

Meeting Report

Holding on for life

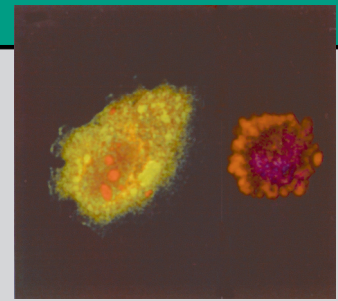
Adenoviruses have co-opted one of their important structural proteins to inhibit apoptosis, according to recent results. The inhibition comes about because the protein binds its protease target so tightly that cleavage takes, on average, three hours.

Felipe Andrade, Antony Rosen (both at the Johns Hopkins University School of Medicine, Baltimore, MD) and colleagues found that adenovirus L4-100K protein is a specific inhibitor of granzyme B (GrB), an apoptosis-inducing protease produced by cytotoxic T and natural killer cells in response to viral infection. Other adenovirus pro-

teins interfere with apoptosis induced by the action of Fas ligand on immune cells, but no inhibitor of granzyme B activity was previously known.

Andrade reported that the rate of binding of 100K to GrB was diffusion-limited, and that the proteins bound with high affinity. But cleavage occurred so slowly that the half-life of the complex averaged 3 hours. If a critical 100K aspartate was mutated, 100K lost its ability to inhibit, and instead was cleaved at an alternative site.

As 100K is an important structural protein for the virus, it is present at significant molar excess over GrB. Andrade stated that, in a typical infected cell, this molar excess would ensure an average lag of 141 hours before any



A cell with 100K (green, at left), is protected from granzyme-mediated apoptosis (red blebs at right).

GrB activity was free to cleave other substrates. By this time the adenovirus will have replicated and departed from the cell. ■

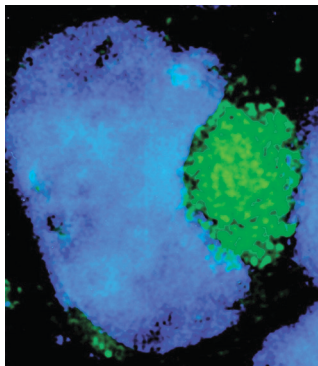
Further reading: Andrade, F., et al. 2001. *Immunity*. 14:751–762.

Aggregation inhibits destruction

Deposits of aggregated proteins have long been associated with many neurodegenerative diseases. But this correlation leaves unanswered the most important questions: is the aggregation a cause or an effect of the disease, and how might aggregates exert a toxic gain of function to cause disease?

Now Neil Bence, Ron Kopito and colleagues from Stanford University (Stanford, CA) have found that protein aggregation impairs the function of the ubiquitin–proteasome system (UPS). Reduced UPS-mediated degradation of certain key substrates could lead to cell-cycle abnormalities and cell death, and indeed Bence et al. find evidence for a cell-cycle delay in cells with aggregates.

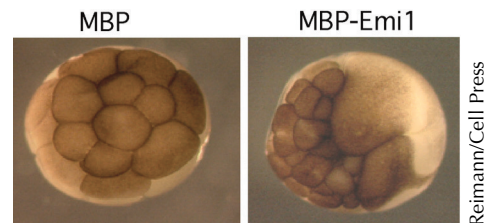
Their reporter for UPS function is an unstable form of GFP. Expression of aggregation-prone proteins leads to an increase in GFP reporter fluorescence, particularly in cells with large inclusions called aggresomes. In 1998, Kopito and colleagues discovered that cells collect large excesses of aggregated protein into aggresomes. These structures may sequester or jam UPS com-



Aggresome (green) forming next to DNA (blue).

ponents. The resulting reduction in UPS function would increase accumulation of unfolded proteins, initiating a positive-feedback loop and a rapid decline in cell viability. ■

Further reading: Bence, N., et al. 2001. *Science*. 292:1552–1555.



Injection of Emi1 into frog cells (right) blocks mitosis.

Delaying degradation

An inhibitor of protein-destruction machinery may explain the delay between cyclin synthesis and degradation. The delay, say Julie Reimann and Peter Jackson of Stanford University School of Medicine (Stanford, California), is essential if mitosis is to occur correctly.

Mitosis has a nice symmetry: accumulation of active cyclin/cdk complexes initiates mitotic events, but the induced events include destruction of the cyclins themselves. Somehow a delay must be built in such that cyclin destruction is one of the last events to occur. The spindle checkpoint helps out—it delays cyclin destruction if there are chromosomes not yet attached to the spindle. But a similar inhibitor of cyclin destruction has not yet been identified for the earlier stages of mitosis.

Reimann, Jackson and colleagues believe that Emi1 is that inhibitor. Excess Emi1 prevents destruction of both mitotic cyclins (cyclin A and B), thus blocking cells in prometaphase. The block appears to occur via Emi1's binding of Cdc20, an activator of the machinery that destroys cyclins. Without Emi1 destruction isn't inhibited, so cells never accumulate cyclins and never enter mitosis.

Like cyclins, Emi1 is destroyed by ubiquitylation during mitosis, but its destruction occurs earlier and is controlled by a different activator. This destruction event may be dependent on the completion of certain prophase events. ■

Further reading: Reimann, J., et al. 2001. *Cell*. 105:645–655.

