

Katy Barglow's Research: General Audience Summary

Apoptosis, or programmed cell death, is commonly impaired in cancers, allowing uncontrolled proliferation of tumor cells. Nitric oxide (NO), a small signaling molecule which can covalently modify proteins via S-nitrosation, is produced at high levels in many tumor types and appears to act as a key regulator of apoptosis. In NO producing cells, multiple apoptosis-regulating proteins such as caspases and bcl-2 are S-nitrosated, with concomitant effects on apoptosis. Nitrosation has also been shown to play a key role in tumor resistance to radio- and pharmaco-therapy.

Despite the importance of nitrosation in regulating apoptosis, the molecular mechanisms that control this process in cells are very poorly understood. *In vitro*, many proteins can be poly-S-nitrosated, but *in vivo* the process is highly specific for certain residues on particular proteins. In order to understand the role of nitrosation in apoptosis in both cancer and normal cells, we need to understand the cellular proteins and factors that control it. One such candidate protein is thioredoxin (Trx), which is overexpressed in many cancer types and has been shown to specifically nitrosate the catalytic cysteine of caspase 3, one of the main proteins in the apoptotic cascade. Because Trx interacts with many proteins besides caspase 3, including the nitrosated apoptotic protein ASK-1, we believe that Trx acts as a general regulator for nitrosation inside cells. The studies we propose here will investigate both the nitrosation of Trx by candidate NO donors, and the downstream targets that Trx may nitrosate. Together, these data will reveal fundamental information about the role of Trx in controlling intracellular nitrosation. Ultimately this information should lead to new therapeutic targets for the regulation of apoptosis in cancer cells.