学 位 論 文 の 要 旨

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主論文の題名

Bcl-2 homology domain 3-only proteins Puma and Bim mediate the vulnerability of CA1 hippocampal neurons to proteasome inhibition *in vivo*

主論文の要旨

Bcl-2 homology domain 3 (BH3)-only proteins are pro-apoptotic Bcl-2 family members that play important roles in upstream cell death signalling during apoptosis. Proteasomal stress has been shown to contribute to the pathology of cerebral ischaemia and many neurodegenerative disorders. Here we explored the contribution of BH3-only proteins in mediating proteasome-inhibition-induced apoptosis in the mammalian brain in vivo. Stereotactic intrahippocampal microinjection of the selective proteasome inhibitor epoxomicin (2.5 nmol) induced a delayed apoptosis within only the CA1 hippocampal neurons and not neurons within the CA3 or dentate gyrus regions, a selective vulnerability similar to that seen during ischaemia. This injury developed over a time-course of 3 days and was characterized by positive terminal deoxynucleotidyl transferase dUTP nick end labelling staining and nuclear condensation. Previous work from our laboratory has identified the BH3-only protein p53-upregulated mediator of apoptosis (Puma) as mediating proteasome-inhibition-induced apoptosis in cultured neural cells. Genetic deletion of puma reduced the number of terminal deoxynucleotidyl transferase dUTP nick end labelling-positive cells within the CA1 following epoxomicin microinjection but it did not provide a complete protection. Subsequent studies identified the BH3-only protein Bim as also being upregulated during proteasome inhibition in organotypic hippocampal slice cultures and after epoxomicin treatment in vivo. Interestingly, the genetic deletion of bim also afforded significant neuroprotection, although this protection was less pronounced. In summary, we demonstrate that the BH3-only proteins Puma and Bim mediate the delayed apoptosis of CA1 hippocampal neurons induced by proteasome inhibition in vivo, and that either BH3-only protein can only partly compensate for the deficiency of the other.

（注）２，０００字以内にまとめて記入すること。