Medical Xpress)—A study by a leading Alzheimer's researcher at the University of Kentucky provides new evidence that will help researchers home in on the molecular mechanisms involved in inflammation of the central nervous system (CNS) and aid drug-development strategies for treating inflammatory neurological diseases.

The research was led by Linda Van Eldik, director of UK's Sanders-Brown Center on Aging, and included co-authors Bin Xing and Adam Bachstetter from the Van Eldik lab. The study demonstrated that the beta isoform of p38 mitogen-activated protein kinase (MAPK) has no apparent effect on inflammatory cytokine response and neurotoxicity in brain-cell cultures or in the brains of living mice.

Others have reported that the p38beta isoform is not involved in peripheral inflammatory disorders, such as arthritis and inflammatory bowel disease. However, whether p38beta is important in brain inflammation had not been studied before.

Taken together with previous studies by Van Eldik's lab, which document the critical role of p38alpha in CNS proinflammatory cytokine production and neuron survival, the new study further supports the idea that p38alpha, and not p38beta, is the key p38 isoform involved in central inflammatory responses.

The new findings also suggest that development of p38-inhibitor drugs to target CNS inflammatory diseases may not need to consider retention of

p38beta inhibitory activity, but should instead focus on selectively targeting the p38alpha MAPK isoform as a potential therapeutic strategy.

The study used mice where the p38beta kinase was specifically eliminated, and asked whether brain cells that did not have p38beta could generate an inflammatory cytokine response and induce subsequent neuron death after treatment with a standard inflammatory stimulus.

The research found that in brain-cell cultures, and in mice treated with the inflammatory stimulus, the inflammatory cytokine response and neurotoxicity were the same whether the mice had normal p38beta levels or were deficient in p38beta. These results showed that, in agreement with peripheral inflammation models, p38beta is also expendable in the brain in terms of regulation of proinflammatory cytokines and downstream neurotoxicity.

Van Eldik's paper, "Deficiency in p38beta MAPK Fails to Inhibit Cytokine Production or Protect Neurons against Inflammatory Insult in In Vitro and In Vivo Mouse Models," appeared online Feb. 15 in *PLOS One*, a peer-reviewed, open-access journal published by Public Library of Science.

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