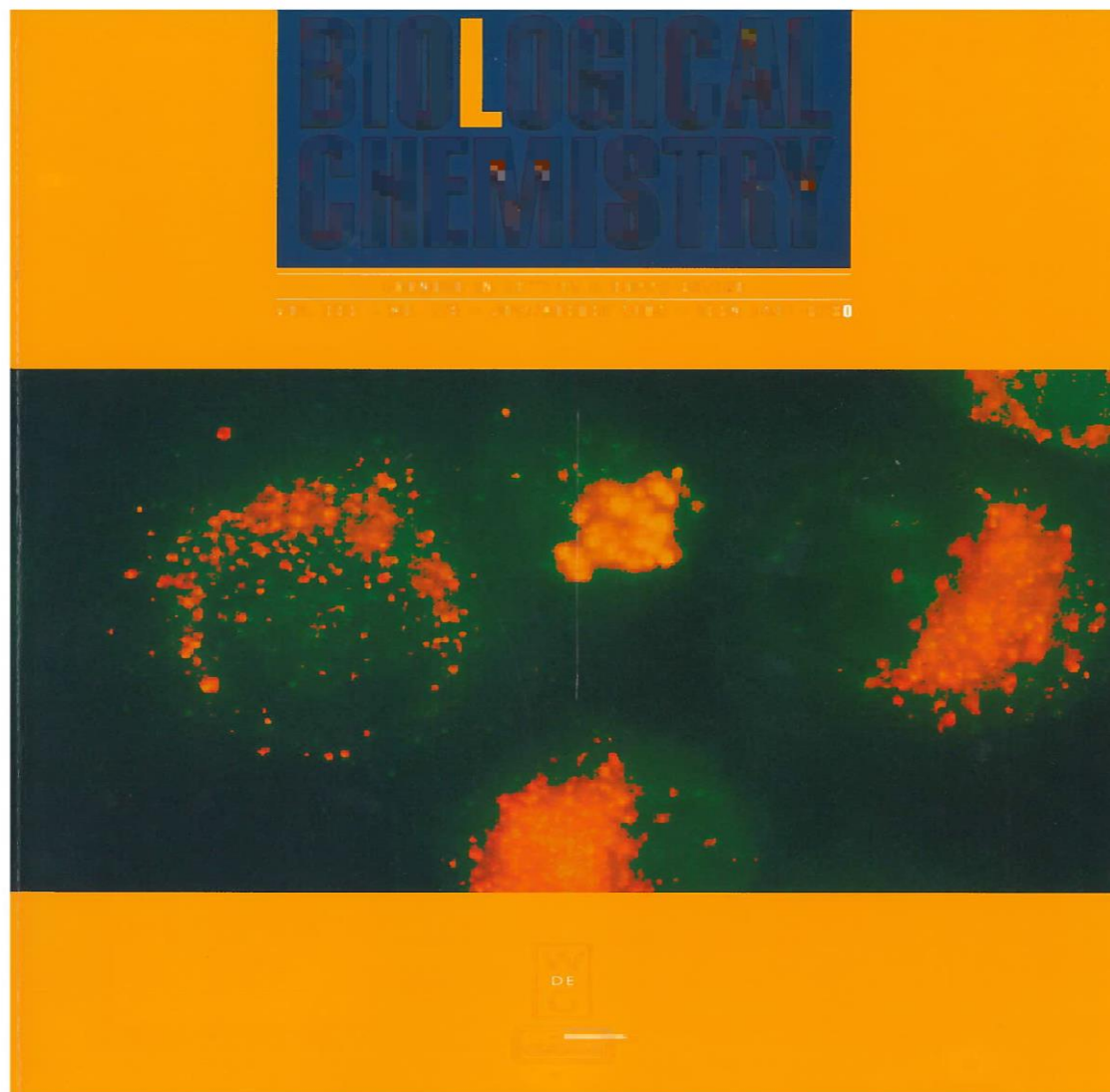
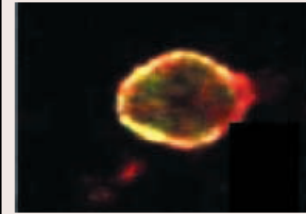
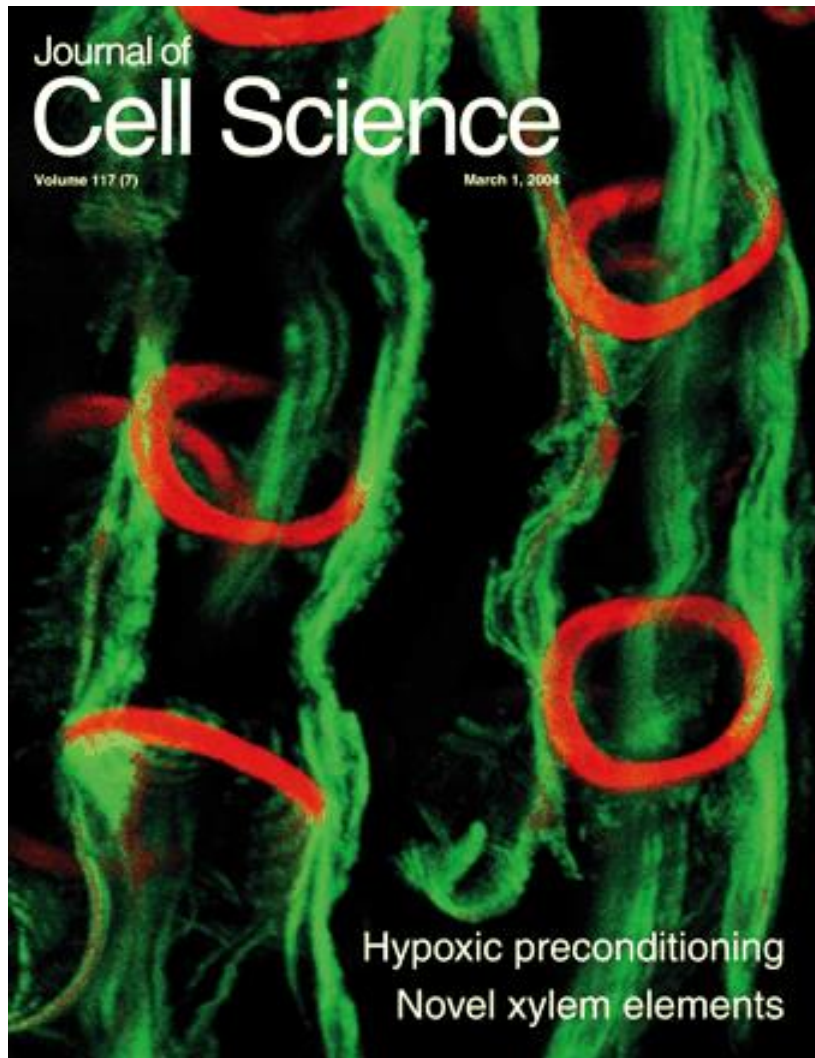


