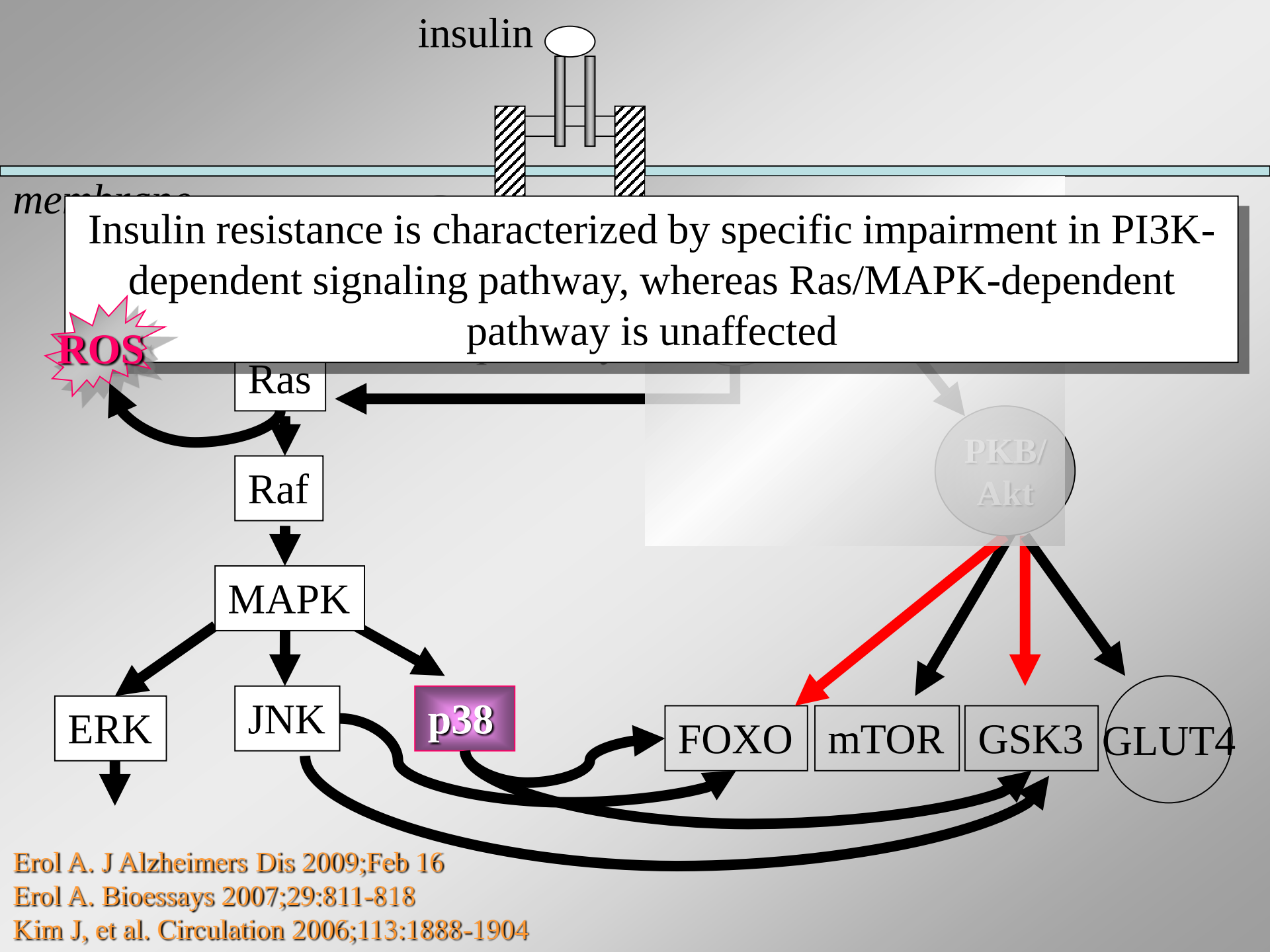
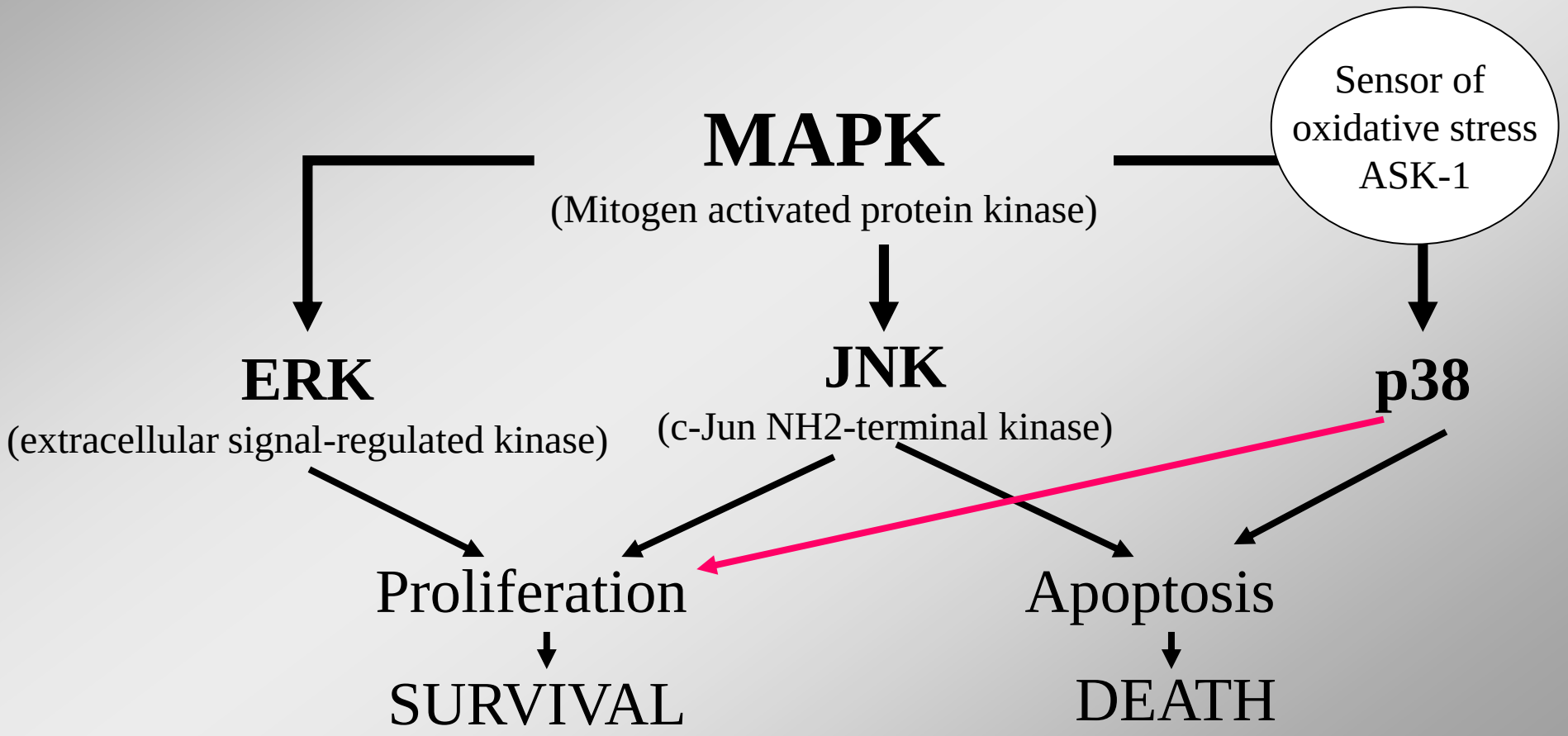
# Metabolically-induced paradoxical cell cycle activity in astrocytes and neurons linked to neurodegeneration

