caused by emission from dust grains that, although cool (tens of kelvin), are much hotter than the primordial background and therefore emit most of their light at these shorter wavelengths. Detection of the extragalactic cosmic submillimeter background required modeling to subtract foreground emission from dust in the Galaxy; several different approaches to this problem (*3–5*) now appear to give concordant results.

This extra light below 0.8 μm was expected and has been interpreted as emission from dust in galaxies at high redshift; the energy ultimately comes from starlight absorbed by the grains (*6*). The interpretation was confirmed (*7–9*) with sensitive imagers on ground-based submillimeter telescopes (such as SCUBA on the James Clerk Maxwell Telescope); much of the background in some narrow fields was found to come from large galaxies forming stars at an extremely rapid rate, when the universe was about one-quarter to one-half of its present size (*10*). It looks like about half the starlight that was ever emitted was absorbed by dust and now appears as submillimeter light (although a substantial part of the submillimeter energy might also originate not from starlight but from quasars).

More recently, the background light in the near infrared (2.2 and 3.5 μm) has been measured (*1*, *2*), with data from another COBE instrument [Diffuse Infrared Background Experiment (DIRBE)] designed to map the absolute flux from the sky at shorter wavelengths than FIRAS. At these wavelengths, the foregrounds to be subtracted include the zodiacal light and that from individual Galactic stars. These again have to be removed by models; in the case of the stars, fields larger than a DIRBE beam have been directly imaged from the ground and the star fluxes removed to find the amount of light coming "from behind," from the universe at large. The total power in this near infrared background is about the same as the submillimeter background. The near infrared background probably comes mostly from starlight that reaches us directly, not absorbed by dust.

Starlight is redshifted by varying degrees by the cosmic expansion; most of the light appears to have been emitted at redshifts between 1 and 3 (when the universe was one-quarter to one-half of its present size), which is why it is at wavelengths two to four times longer than the original emission. This period in cosmic history corresponds to the epoch of greatest conversion of cosmic gas to stars; time before that was short (about 3 billion years), although some stars certainly did form, and after that time the remaining gas was mostly too hot to cool and collapse into galaxies and stars.

The measured strength of the background is close to theoretical estimates based on the stellar populations we see today (*11*). We now see only the low-mass, long-lived descendants of the bright early population that emitted the backgrounds. The measured background tells us, among other things, that the cosmic "dark ages" really were dark; there is no surprising new population of previously unaccounted stars contributing a substantial amount of energy at early times and little room for a population of progenitors to make dark remnants—such as black holes or degenerate dwarfs—in large quantities. The amount of light we see agrees roughly with the global production of heavy elements as estimated from x-ray line emission from hot gas in galaxy clusters. (An interesting conclusion is that a substantial fraction of heavy nuclei are ejected from the galaxies where they are born, because otherwise the galaxies would contain more heavy nuclei, and the cluster gas less, than is observed.) The amount of material forming into stars agrees roughly with the amount of gas available for forming stars, as estimated from quasar absorption systems. The infrared backgrounds thus fit well into the growing list of phenomena that give us a direct view of the birth of galaxies and of most of the stars in the universe.

References and Notes

1. E. L. Wright and E. D. Reese, in preparation (preprint available at xxx.lanl.gov/abs/astro-ph/9912523).
2. V. Gorjian *et al.*, *Astrophys. J.*, in press (preprint available at xxx.lanl.gov/abs/astro-ph/9909428).
3. D. Fixsen *et al.*, *Astrophys. J.* **508**, 123 (1998).
4. D. Schlegel *et al.*, *Astrophys. J.* **500**, 525 (1998).
5. M. G. Hauser *et al.*, *Astrophys. J.* **508**, 25 (1998).
6. J. R. Bond *et al.*, *Astrophys. J.* **367**, 420 (1991).
7. I. Smail *et al.*, *Astrophys. J. Lett.* **490**, L5 (1997).
8. D. Hughes *et al.*, *Nature* **394**, 241 (1998).
9. D. B. Sanders, in *Toward a New Millennium in Galaxy Morphology*, Eds., D. L. Block, I. Puerari, A. Stockton, D. Ferreira (Kluwer Academic Publishers, Dordrecht, Netherlands, in press) (preprint available at xxx.lanl.gov/abs/astro-ph/9910028).
10. We see the same population of galaxies nearby today as normal "ellipticals," dominated by old populations of stars and rather little gas left to form new stars.
11. Y. C. Pei *et al.*, *Astrophys. J.* **522**, 604 (1999).

PERSPECTIVES: NEUROBIOLOGY

Stay the Executioner's Hand

Mark E. Gurney, Alfredo G. Tomasselli, Robert L. Heinrikson

The French physician Charcot provided the original clinical description of the motor neuron disease amyotrophic lateral sclerosis (ALS) back in 1869. The disease causes astonishingly rapid loss of motor neurons in the cortex, brainstem, and spinal cord over 1 to 5 years with consequent paralysis and death. Patients with ALS (commonly referred to as Lou Gehrig's disease in the United States after the baseball star who died of the illness) are typically 40 to 50 years of age at diagnosis. Why motor neurons are selectively vulnerable to disease, and what triggers their destruction, still remains a mystery more than a century later.

