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INDUCTION OF MICROSOMAL EPOXIDE HYDROLASE BY SULFUR AMINO ACID-DEPRIVATION VIA THE PATHWAY OF C-JUN N-TERMINAL KINASE AND ITS EXTRACELLULAR EXPOSURE DURING CELL DEATH

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Microsomal epoxide hydrolase (mEH), an epoxide detoxifying enzyme and putative cell surface autoantigen, is inducible by xenobiotics and by certain pathophysiological conditions. The present study was designed to determine mEH expression in H4IIE cells during cell death initiated by sulfur amino acid deprivation (SAAD) and to identify the signaling pathway for the enzyme induction. SAAD induced cell death at 48-72 h with translocation of Bax to mitochondria and increased mitochondrial permeability with cytochrome c release, both of which were prevented by SB203580 or by dominant-negative JNK1 stable transfection. Caspase-3 activity was only marginally increased by SAAD. Neither genomic DNA fragmentation nor poly(ADP-ribose) polymerase cleavage was observed during SAAD-induced cell death. Thus, SAAD induced cell death independent of caspase activation. The levels of mEH mRNA and protein were notably increased in cells under SAAD for 48-72 h. Whereas SAAD-induced cell death resulted from both JNK1 and p38 kinase activation, mEH induction was decreased only by JNK1(-) transfection. mEH protein was intensely stained in dying cells, the number of cells positive for surface mEH substantially increased by SAAD. These results demonstrated that SAAD induced non-apoptotic cell death and that mEH was induced by SAAD via the pathway of JNK1, but not ERK1/2 or p38 kinase, in parallel with cell death.

keyword : mEH, Cell death, JNK1