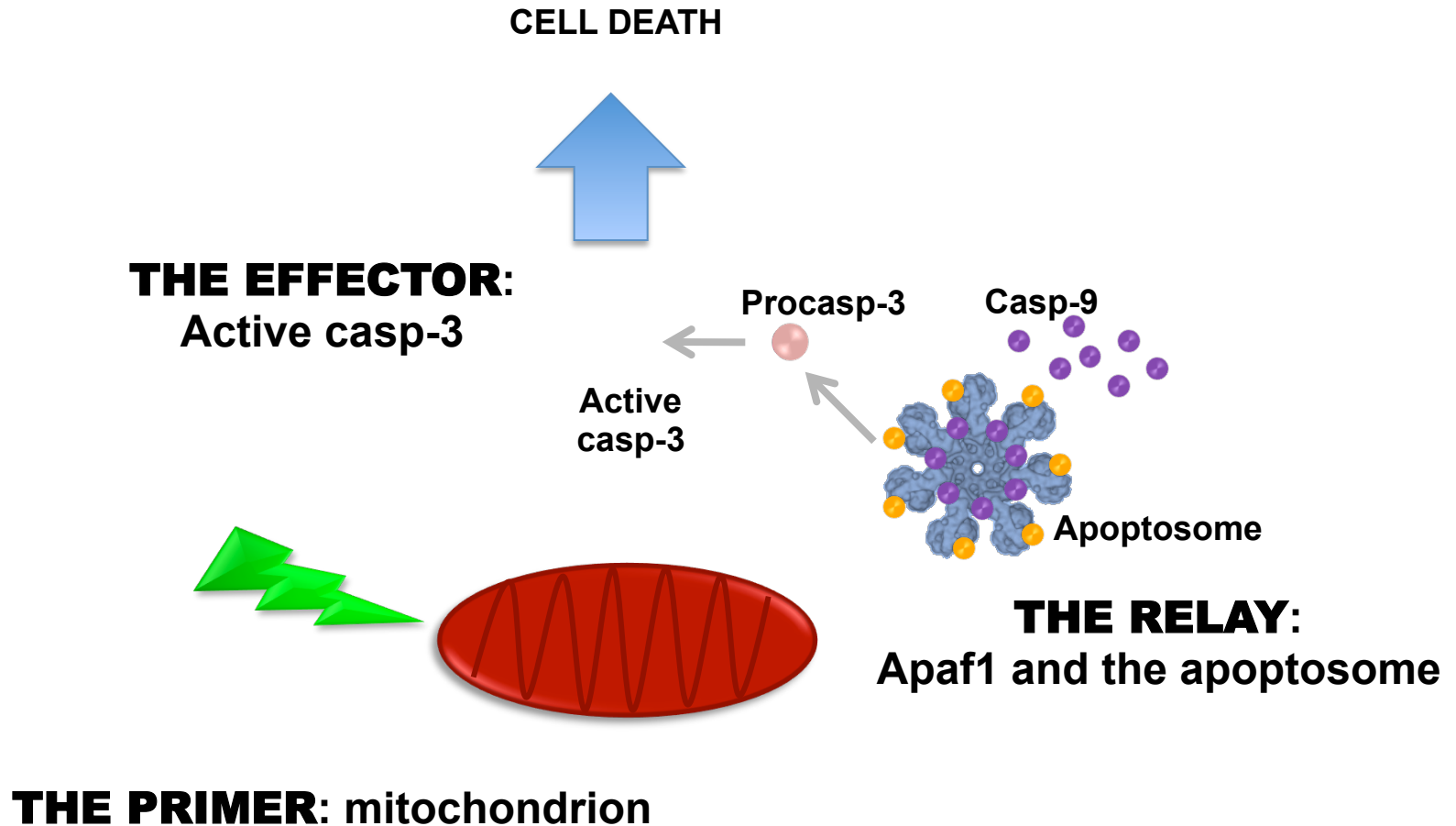


Canonical activity of Apaf1 and Caspase-3 in mitochondria-dependent cell death



Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer's disease

Marcello D'Amelio^{1,2}, Virve Cavallucci¹, Silvia Middei³, Cristina Marchetti⁴, Simone Pacioni⁵, Alberto Ferri⁶, Adamo Diamantini⁷, Daniela De Zio⁸, Paolo Carrara⁹, Luca Battistini⁷, Sandra Moreno⁹, Alberto Bacci⁵, Martine Ammassari-Teule³, Hélène Marie^{4,10} & Francesco Cecconi^{1,8}