**Adnan Erol MD.**

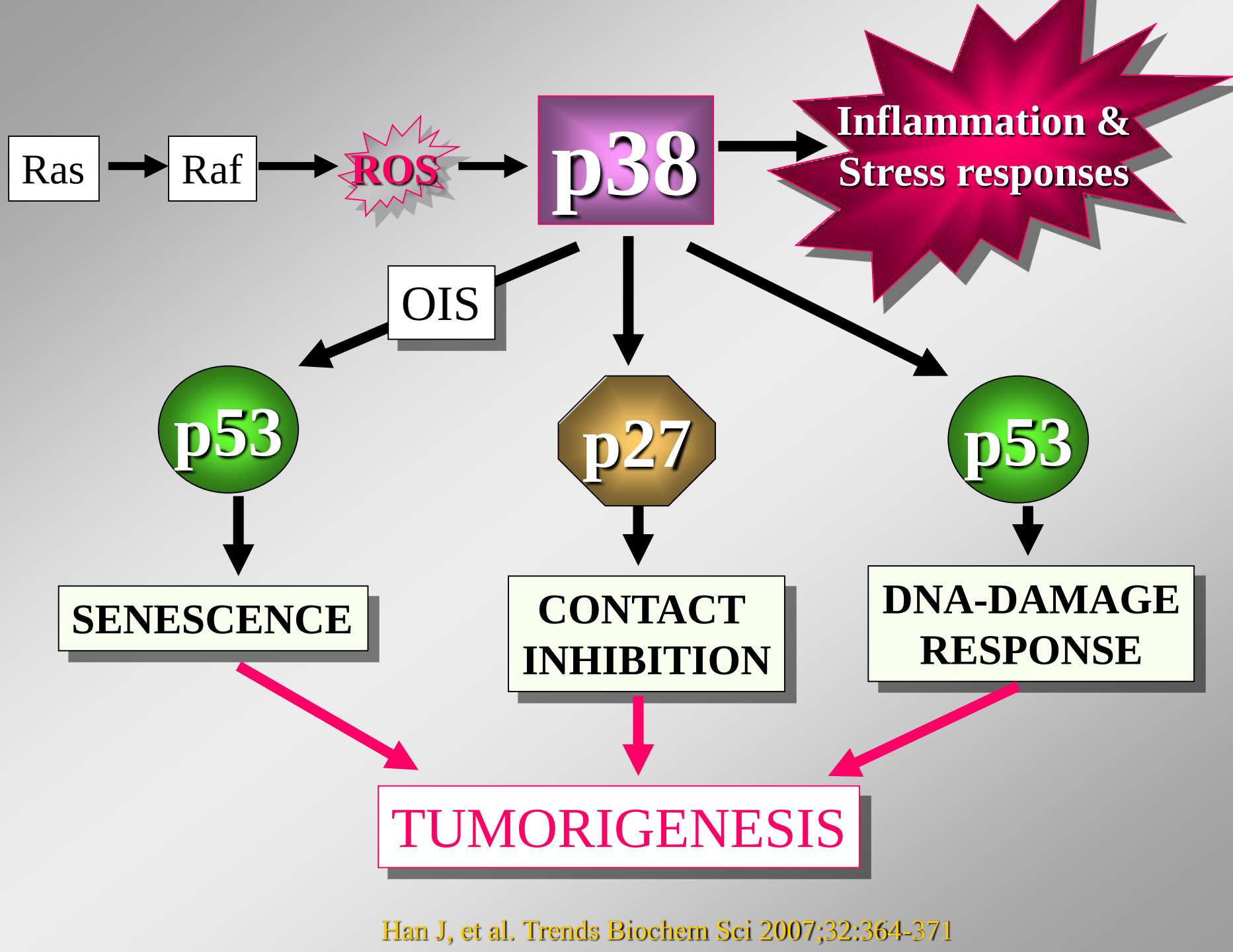



Erol A. J Alzheimers Dis 2009;Feb 16
Erol A. Bioessays 2007;29:811-818
Kim J, et al. Circulation 2006;113:1888-1904

