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Cover photo. Hypothetical model of the mechanisms involved in AIF processing and release. Exposure of NSCLC cells to the protein kinase C inhibitors, staurosporine or PKC412, results in a hyperpolarization of the plasma membrane. As a consequence, the hyperpolarization-activated HCN2 channel opens and permits Ca^{2+} to enter the cell. Both plasma membrane hyperpolarization and the activation of HCN2 channel are inhibited by Cs^{+}. The resulting Ca^{2+} elevation in the cytosol also translocates to the intermembrane space of the mitochondria and results in the activation of calpain as well as enhanced ROS formation. The calcium chelator, BAPTA is able to inhibit both calpain activation and ROS accumulation, whereas only the latter is inhibited by NAC and Trolox. AIF is cleaved by mitochondrial calpain-I. This cleavage is prevented by PD150606, a selective calpain inhibitor. Cleaved AIF is released into the cytosol and translocates to the nucleus, where it contributes to chromatin condensation and highmolecular weight DNA fragmentation. Nuclear translocation of AIF can be inhibited by binding to Hsp70 in the cytosol. (BBRC Volume 396, pages 95–100). It is reproduced by kind permission of the authors – Sten Orrenius, et al.