Synaptic loss is the best pathological correlate of the cognitive decline in Alzheimer's disease; however, the molecular mechanisms underlying synaptic failure are unknown. We found a non-apoptotic baseline caspase-3 activity in hippocampal dendritic spines and an enhancement of this activity at the onset of memory decline in the Tg2576-APPswe mouse model of Alzheimer's disease. In spines, caspase-3 activated calcineurin, which in turn triggered dephosphorylation and removal of the GluR1 subunit of AMPA-type receptor from postsynaptic sites. These molecular modifications led to alterations of glutamatergic synaptic transmission and plasticity and correlated with spine degeneration and a deficit in hippocampal-dependent memory. Notably, pharmacological inhibition of caspase-3 activity in Tg2576 mice rescued the observed Alzheimer-like phenotypes. Our results identify a previously unknown caspase-3-dependent mechanism that drives synaptic failure and contributes to cognitive dysfunction in Alzheimer's disease. These findings indicate that caspase-3 is a potential target for pharmacological therapy during early disease stages.

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Review

Neuronal caspase-3 signaling: not only cell death

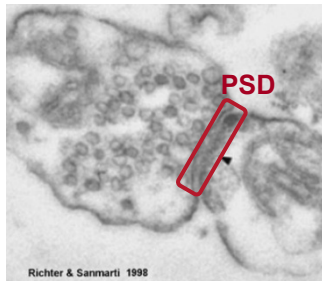
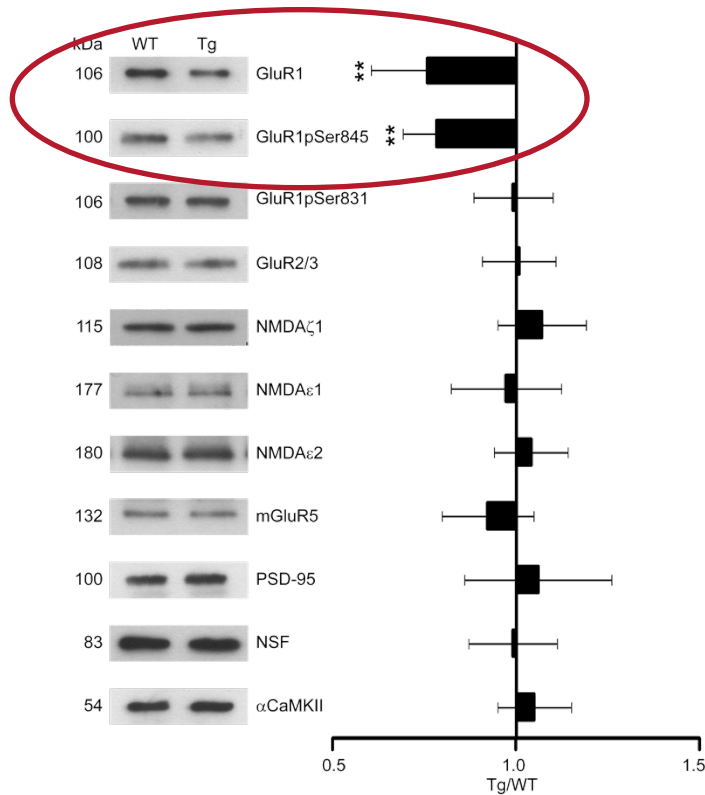
M D'Amelio^{1,2}, V Cavallucci^{1,2} and F Cecconi^{1,2}

Caspases are a family of cysteinyl aspartate-specific proteases that are highly conserved in multicellular organisms and function as central regulators of apoptosis. A member of this family, caspase-3, has been identified as a key mediator of apoptosis in neuronal cells. Recent studies in snail, fly and rat suggest that caspase-3 also functions as a regulatory molecule in neurogenesis and synaptic activity. In this study, in addition to providing an overview of the mechanism of caspase-3 activation, we review genetic and pharmacological studies of apoptotic and nonapoptotic functions of caspase-3 and discuss the regulatory mechanism of caspase-3 for executing nonapoptotic functions in the central nervous system. Knowledge of biochemical pathway(s) for nonapoptotic activation and modulation of caspase-3 has potential implications for the understanding of synaptic failure in the pathophysiology of neurological disorders. Fine-tuning of caspase-3 lays down a new challenge in identifying pharmacological avenues for treatment of many neurological disorders.

