

P019 ALIX and ALG-2 form an adaptor complex for apical caspases on endocytosed death receptors
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Alix/AIP1 regulates cell death in a way involving interactions with the calcium binding protein ALG-2 and with ESCRT proteins (Mahul et al. J. Neuroscience, 2006). Using mass spectrometry, we identified caspase-8 among proteins co-immunoprecipitating with Alix in extracts of dying neurons. Caspase-8 is an apical caspase activated by death receptors following their activation and endocytosis. We demonstrated that Alix and ALG-2 interact with pro-caspase-8 in presence of calcium. Furthermore Alix forms a complex with the TNF α receptor-1 (TNF-R1), in a way dependent on its capacity to bind ESCRT proteins.

Expression of Alix deleted of its ALG-2 binding site (Alix Δ ALG-2) significantly reduced TNF-R1 induced cell death, without affecting endocytosis of the receptor. In a more physiological setting, we showed that developmental death of motoneurons in the chick embryo, is regulated by TNF-R1 and can be inhibited by Alix Δ ALG-2.

Taken together, our results suggest that Alix bound to ALG-2 act as an adaptor protein to recruit pro-caspase-8 onto endocytosed TNF-R1, a necessary step towards activation of the zymogen through autocatalysis.