Tissue plasminogen activator (tPA) participates in relevant physiological roles in brain such as memory and learning but it has also been involved in a number of pathological situations where it can be either neuroprotective or mediator of cell death. In a recent report (Medina et al, 2005) we described a relationship between tPA and Alzheimer's disease (AD):

i) tPA is over expressed in amyloid rich areas and senile plaques of AD;

ii) tPA induces activation of Erk1/2 intracellular signalling, tau phosphorylation and neuronal death in hippocampal neurons;

iii) tPA mediates amyloid toxicity in vitro.

Neuroinflammation around senile plaques is a pathological hallmark in AD and it has been proposed that high levels of Abeta induce microglial activation and the release of several pro-inflammatory cytokines that can cause neuronal cell death. Previous reports described that microglia cells produce tPA and that this protease mediated microglial activation via a non-proteolytic mechanism. However the molecular mechanism leading to these events have not been elucidated. Here, we have analyzed the molecular pathways induced by tPA in mixed and purified microglial primary cultures. We show that tPA induces a dramatic change in the morphology of both cell cultures and also an increase in the production of TNFα and reactive oxygen radicals, consistent with the role of tPA in glial activation. We also report an activation of Erk1/2, JNK, p38 and AKT pathways in response to tPA both in mixed and microglial cells, suggesting that these pathways could be responsible of tPA-mediated activation in microglial cells.