

## Fas and neuroprotection with

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### What are some of the non-apoptotic roles for Fas?

**Julie Desbarats and Anne M. Landau:** Fas, a member of the tumor necrosis factor receptor (TNFR) superfamily, is a 45 kD homotrimeric membrane receptor. Fas is expressed on many cell types, principally in the immune system, where it regulates cell numbers by inducing apoptosis (1), in the nervous system, and in the reproductive system. The Fas apoptosis cascade is initiated by the death domain (DD) located in the cytoplasmic tail of Fas, which associates with a second DD containing protein, the Fas-Associated DD (FADD). FADD recruits caspase-8 (also known as the FADD-like interleukin-1 $\beta$ -converting enzyme, FLICE), and upon binding of Fas

Ligand to Fas, caspase-8 autocatalyzes its own cleavage and triggers a cascade of caspase activation culminating in apoptosis. Although historically Fas is known mainly as a “death receptor”, Fas can also induce proliferation, differentiation, cytokine secretion and tissue regeneration. Unlike the well-defined apoptotic pathway, the molecular mechanisms underlying other Fas functions have not yet been established in detail, although the Extracellular-signal Regulated Kinase (ERK), nuclear factor (NF)- $\kappa$ B, and c-Jun N-terminal kinase (JNK) pathways have all been implicated (2). In some of our recent work, we identify Fas as a pro-regenerative and neuroprotective agent in the nervous system (3,4).

### What is known about Fas expression in the nervous system?

**Julie Desbarats and Anne M. Landau:** During embryonic development and in the early postnatal period, neurons co-express Fas and Fas Ligand. In this context, Fas / Fas Ligand probably promote branching in axons and dendrites rather than control cell death (5). In adults,

neurons generally express very low or undetectable levels of Fas constitutively, but readily upregulate Fas in response to stressors, including oxidative stress, traumatic injury, ischemia, pharmacological toxicity, excitotoxicity, and during some neurodegenerative diseases (2).

### What are some brain diseases associated with Fas-mediated death?

**Julie Desbarats and Anne M. Landau:** Fas is an important mediator of cell death in motoneurons both *in vitro*, when the neurons are deprived of neurotrophic factors, and *in vivo*, after facial nerve axotomy. In Amyotrophic Lateral Sclerosis,

a disease characterized by motoneuron degeneration, Fas-induced death is thought to involve crosstalk between two signaling pathways; the classical apoptosis cascade as outlined above, and a newly identified cascade involving

the upregulation of neuronal nitric oxide (6). Fas-induced apoptosis has also been implicated in spinal cord injury and stroke. In mouse models, functional recovery was improved in Fas-deficient mice, and was promoted in wild-type mice by neutralizing antibodies to Fas (7-9). On the other hand, some neurons are resistant to Fas-

induced apoptosis, and may instead respond to Fas engagement by neurite outgrowth or enhanced branching of processes (5). Certain intracellular molecules can regulate the outcome of Fas signaling. For example, lifeguard, a post-synaptic neural membrane protein, is upregulated by the Phosphatidylinositol 3-kinase-Akt/Protein Kinase B (PI3K / PKB) pathway and mediates the resistance of cerebellar granule neurons to Fas Ligand-induced death. Motoneurons which have undergone *in vitro* maturation and differentiation are resistant to Fas-induced apoptosis, possibly due to the upregulation of FLICE Inhibitory Protein (FLIP) (7).

### What is the evidence for Fas as a neuroprotective agent?

**Julie Desbarats and Anne M. Landau:** Most of the evidence for Fas as a neuroprotective factor comes from our work on Parkinson’s disease (PD) (4). PD is a chronic and debilitating neurodegenerative disorder in which the dopaminergic neurons in the substantia nigra of the brain degenerate, leading to the cardinal symptoms of the disease, namely tremor, slowness of movement (bradykinesia), postural instability and rigidity. A PD-like syndrome can be induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in rodents, primates and humans, and has become one of the most prominent models of PD. MPTP is a neurotoxin that selectively kills the dopaminergic neurons, the cells which degenerate in PD. Due to the historical emphasis of Fas-induced apoptosis over other Fas functions, Fas was originally considered as a potential effector of apoptosis in PD. However, we have recently found that Fas-deficient mice are acutely sensitive to PD induced by MPTP compared with wild-type mice, suggesting a neuroprotective role for Fas. Another Fas

mutant in which the Fas-DD is disrupted is resistant to MPTP induced neurodegeneration (4,10), implying that the neuroprotective signal does not occur via the DD. Consistent with the studies on mice, we found that patients with PD manifest a defect in inducible Fas expression (4). Together, findings from PD patients and mice bearing mutations in *Fas* suggest that PD neurodegeneration is related to decreased Fas, and therefore that Fas is neuroprotective in PD. Our findings suggest that lack of stimulatory Fas signals, rather than Fas-mediated apoptotic signals, are involved in the molecular pathogenesis of PD. Studies are currently underway in our lab focusing on the mechanism(s) of Fas-mediated neuroprotection in PD.

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