Nature Reviews Neuroscience | AOP, published online 30 October 2013; doi:10.1038/nr3630

NEUROLOGICAL DISORDERS

Eaten alive!

> brain macrophages can phagocytose functional, living neurons after transient ischaemia and actually promote brain atrophy

Phagocytosis of dead or dying neurons after ischaemia has generally been thought to be beneficial, as it clears harmful cellular components and decreases inflammation. However, a new study by Neher *et al.* shows that brain macrophages can phagocytose functional, living neurons after transient ischaemia and actually promote brain atrophy.

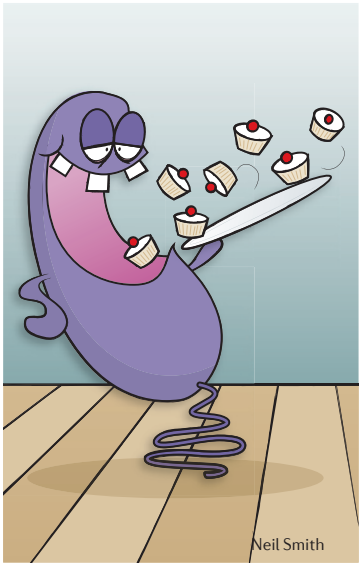
In areas of the ischaemic brain in which the interruption of blood supply is most pronounced, rapid neuronal death ensues owing to energy depletion, but in surrounding areas, there is a delayed cell loss, which offers an opportunity for therapeutic intervention. Previous studies have shown that viable neurons exposed to toxic stimuli at sublethal levels can display the 'eat me' signal phosphatidylserine (PS), which induces their phagocytosis by macrophages. After ischaemia, neurons in the peri-infarct area have been shown to display PS at levels that peak after 3 days.

The PS signal is recognized by the phagocytic proteins Mer receptor tyrosine kinase (MERTK) and milk fat globule EGF-like factor 8 (MFGE8; also known as lactadherin), which are upregulated in brain macrophages in response to inflammation. Here, the authors showed that MERTK and MFGE8 were temporarily upregulated in rodent brain macrophages 3–7 days after transient, focal brain ischaemia and that peak expression of these proteins coincided with macrophage activation.

To determine the contribution of phagocytosis to delayed neuronal death after ischaemia, they examined *Mertk*-mutant rats and *Mfge8*-knockout mice and showed that ischaemia-induced motor deficits were greatly reduced in these animals compared with wild-type controls. Further analyses revealed that although the initial damage and neuronal death caused by ischaemia were similar between the different genotypes, there were significant differences in brain atrophy 7–28 days after the infarct, as the loss of tissue in *Mertk*- and *Mfge8*-mutant rodents was much reduced compared with wild-type animals.

Interestingly, the inflammatory response and time course of macrophage recruitment and activation did not differ between wild-type and mutant animals. However, when the authors quantified the number of macrophages containing neuronal nuclear material 3 days after ischaemia, they found that, in *Mertk*- or *Mfge8*-deficient animals, there were far fewer of these cells than in wild-types, confirming that these proteins promote the engulfment of neurons after ischaemia.

Finally, *in vitro* experiments revealed that non-toxic levels of glutamate caused neurons to reversibly express PS on their surface, which promoted MERTK- and MFGE8-dependent phagocytosis of the stressed neurons. Despite the ability of macrophages from *Mertk*- or *Mfge8*-deficient animals to phagocytose dead neurons as efficiently as those from wild-type animals, they did not induce the same levels of neuronal loss in the glutamate-treated neuronal cultures as did the wild-type macrophages. These findings indicate that MERTK and MFGE8 are specifically involved in the phagocytosis of viable neurons subjected to stress or inflammatory conditions, and highlight them as potential targets for reducing brain damage caused by ischaemia.



Monica Hoyos Flight

ORIGINAL RESEARCH PAPER Neher, J. J. *et al.* Phagocytosis executes delayed neuronal death after focal brain ischemia. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1308679110 (2013)