Endosomal-Lysosomal Proteolysis Mediates Death Signalling by $\text{TNF}\alpha$, Not by Etoposide, in L929 Fibrosarcoma Cells: Evidence for an Active Role of Cathepsin D



Preconditioning-induced cytoprotection in hepatocytes requires Ca^{2+} -dependent exocytosis of lysosomes

Rita Carini¹, Roberta Castino², Maria Grazia De Cesaris¹, Roberta Splendore¹, Marina Démoz², Emanuele Albano¹ and Ciro Isidoro^{2,*}



Forewarned is forearmed: getting ready for hypoxia

A brief exposure of cells or organs to

hypoxia reduces the cytotoxicity of a later prolonged period of hypoxia. A better understanding of the cellular events involved in such 'hypoxic preconditioning' could therefore improve the success rate of human organ transplantation. On p. 1065, Ciro Isidoro and colleagues report that in rat hepatocytes, preconditioning-induced cytoprotection involves Ca^{2+} -dependent exocytosis of lysosomes. They show that hypoxic preconditioning induces the movement of endosomes and lysosomes from their perinuclear position in oxygenated hepatocytes to the plasma membrane. There, the lysosomes in particular fuse with the membrane and release their contents. Inhibition of lysosomal exocytosis by disruption of the actin cytoskeleton or by inhibition of phosphoinositide 3-kinase (PI3K) prevents cytoprotection in response to hypoxic preconditioning. Furthermore, an increase in cytosolic free Ca^{2+} concentration, which is induced by PI3K, is necessary for exocytosis of endosomal/lysosomal organelles and for cytoprotection. On the basis of these findings, the authors suggest that drugs that stimulate membrane recycling could help to protect organs destined for transplantation from hypoxia.

