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The Japanese traditional therapy, honokiol, blocks key protein in inflammatory brain damage

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Microglia are the first line defence of the brain and are constantly looking for infections to fight off. Overactive microglia can cause uncontrolled inflammation within the brain, which can in turn lead to neuronal damage. New research published in BioMed Central's open access journal *Journal of Neuroinflammation* shows that, honokiol (HNK) is able to down-regulate the production of pro-inflammatory cytokines and inflammatory enzymes in activated microglia via Klf4, a protein known to regulate DNA.

Scientists from the National Brain Research Centre, Manesar, India, used lipopolysaccharide (LPS), a molecule present on the surface of bacteria, to stimulate an immune response from microglia cells. LPS mimics the effect of a bacterial infection and the microglia cells spring into action, releasing proinflammatory cytokines, such as TNFa.

Activation of microglia also stimulates the production of nitric oxide (NO) and Cox-2, which co-ordinate the immune response, leading to inflammation. However uncontrolled inflammation can lead to neuronal death and permanent brain damage. Microglial inflammation is also observed in several neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and multiple sclerosis.

The team led by Dr Anirban Basu found that the inflammatory response was mediated by Klf4, a 'transcription' factor which binds directly to

DNA to enhance or impede gene expression. Treating microglia with HNK reduced their activation and HNK treated cells secreted less cytokines in response to LPS. HNK also down regulated the activity of Klf4 (and pNF-kb - another regulator of inflammation).

Dr Basu suggested that HNK down regulates Klf4 which in turn down regulates NO and Cox-2 production. He said, "HNK can easily move across the blood brain barrier and we found that HNK reduced levels of pNF-kb and Klf4 as well as the number of activated microglia in the brains of LPS treated mice."

He continued, "Our work with HNK has found that Klf4 is an important regulator of inflammation. Both HNK and Klf4 may be important not only in regulating inflammation due to infection, but may also have applications in other diseases which affect the brain and nervous system."

More information: Therapeutic targeting of Kruppel-like factor 4 abrogates microglial activation, Deepak K Kaushik, Rupanjan Mukhopadhyay, Kanhaiya L Kumawat, Malvika Gupta and Anirban Basu, *Journal of Neuroinflammation* (in press)

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