CONTRIBUTION OF TRAIL DEATH PATHWAY IN β-AMYLOID NEUROTOXICITY

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Here we report that a novel member of the TNF-α family, TNF-related apoptosis inducing ligand (TRAIL), contributes substantially to amyloid-induced neurotoxicity in human SH-SY5Y neuronal cell line.

Involvement of TRAIL in the amyloid-induced cell death is supported by cDNA array, Northern blot, and Western blot data, demonstrating increased TRAIL expression after treatment of the cells with a neurotoxic fragment of amyloid protein (βAP). TRAIL was also found to be released in the culture media after βAP treatment with a time-course overlapping to contents of the intracellular protein. Contribution of TRAIL to βAP neurotoxicity is demonstrated by data showing that TRAIL-neutralizing monoclonal antibody protects neuronal SH-SY5Y cells from βAP neurotoxicity. Moreover, exposure of neuronal SH-SY5Y cells to TRAIL leads to cell death, indicating that this substance per se is endowed with neurotoxic properties.

We also found that, similarly to βAP and TRAIL, activation of the death domain adaptor protein FADD results in neuronal cell death. Lack of FADD function, by over-expression of its dominant negative, rescued cells from either TRAIL-, or βAP-induced neurotoxicity, supporting the hypothesis that these three molecules share common intracellular pathways. Finally, we found that βAP strongly activated caspase 8 and the cell-permeable, selective caspase-8 inhibitor z-IETD-FMK prevents both βAP- and TRAIL-induced neurotoxicity.

In view of TRAIL’s potency in inducing neuronal death, and of its role as mediator of βAP, it is plausible to hypothesize that TRAIL can be regarded as a molecule that provides substantial contribution to βAP-dependent cell death which takes part in the progression of the neurodegenerative process and related chronic inflammatory response.

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Effects of TRAIL and anti-TRAIL neutralizing antibody on cell viability. Cells were exposed for 48 h to 25 µM βAP 25-35 or 100 µg/ml TRAIL in the presence or absence of the anti-TRAIL neutralizing antibody (α-TRAIL) as indicated, and then apoptosis was evaluated. Upper panels show representative images of cells exposed to 25 µM βAP 25-35 (B, F), 100 µg/ml TRAIL (C, G) in the presence (D, H) or absence (A-C, E-G) of α-TRAIL, and subjected to Annexin V (upper panel B, left) and MG (upper panel B, right) staining. Lower panel: quantitative analysis of Annexin V fluorescent staining (left) and apoptotic cells (right). Bars represented the data as the mean ± SEM of at least three separate experiments from two separate culture preparations. Arrows in F and G indicate condensed nuclei.

Schematic representation of β-AP mechanism of action. β-AP induces the increased of TRAIL and DR5 expression, both in term of mRNA and protein levels in SY5Y neuronal cells. Soluble TRAIL released in the media binds to its receptor DR5. The interaction TRAIL/DR5 activates an intracellular pathway that involves the recruitment of FADD and the activation of caspase 8. These events lead to apoptotic cell death. The significant of such effect is demonstrated by the evidences that anti-TRAIL neutralizing antibody, the over-expression of FADD dominant negative and the caspase 8 inhibitor z-IETD-FMK prevent β-AP induced apoptosis.