Research Update

No. 1

OXIDATIVE STRESS NOT THE WHOLE STORY

Much of ALS research focuses on the role of oxidative stress in cells. That's partly because in 1993 researchers discovered that mutations in the gene for an antioxidant enzyme, called superoxide dismutase (SOD1), cause about 20 per cent of cases of the familial form of ALS (fALS). Every cell contains anti-oxidant agents that inactivate highly reactive molecules called free radicals. Antioxidants are vital to healthy, functioning cells. In the absence of antioxidants, unchecked free radicals run amok, reacting with proteins and disrupting the cell's normal functions. The resulting oxidative stress can overwhelm the cell. Post-mortem tissue donated by people who died of ALS reveals oxidative stress contributed to the disease. Clumps of oxidatively modified proteins loom conspicuously in the cytoplasm of the dead motor neurons.

Somehow the mutated antioxidant SOD1 is to blame, but not because it has lost its antioxidant function. ALS researcher **Heather Durham** at the Montreal Neurological Institute points out that even though the antioxidant is mutated in fALS, and even though oxidative stress is involved, oxidative stress is not the whole story – and may not even play a primary role. She emphasizes that the real issue is what the mutant SOD1 is doing, rather than what it is not doing.

"Mutations in SOD1 cause disease through a gain of toxic function," says Durham, proposing that the mutated SOD1 may be changed in its shape or conformation. These changes could alter the way the protein acts and is acted upon. This could cause toxic interactions and also account for the way SOD1 ultimately clusters into those ominous clumps in the cell.

Durham points out that in most cases the cells manage to live with this toxic protein and function well into adulthood. "This indicates that at some point the circumstances have changed because the cells could function before. The coping mechanisms must be compromised."

It appears that the cells may successfully prevent or repair most damage until a threshold is reached. The demand eventually becomes too much, and soon unchecked damage begets more damage (including oxidative stress), creating a vicious cycle of destruction that ultimately triggers cell death. The motor neurons reach a point beyond which they can't come back from the brink.

The key may be in the coping mechanism. Durham's lab is investigating the importance of protein chaperones and proteosomes in helping cells deal with damaged proteins.

The chaperones' job is to round up damaged proteins (in this case, the mutant SOD1) and shuttle them to the proteosomes where they are chopped up and discarded. So far, experiments with cultured cells and mice support this idea, and Durham's recent findings show that proteosome activity is reduced by 50 per cent in the lumbar spinal cords of SOD1 mouse models. Either the system is overburdened, or the mutant SOD1 is impairing the proteosome function.

Durham proposes that future drug interventions for ALS will comprise combined therapies, including agents to increase the activity of the chaperones and proteosomes, as well as antioxidants to target the secondary oxidative stress involved in the disease. "The idea," she says, "is to keep things calm in the cell so that the vicious cycle of destruction can't happen."

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