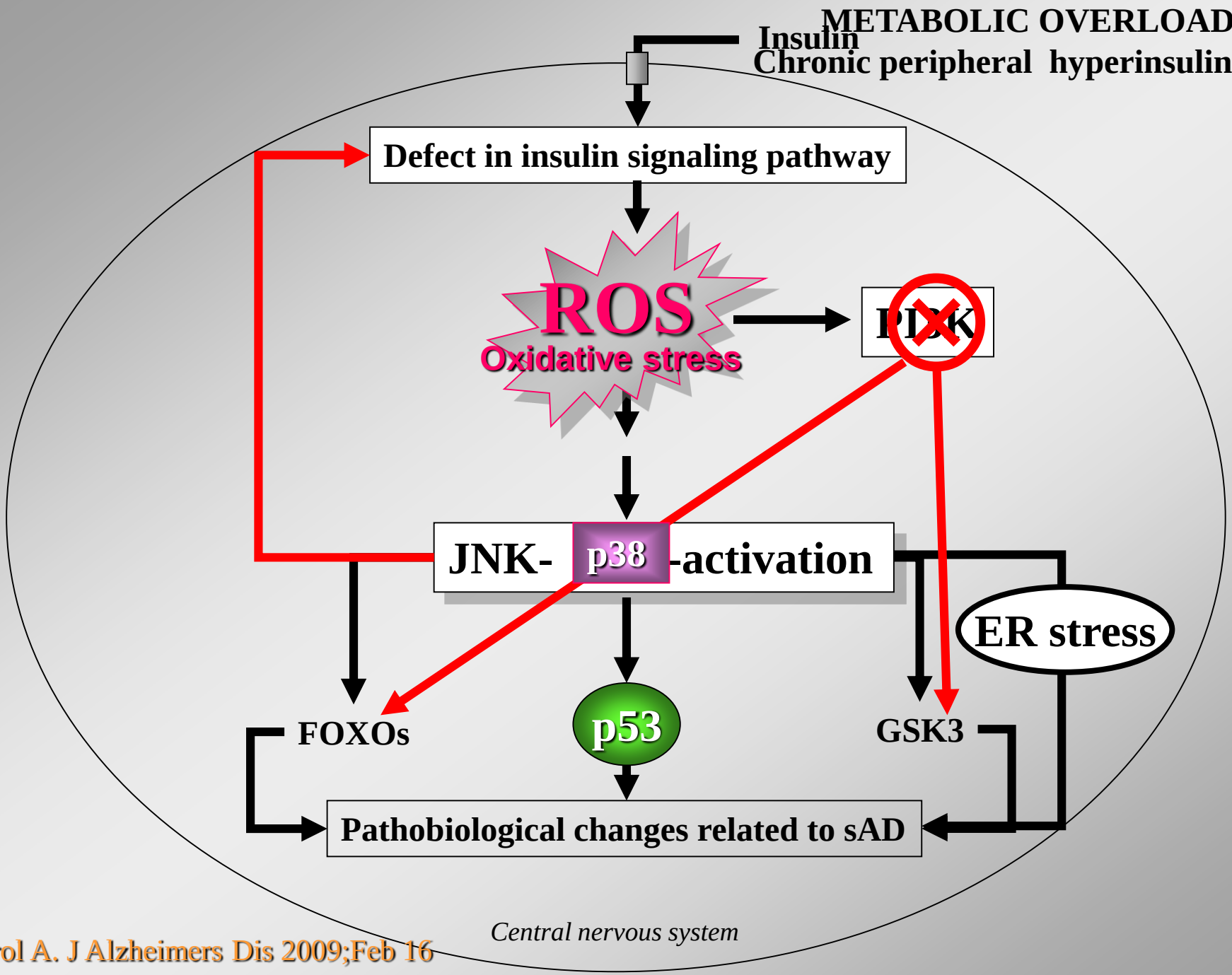
Cells sense changes in their environment and activate signal transduction pathways to mediate proliferation, differentiation, and survival