The great leap forward in our understanding of ALS began in 1993 with the demonstration (*1*) that a familial form of the illness could be attributed to mutations in the *SOD1* gene, which encodes the cytosolic antioxidant enzyme, copper/zinc superoxide dismutase (Cu,Zn SOD). At first it seemed that the mutations might cause disease by reducing the amount or activity of Cu,Zn SOD, thereby decreasing the protection from oxidative stress of motor neurons in ALS patients. But mice lacking Cu,Zn SOD do not develop motor neuron disease, whereas transgenic mice overexpressing a mutant human *SOD1* gene do (*2, 3*). This suggested that the mutant protein itself is in some way selectively toxic for motor neurons, perhaps through altered oxidative chemistry, protein misfolding, or protein aggregation (*4*).

On page 335 of this issue, Li *et al.* (*5*) provide evidence that a mutant *SOD1* transgene causes motor neuron death in mice through caspase-mediated programmed cell death (apoptosis). Initiator caspases—enzymes activated from their dormant precursor forms in response to a variety of cellular insults—act on the precursors of downstream caspases such as caspase-3, which are the executioners in the breakdown of essential cellular proteins (see the figure). Apoptosis is characterized by a complex series of cellular changes leading to the noninflammatory demise of the cell. It is a normal, highly regulated process that is crucial for proper cell growth and development. In pathological states, however, it can be abrogated (cancer) or exacerbated (neurodegeneration), either condition leading to some of the most devastating diseases known.

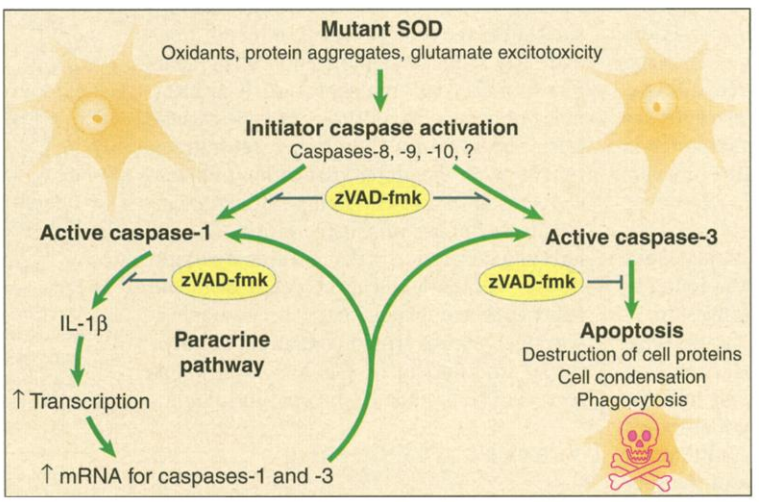
The idea that motor neuron death in SOD1 transgenic mice is through an apoptotic pathway is bolstered by experiments in which overexpression of *bcl-2*, a well known mitochondrial inhibitor of apoptosis, protects against neuronal loss (*6*). Indeed, mitochondrial involvement in the

M. E. Gurney is at Genomics and A. G. Tomasselli and R. L. Heinrikson are at Protein Sciences, Pharmacia Corp., 301 Henrietta Street, Kalamazoo, MI 49007, USA. E-mail: mark.e.gurney@am.pnu.com

apoptotic pathway leads to release of cytochrome c, an activator of the initiator caspase-9 that, in turn, activates the executioner caspase-3 (*7*). The Li *et al.* study builds on previous observations that caspase-1 and caspase-3 are activated in SOD1^{G93A} mice (which overexpress an *SOD1* transgene carrying an ALS mutation that results in glycine being substituted for alanine at position 93). When these mice are crossed with transgenic mice expressing a dominant negative mutant form of caspase-1 that is inactive, they have a slight increase in lifespan (*8*). Li and co-workers (*5*) show that a small peptide caspase inhibitor (zVAD-fmk) prolongs the survival of SOD1^{G93A} transgenic mice, and they provide evidence for the activation of both caspase-1 and caspase-3 in neurons within the ventral horn of the mouse spinal cord.

The caspase inhibitor zVAD-fmk blocks all known caspases and acts at several points in the activation cascade (see the figure). The VAD backbone positions the inhibitor within the caspase active site with the aspartate carboxylic acid facing downward into a deep, positively charged pocket, so that the fluoromethyl ketone warhead is positioned to react covalently with the cysteine in the caspase active site. Because of low oral bioavailability and limited brain penetrance, zVAD-fmk was delivered by infusion into the cerebral ventricle, which communicates with the spinal cord central canal through the fourth ventricle. In humans, intrathecal perfusion within the vertebral column would be preferred, but the small size of mice prevents access to that site for chronic infusion.

