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Newsdesk

MMPs activated by nitric oxide

James Butcher

Matrix metalloproteinases (MMPs) have been implicated in the pathogenesis of neurodegenerative diseases and stroke, though the precise mechanism of MMP activation was unclear. Now, Stuart Lipton (Burnham Institute, La Jolla, CA, USA) and co-workers report that nitric oxide activates MMP enzymes, causing neuronal apoptosis.

“Our results link two previously unrelated scientific fields studying MMP enzymes and nitric oxide gas”, says Lipton, “both of which were thought to be important in the life and death of nerve cells, but the fact that NO could activate these enzymes was not previously recognised.”

MMPs are a family of extracellular soluble or membrane-bound proteases that are involved in remodelling the extracellular matrix. However, when activated in excess, for example after stroke, these enzymes degrade the neuronal membrane, resulting in neuronal apoptosis.

In the latest experiments, Lipton and colleagues showed that neuronal NO synthase is colocalised with MMP-9 after ischaemia and reperfusion in rodents. They also used mass spectrometry to show that the active derivative of MMP-9 is a stable sulphinic or sulphonic acid, whose formation is triggered by S-nitrosylation (transfer of NO to a cysteine sulphhydryl group in the MMP protein; *Science* 2002; **297**: 1186–90).

“The work gives us a new way to think about preventing excessive activity of MMP enzymes, and as such it could lead to new therapies for stroke and several neurodegenerative diseases”, says Lipton. Hans-Peter Hartung (Heinrich-Heine-University, Düsseldorf, Germany) agrees that these results could have clinical implications, not only for stroke and

neurodegenerative diseases but also autoimmune diseases such as multiple sclerosis and Guillan-Barré syndrome.

However, he expresses a note of caution: “Particularly in neuroinflammatory conditions, NO can be both proinflammatory and anti-inflammatory, or can downregulate ongoing immune responses, and therefore has a Janusian head. It may critically depend on the local environment, the evolutionary stage of the disease, and whether inhibition of NO will turn out to be protective or even worsen the disease.”



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