BioWorld Today April 22, 2005



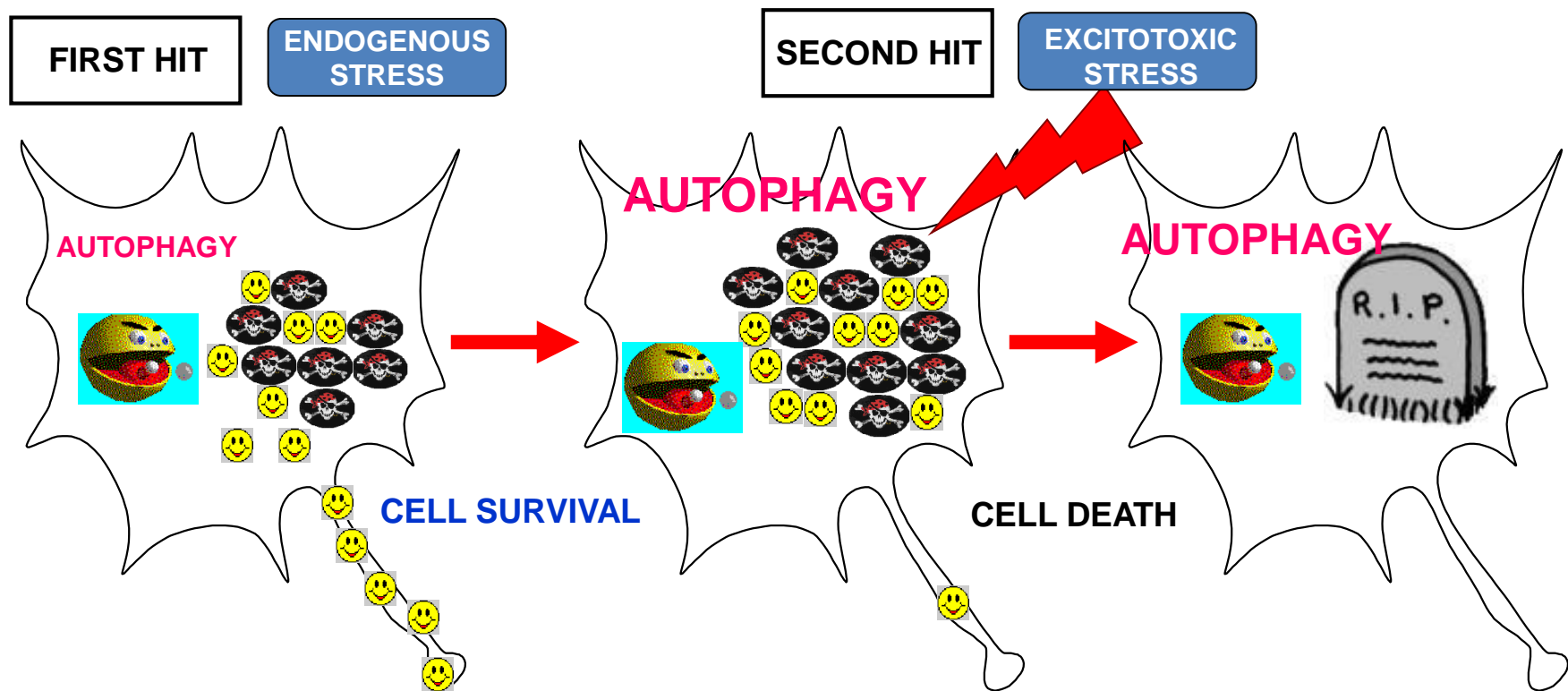
BioWorld Today

26/4/05 13:21

- *Adding Insult To Insult Equals Injury*
- **Autophagy Goes From Good To Bad In Neurodegeneration**
- **By Anette Breindl**
- **Science Editor**

Autophagy-dependent cell survival and cell death in an autosomal dominant familial neurohypophyseal diabetes insipidus in vitro model

Roberta Castino,^{*†} Ciro Isidoro,[†] and David Murphy^{*}



THE TWO-HITS MODEL explains the pro-survival and pro-death roles of AUTOPHAGY: the FIRST hit (intrinsic genetic defect) induces pro-survival autophagy, while a SECOND hit (environmental stress) over-induces autophagy and precipitates CELL DEATH

Lithium delays progression of amyotrophic lateral sclerosis

Francesco Fornai*^{†‡}, Patrizia Longone[§], Luisa Cafaro[†], Olga Kastsuichenka*, Michela Ferrucci*, Maria Laura Manca[¶], Gloria Lazzeri*, Alida Spalloni[§], Natascia Bellio^{||}, Paola Lenzi*, Nicola Modugno[†], Gabriele Siciliano[¶], Ciro Isidoro^{||}, Luai Murri[¶], Stefano Ruccaieri[†], and Antonio Paparelli*

2052-2057 | PNAS | February 12, 2008 | vol. 105 | no. 6

www.pnas.org/cgi/doi/10.1073/pnas.0708022105



28

Lithium Treatment for ALS

Few diseases are as devastating as the progressive neurodegenerative disease ALS (amyotrophic lateral sclerosis), also known as Lou Gehrig's disease. Over time, a patient with ALS will lose almost all ability to move. The paralysis is caused by the gradual death of the neurons that control movement. Just one FDA-approved drug, riluzole, has been shown to slow the disease's progression—and only minimally.