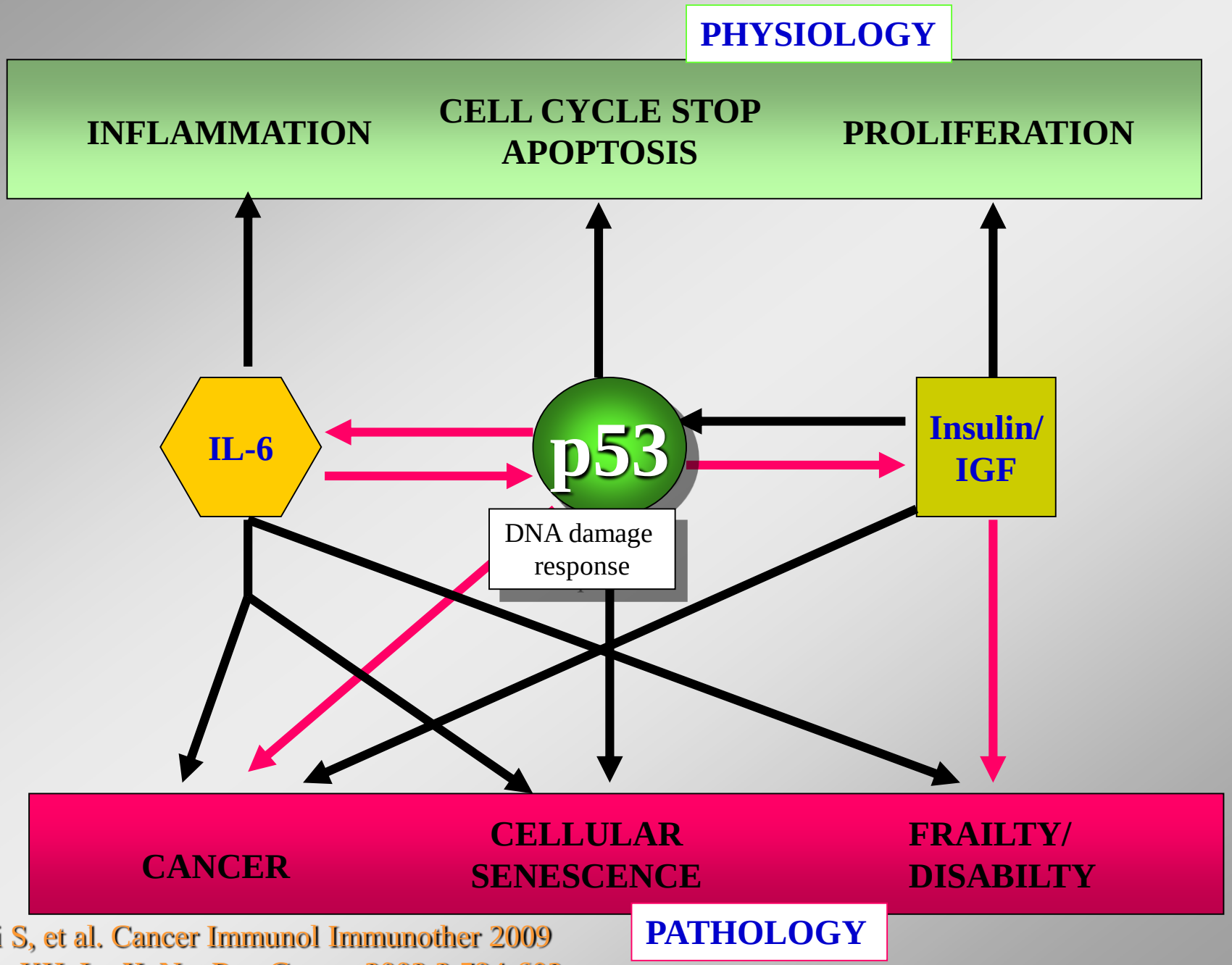

Kennedy NJ, et al. Cancer cell 2007;11:101-103




Han J, et al. Trends Biochem Sci 2007;32:364-371

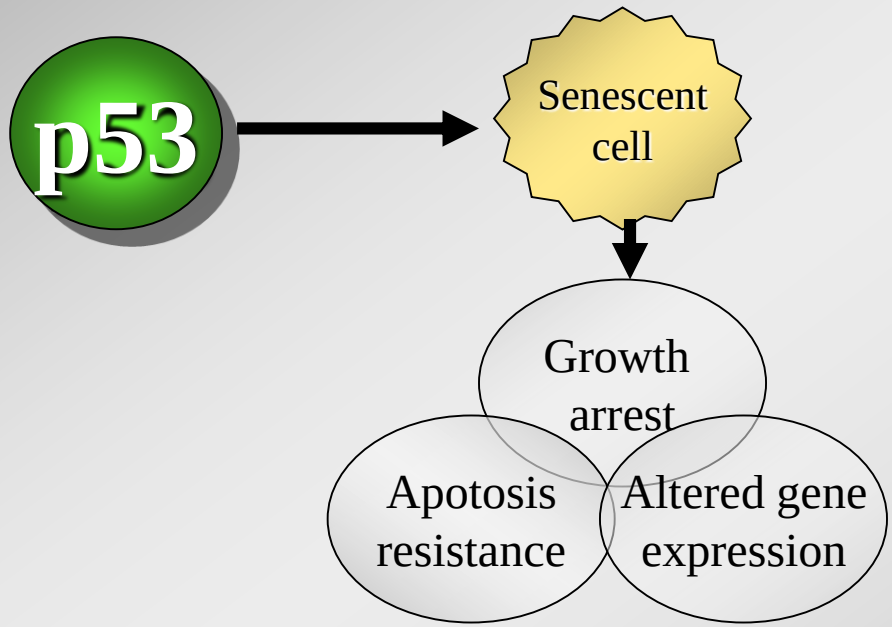



Erol A. J Alzheimers Dis 2009;Feb 16
Smith MA, Perry G, et al. Mech Ageing Dev 2001;123-39-46