Infusion of zVAD-fmk into the cerebral ventricle extended survival of the SOD1^{G93A} mice by nearly 4 weeks. At an intermediate time point after zVAD-fmk administration, there were a greater number of motor neurons in cervical sections of the spinal cord—although fewer in lumbar segments (perhaps because of poor penetrance of the inhibitor down the length of the spinal column)—in treated compared to control animals. There was also improved preservation of the axons of thoracic phrenic neurons that innervate the diaphragm. Treatment with zVAD-fmk also decreased interleukin-1β (IL-1β), an indication that caspase-1 activity was inhibited. The particular SOD1^{G93A} transgenic mouse line used by Li *et al.* (*5*) normally shows the first outward signs of clinical disease at 3 months of age, as evidenced by tremor in two or more limbs. The duration of disease averages 30 to 40 days in the many laboratories that use this model. Thus, zVAD-fmk probably extends survival after the onset of clinical disease by ~70%. In comparison, riluzole, which is thought to decrease the neurotoxic effects of the excitatory neurotransmitter glutamate, extends survival by ~30% in the same SOD1^{G93A} transgenic line and by about 3 months in ALS patients. Antioxidants and copper chelators also show neuroprotection in the mouse model, although their effect is primarily on disease onset rather than on disease duration. Clearly, an open issue is the extent to which treatment with multiple neuroprotective agents might produce an even greater clinical response, much as cocktails of protease and reverse transcriptase inhibitors produce greater clinical benefit in AIDS patients.



Players in a deadly game. Pathways for caspase activation in the mutant SOD1^{G93A} transgenic mouse model of ALS. Cellular insults that result from expression of mutant Cu,Zn SOD lead to activation of endogenous proforms of caspase-1 and caspase-3. Caspase-3 initiates destruction of cellular proteins and cell death by apoptosis. Caspase-1 promotes production of the proinflammatory cytokine IL-1β, which increases transcription of both caspases and exacerbates cell death.

Caspase-3 is an obvious target for inhibiting the apoptotic cascade; its modes of activation have been well characterized, and its activity is largely responsible for the destruction of structural and maintenance proteins in the cell (*9*). Caspase-1 is another matter. Originally referred to as ICE (interleukin converting enzyme) because it promotes production of IL-1β from the proform, caspase-1 is considered to be a proinflammatory rather than an apoptotic caspase. An interesting aspect of the Li *et al.* report is the observation of increased levels of active caspase-1, both in the SOD1^{G93A} mice and in the spinal cord of ALS patients, as well as increased levels of caspase-1 and caspase-3 mRNA in the transgenic mice. Up-regulation of caspase-1 correlates with increased levels of IL-1β, an activator of transcription, and this could explain the increased production of mRNAs for these caspases. Accordingly, the authors propose a non–cell-autonomous pathway of apoptosis that is subject to paracrine control through IL-1β (see the figure). These findings strongly suggest that apoptosis is a process that can be influenced by proinflammatory agents such as the cytokine IL-1β.

A number of hypotheses have been proposed to explain how mutant Cu,Zn SOD triggers the destruction of motor neurons. These include altered chemical reactivity of the mutant enzyme leading to the generation of reactive radicals, its aggregation (seen in SOD1^{G93A} transgenic mice and ALS patients), and alterations in glutamate excitotoxicity. Fundamental questions remain with respect to how one or more of these mechanisms ultimately might trigger caspase activation and consequent motor neuron death. However, the links between earlier work (*10, 11*), the Li *et al.* findings, and these possible triggers of motor neuron death provide a compelling argument for the participation of apoptotic pathways, and for the value of caspase inhibitors as potential therapeutic agents in the treatment of ALS and other neurodegenerative diseases.

It is more than 60 years since Lou Gehrig, the champion of the New York Yankees, in his last press conference before retiring as a consequence of ALS, claimed to be "the luckiest man alive." Although we have yet to hit a home run in the quest for a treatment or cure for ALS, work with transgenic mice builds hope that we are at bat in the final inning against this deadly disease.

References

1. D. R. Rosen *et al.*, *Nature* **362**, 59 (1993).
2. M. E. Gurney *et al.*, *Science* **264**, 1772 (1994).
3. P. C. Wong *et al.*, *Neuron* **14**, 1105 (1995).
4. D. W. Cleveland, *Neuron* **24**, 515 (1999).
5. M. Li *et al.*, *Science* **288**, 335 (2000).
6. V. Kostic *et al.*, *Science* **277**, 559 (1997).
7. D. R. Green and J. C. Reed, *Science* **281**, 1309 (1998).
8. R. M. Friedlander *et al.*, *Nature* **388**, 31 (1997).
9. N. A. Thornberry and Y. Lazebnik, *Science* **281**, 1312 (1998).
10. L. J. Martin, *J. Neuropathol. Exp. Neurol.* **58**, 459 (1999).
11. P. Pasinelli *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 15763 (1998).