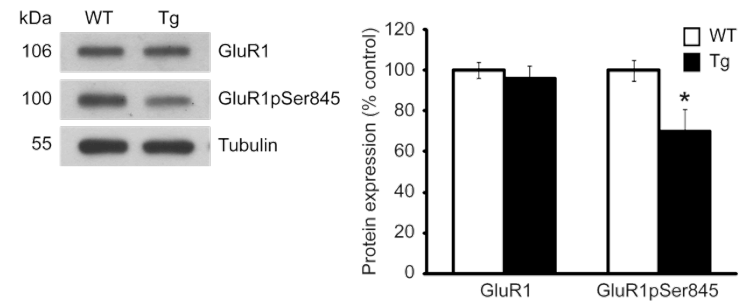
Cell Death and Differentiation advance online publication, 4 December 2009; doi:10.1038/cdd.2009.180

Detection of early synaptic alterations

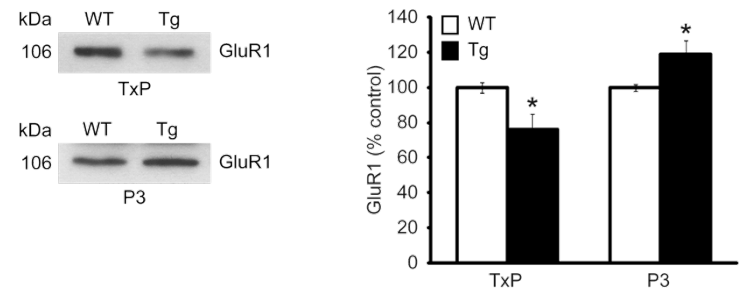
Hippocampal post-synaptic density (PSD)



