NASCIC
SCI RESEARCH
ADVOCACY COURSE

Module 6 – Neuroprotection

Stopping Apoptosis

Apoptosis, or "programmed cell death," is not only one of the consequences of excitotoxicity. It also is a distinct process that is another target of neuroprotection research. Similar to the other topics in this module, apoptosis is a necessary biological process that becomes unbalanced after an SCI.

The body uses apoptosis to rid itself of diseased or damaged cells in an orderly way without triggering inflammation and other damaging processes. When a cell becomes too damaged, diseased, or old to work properly, chemical and molecular signals are activated that cause the cell to shrink and then to fragment into smaller, self-contained packages. The small size of the packages makes them easier for immune cells to ingest. And the packages are enclosed in a membrane keeps toxins and other harmful materials from spilling out and triggering danger signals that could lead to damage.

Apoptosis is tightly regulated to prevent accidental activation. Under healthy conditions, molecules inside the cell act as brakes to prevent apoptosis from happening when it isn't needed. When apoptosis is needed, the brakes must be released and the signals that allow apoptosis to start must be activated.

In the case of disease or injury, researchers have long believed that it may be possible to repair cells or prevent cell death by blocking the process of apoptosis. But there are many different ways to approach this task, and it isn't yet clear which ways might be best.

To begin with, there is more than one biological pathway that can trigger apoptosis, depending on the stimulus.

For example, toxins that damage cells after an SCI trigger apoptosis via a process called the **caspase pathway**. Caspases are a family of closely related proteins. They function as "proteases" which are enzymes that break down other proteins by cutting, or "cleaving" them.

In the caspase pathway, a cascade of molecular interactions inside the damaged cell activates caspase-9. Caspase-9 cleaves, or cuts, a precursor protein to release the active form of caspase-3. Caspase-3, often called an "executioner caspase," coordinates the destruction of proteins and DNA, leading directly to cell disassembly and death.

Excess calcium can trigger apoptosis in a different way, by activating a different type of protease called a **calpain**. Calpains are a different family of closely related proteins that break

down proteins. In some cell types, calpains can trigger apoptosis without involving caspases. In other types of cells, calpains activate the caspase pathway.

These are just two examples; there are many different apoptosis pathways involving several different members of the caspase or calpain families. In some cells, blocking one pathway will activate an alternative pathway that results in a different process that leads to cell death. And what's more, caspases and calpains have other functions besides their roles in apoptosis, and researchers are still learning about those functions.

As a result, researchers are still working on several important questions about blocking apoptosis, including:

- Could inhibiting caspases or calpains reduce unwanted cell death without turning apoptosis all the way off?
- *Which* caspases or calpains should we inhibit?
- Can a drug candidate target a *particular* caspase or calpain with enough selectivity to avoid ones we don't want to inhibit, given how similar the members of each family are?
- If we inhibit these targets, what other biological processes might be affected?
- And, could a successful inhibitor avoid triggering an alternative pathway to cell death?