Now a small study suggests how treatment might be improved. In a February report in *Proceedings of the National Academy of Sciences*, Francesco Fornai, an anatomy professor and physician at the University of Pisa, found that lithium—well known as a treatment for bipolar disorder—might also work against ALS.

In the study, 16 ALS patients received a drug combo that consisted of

riluzole and lithium. Twenty-eight other patients were treated with riluzole alone. After 15 months, eight of the patients who had taken only riluzole had died, and the disease had progressed markedly in the other controls. The patients who took both riluzole and lithium fared much better. None died, and their condition worsened only a little bit.

Why would lithium help? In a related study using mice, Fornai found that lithium counteracted the damage to motor neurons brought on by the disease. The drug also stimulated the production of mitochondria, the energy-generating structures within cells. Although the findings are promising, Fornai cautions that "it will take some time to establish whether the use of lithium should be considered as a novel therapy for ALS."

Jane Bosveld

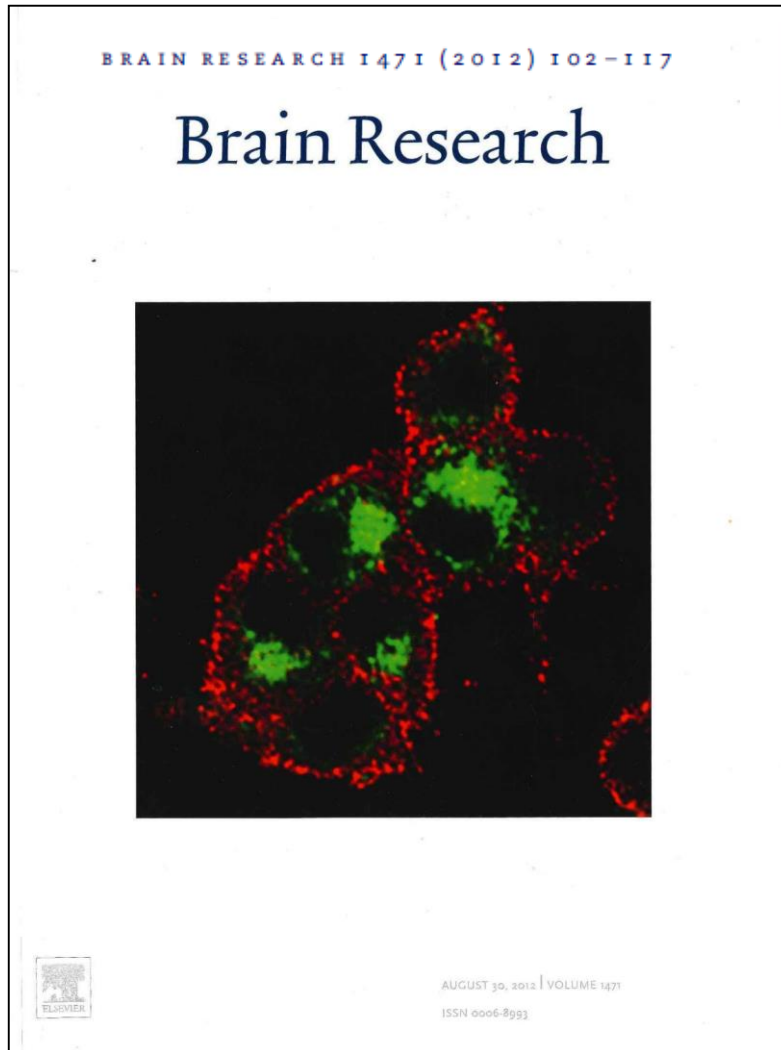
Research Highlights

Nature Clinical Practice Neurology (2008) 4, 239-240
doi:10.1038/ncpneuro0780

Lithium inhibits progression of amyotrophic lateral sclerosis

Dopamine induces apoptosis in APPswe-expressing Neuro2A cells following Pepstatin-sensitive proteolysis of APP in acid compartments

Monica Cagnin, Matteo Ozzano, Natascia Bellio, Ilaria Fiorentino, Carlo Follo, *Ciro Isidoro**



COVER = Figure 4C

Neuro2A-APPswe cells were exposed to Dopamine for 16 h and then processed for immunofluorescence labeling of dynamin (in red) and APP (in green). Images show that APP moves toward intracellular compartments upon exposure to DA, while dynamin consistently remains localized beneath the plasma membrane.