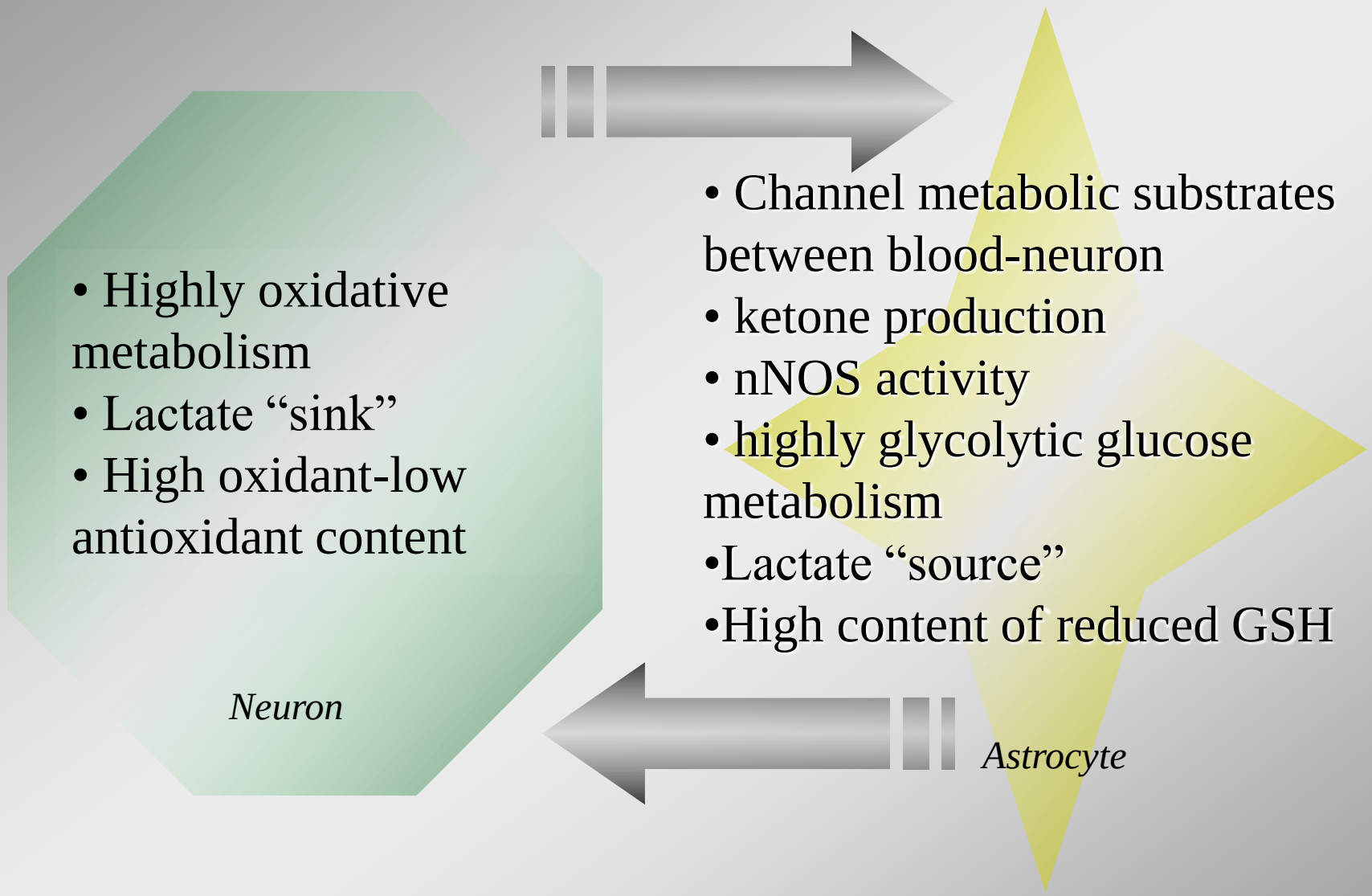

Salvioli S, et al. Cancer Immunol Immunother 2009
Vousden KH, Lu X. Nat Rev Cancer 2002;2:594-602

**SENESCENCE**
**Metabolically viable cell cycle arrest with persistent DNA damage signaling**

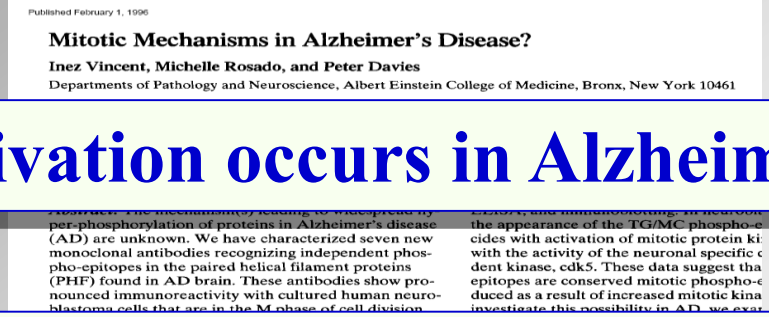



**Cellular senescence is confined to mitotic cells, which are at risk for neoplastic transformation**

Campisi J, fagagna F. Nat Rev Molec Cell Biol 2007;8:729-740
Mallete FA, Ferbeyre G. Cell cycle 2007;6:1831-1836




Erol A. *J Alzheimers Dis* 2008;13:241-253
Pellerin L. *Mol Neurobiol* 2005;32:59-72


Published February 1, 1996

Mitotic Mechanisms in Alzheimer's Disease?

Inez Vincent, Michelle Rosado, and Peter Davies
Departments of Pathology and Neuroscience, Albert Einstein College of Medicine, Bronx, New York 10461

