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Meeting abstract

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Compartimentalization of TNF-receptor 1 signalling: acid sphingomyelinase is activated by Caspase-8 in internalized TNF-R1 receptosomes

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In a recently identified novel TNF-induced apoptotic signaling pathway the generation of ceramide by acid sphingomyelinase (A-SMase) and the activation of the aspartic protease cathepsin D (CTSD) occur in the same endosomal compartment [1]. CTSD subsequently mediates cleavage of Bid leading to activation of caspase-9 and -3. Since activation of A-SMase is linked to the death domain of TNF-receptor 1 (TNF-R1) and since the death domain adapter proteins FADD and caspase-8 are recruited during internalization of TNF-R1 in endosomes (TNF-receptosomes) [2], we addressed the question, whether A-SMase can be activated directly by caspase-8 within this compartment. We here show by confocal laser scan microscopy and in immunomagnetically isolated TNF-receptosome preparations that the active form of caspase-8 colocalizes with A-SMase within TNF-receptosomes. Activation of caspase-8 correlates with cleavage of a 70/72 kDa pro-A-SMase molecule, paralleled by enhanced A-SMase activity, activation of CTSD as well as Bid-cleavage in isolated TNF-receptosomes. The functional link between caspase-8 activity and A-SMase stimulation is revealed by the lack of TNF-induced A-SMase activation in caspase-8 deficient Jurkat cells, which can be restored in vivo after retransfection of caspase-8 as well as in vitro by the addition of exogenous caspase-8 to lysates from caspase-8 deficient cells.

References

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