Both dimerization and interdomain processing are essential for caspase-4 activation.


Source

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Abstract

A subgroup of caspase family of inflammatory caspases (-1, -4, -5, -11, and -12) play important role during cytokine maturation and inflammation but their regulation is not well understood as much as the initiator and effector caspases. Here, the biochemical mechanism of caspase-4 activation is elucidated. With citrate, a well-known kosmotrope to enhance the monomer-dimer transition, caspase-4 was activated approximately 40 times that was comparable with that of caspase-9 (approximately 75-fold increments). The activation reaction was mainly bimolecular (n=1.67+/-.04) for monomeric caspase-4. In addition, the interdomain cleavage was also responsible to activate caspase-4 more than 100-fold, again comparable with that of effector caspases where the proteolytic processing is considered as the sole activation mechanism. Thus, caspase-4 shows a novel activation mechanism of the synergism between dimerization and proteolysis that sharply differs from the established activation mechanism of dimerization for initiators and interdomain cleavage for effector caspases.

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Apaf-1-deficient fog mouse cell apoptosis involves hypo-polarization of the mitochondrial inner membrane, ATP depletion and citrate accumulation.
To explore how the intrinsic apoptosis pathway is controlled in the spontaneous fog (forebrain overgrowth) mutant mice with an Apaf1 splicing deficiency, we examined spleen and bone marrow cells from Apaf1(+/+)(+/+) and Apaf1(fog/fog)(fog/fog) mice for initiator caspase-9 activation by cellular stresses. When the mitochondrial inner membrane potential (Deltapsim) was disrupted by staurosporine, +/+ cells but not fog/fog cells activated caspase-9 to cause apoptosis, indicating the lack of apoptosome (apoptosis protease activating factor 1 (Apaf-1)/cytochrome c/(d)ATP/procaspase-9) function in fog/fog cells. However, when a marginal (approximately 20%) decrease in Deltapsim was caused by hydrogen peroxide (0.1 mM), peroxynitriedonor 3-morpholinosydnonimine (0.1 mM) and UV-C irradiation (20 J/m²), both +/+ and fog/fog cells triggered procaspase-9 auto-processing and its downstream cascade activation. Supporting our previous results, procaspase-9 pre-existing in the mitochondria induced its auto-processing before the cytosolic caspase activation regardless of the genotypes. Cellular ATP concentration significantly decreased under the hypoactive Deltapsim condition. Furthermore, we detected accumulation of citrate, a kosmotrope known to facilitate procaspase-9 dimerization, probably due to a feedback control of the Krebs cycle by the electron transfer system. Thus, mitochondrial in situ caspase-9 activation may be caused by the major metabolic reactions in response to physiological stresses, which may represent a mode of Apaf-1-independent apoptosis hypothesized from recent genetic studies.

PMID:18663378

Citrate kills tumor cells through activation of apical caspases.

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Source

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Abstract

Most tumor cells exhibit a glycolytic phenotype. Thus, inhibition of glycolysis might be of therapeutic value in antitumor treatment. Among the agents that can suppress
glycolysis is citrate, a member of the Krebs cycle and an inhibitor of phosphofructokinase. Here, we show that citrate can trigger cell death in multiple cancer cell lines. The lethal effect of citrate was found to be related to the activation of apical caspases-8 and -2, rather than to the inhibition of cellular energy metabolism. Hence, increasing concentrations of citrate induced characteristic manifestations of apoptosis, such as caspase-3 activation, and poly-ADP-ribose polymerase cleavage, as well as the release of cytochrome c. Apoptosis induction did not involve the receptor-mediated pathway, since the processing of caspase-8 was not attenuated in cells deficient in Fas-associated protein with Death Domain. We propose that the activation of apical caspases by citrate could be explained by its kosmotropic properties. Caspase-8 is activated by proximity-induced dimerization, which might be facilitated by citrate through the stabilization of intermolecular interactions between the proteins.

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