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Grant Title: **p75-Mediated Cell Death After Spinal Cord Injury**

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Dates: 6/15/2002 –6/14/2004 (No cost extension through 6/14/2006)

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1. Aims:

The hypothesis of the application was that neurotrophins can signal cell survival or cell death depending on which receptor and signaling pathways are activated. The specific aims were (1) To determine whether induction of p75 after spinal cord injury (SCI) mediates cell death; and (2) To investigate signaling pathways necessary for p75-mediated neuronal death.

2. Project Successes:

We have made significant progress in our investigation of the signaling mechanisms governing p75-mediated neuronal apoptosis. We had previously demonstrated that this receptor signals apoptosis by activating JNK, mitochondrial release of cytochrome c, and the intrinsic caspase pathway. Our current studies have demonstrated that while stimulating apoptosis, the p75 receptor simultneously suppresses survival signaling via Trk receptors by blocking activation of Akt, an important protein in regulating survival. The p75 receptor is specifically activated by proneurotrophins (the neurotrophin precursors), while Trk signaling is activated by cleaved neurotrophins. We have demonstrated the induction of proNGF in the CNS after injury, and the ability of that induced proNGF in induce neuronal apoptosis. The analysis of p75 signaling has been performed in several different CNS neuronal populations.

3. Project Challenges:

In the first specific aim we examined whether the p75 receptor would be induced on injured neurons after spinal cord injury to potentially mediate death of these cells. We obtained injured spinal cord sections from our collaborator, Dr. Ron Hart to perform immunostaining for p75 expression. However, although there was increased p75 expression at the site of injury, it was very difficult to distinguish which cells were labeled due to the disorganization of the injured tissue. Thus, it was not possible to determine that this receptor was specifically being expressed on the dying neurons.

4,5. Implications and Plans for Future Research:

We have demonstrated that the p75 receptor can be specifically activated by proneurotrophins, which can be induced in the CNS after injury. The p75 receptor can signal neuronal apoptosis, and simultaneously suppress survival signaling. The mechanisms mediating the interaction of survival and apoptotic signaling require further investigation. Moreover, in the future these processes will be specifically characterized in spinal cord neurons.

6. Publications:

Friedman, W.J., Interactions of interleukin-1 with neurotrophic factors in the CNS: Beneficial or Detrimental? *Mol. Neurobiol.*, 32 (2): 133-144, 2005