

POSTER PRESENTATION

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# Cytoprotective functions of amyloid precursor protein family members in stress signaling and aging

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## Background

The amyloid precursor protein (APP) is processed via two different metabolic pathways: the amyloidogenic and the non-amyloidogenic pathway, the latter of which leading to generation of the secreted N-terminal APP fragment sAPP $\alpha$  [1]. Previous studies from our group suggest that sAPP $\alpha$  exerts potent neuroprotective effects and inhibits stress-triggered cell death via modulation of gene expression, as well as by antagonizing different types of neurotoxic stress [2]. It was also observed that the biochemical processing of APP is downregulated during aging which in turn reduced the secretion of sAPP $\alpha$  [3]. Based on these observations, we have studied the potential physiological function of sAPP $\alpha$ /APP and APLPs (APP like proteins) on the regulation of age-associated, stress induced signaling pathways, apoptosis and senescence.

## Materials and methods

SH-SY5Y, PC12, IMR90 cells were used as cellular models. Depletion of APP, APLP1 (APP like protein 1) and APLP2 (APP like protein 2) in SH-SY5Y cells was achieved by stable lentiviral knockdown. To analyze the protective function of sAPP $\alpha$ , we have used conditioned supernatants of wild type APP overexpressing HEK cells and recombinant His-tagged sAPP $\alpha$  purified from yeast. The cells were treated with sAPP $\alpha$  prior to the addition of different stress stimuli (MG132, epoxomicin, UV, H<sub>2</sub>O<sub>2</sub>) after which cell death, gene expression and senescence were analyzed by MTT assays, caspase activity assays, Western blots and X-Gal staining respectively.

## Results

Our data show that sAPP $\alpha$  can antagonize premature senescence induced by repetitive short term induction of proteasomal stress in IMR-90 cells and apoptosis triggered by prolonged proteasomal stress and other death stimuli in PC12, SH-SY5Y and IMR90 cells which was accompanied by a sAPP $\alpha$ -dependent inhibition of the JNK stress signaling pathway. In contrast, no significant changes in cell viability and apoptosis were observed when APP knockdown cells were pretreated with sAPP $\alpha$ .

## Conclusions

Our observations suggest that sAPP $\alpha$  can antagonize both apoptosis and cellular senescence and requires expression of holo-APP to mediate its cytoprotective effects. They also support the notion that the physiological function of APP is linked to modulation of neuronal and brain aging.

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