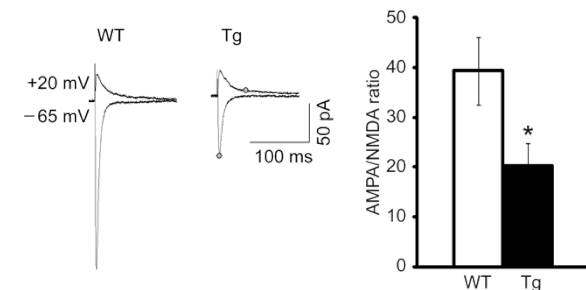
Hippocampal total extract



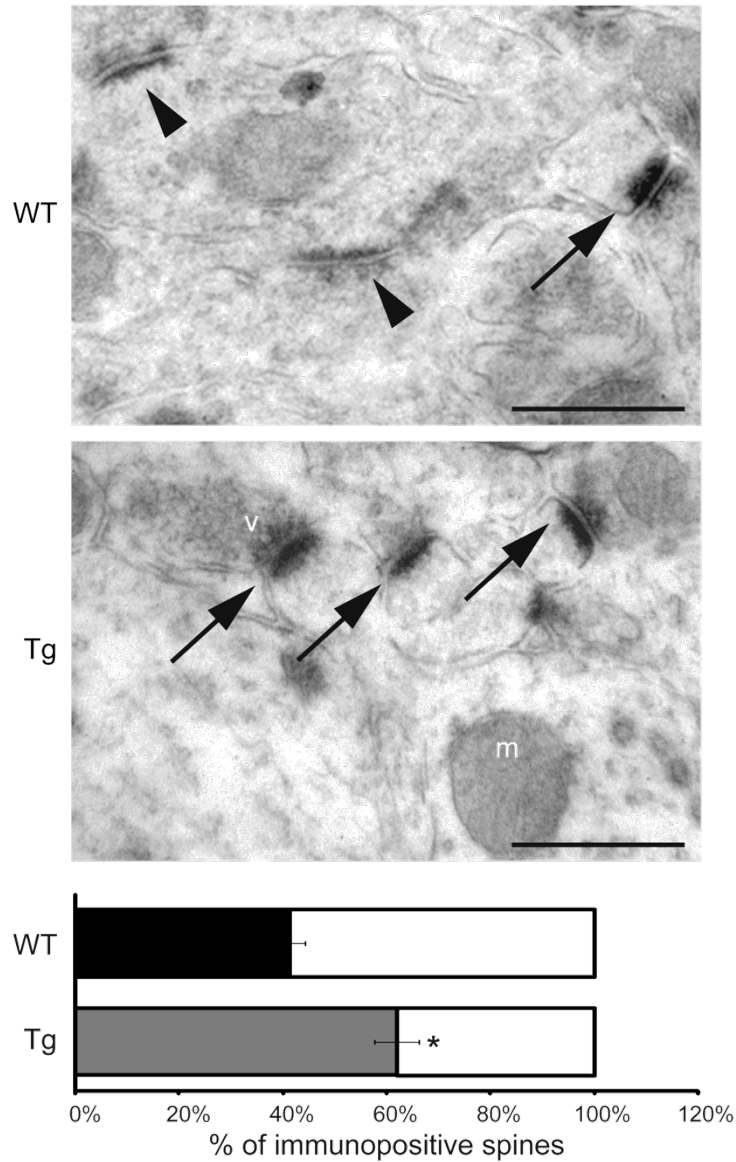
Hippocampal synaptic fractionation



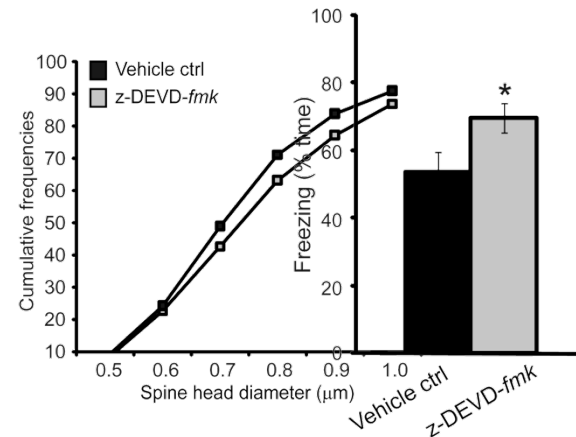
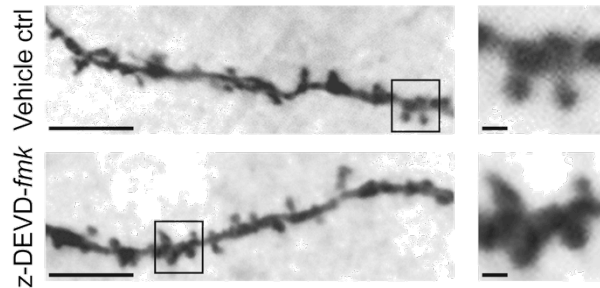
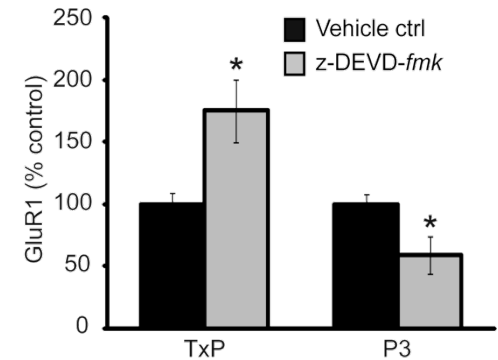
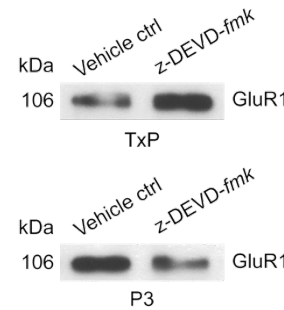
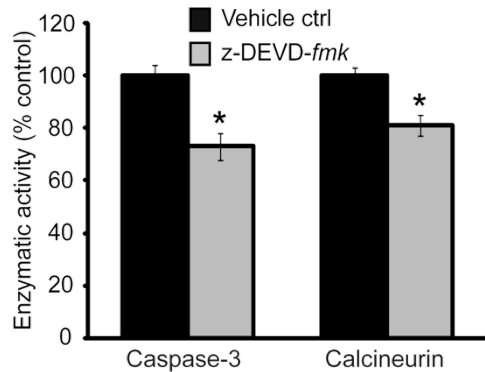
Basic glutamatergic transmission



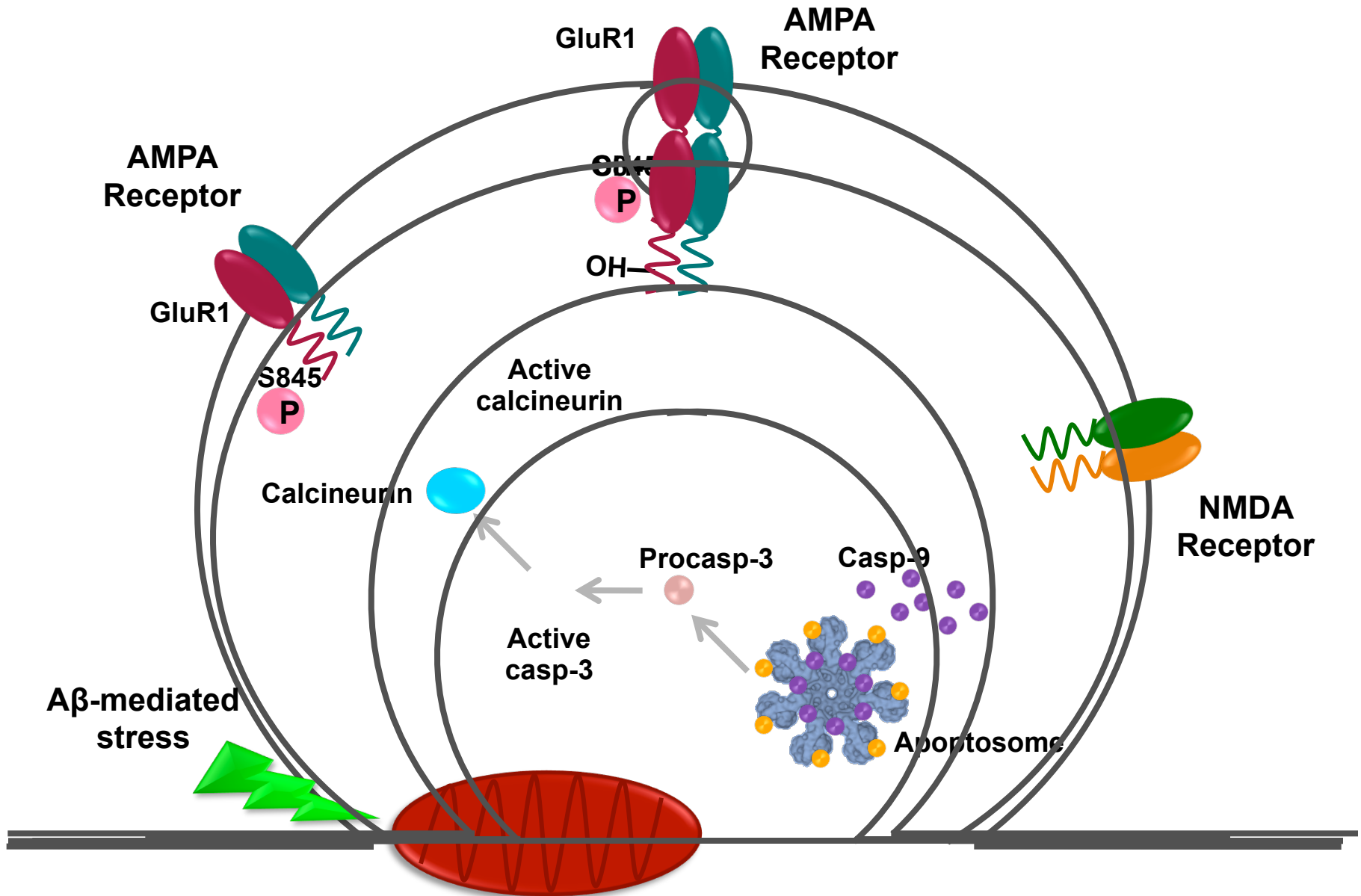
Active caspase-3 localizes in post-synaptic compartment



Caspase-3 inhibition in vivo influences GluR1 distribution and rescues spine head size and memory performance



Model of caspase-3 role in dendritic spine degeneration



*An alternative role for **THE EFFECTOR**:
Caspase-3 in mitochondria-dependent nonapoptotic
cleavage of a synaptic substrate*