per-phosphorylation of proteins in Alzheimer's disease (AD) are unknown. We have characterized seven new monoclonal antibodies recognizing independent phospho-epitopes in the paired helical filament proteins (PHF) found in AD brain. These antibodies show pronounced immunoreactivity with cultured human neuro-

the appearance of the TG/MC phospho-e
cides with activation of mitotic protein ki
with the activity of the neuronal specific c
dent kinase, cdk5. These data suggest tha
epitopes are conserved mitotic phospho-e
duced as a result of increased mitotic kina

# "Cell cycle activation occurs in Alzheimer's Brain"

# "Two-hit hypothesis"

First hit

- Activation of the mitotic processes
- Induction of oxidative stress

Second hit

- Increased oxidative stress
- Activation of cell cycle

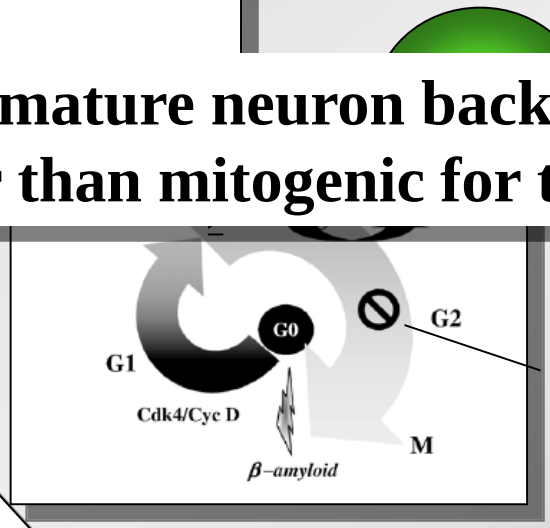
Neuronal adaptive changes

Apoptotic neuronal loss & neurodegeneration

Vincent, IR, Davies P, J Cell Biol 1996;132:413-425
Perry G, Smith MA, et al. Biochim Biophys Acta 2007;1772:494-502

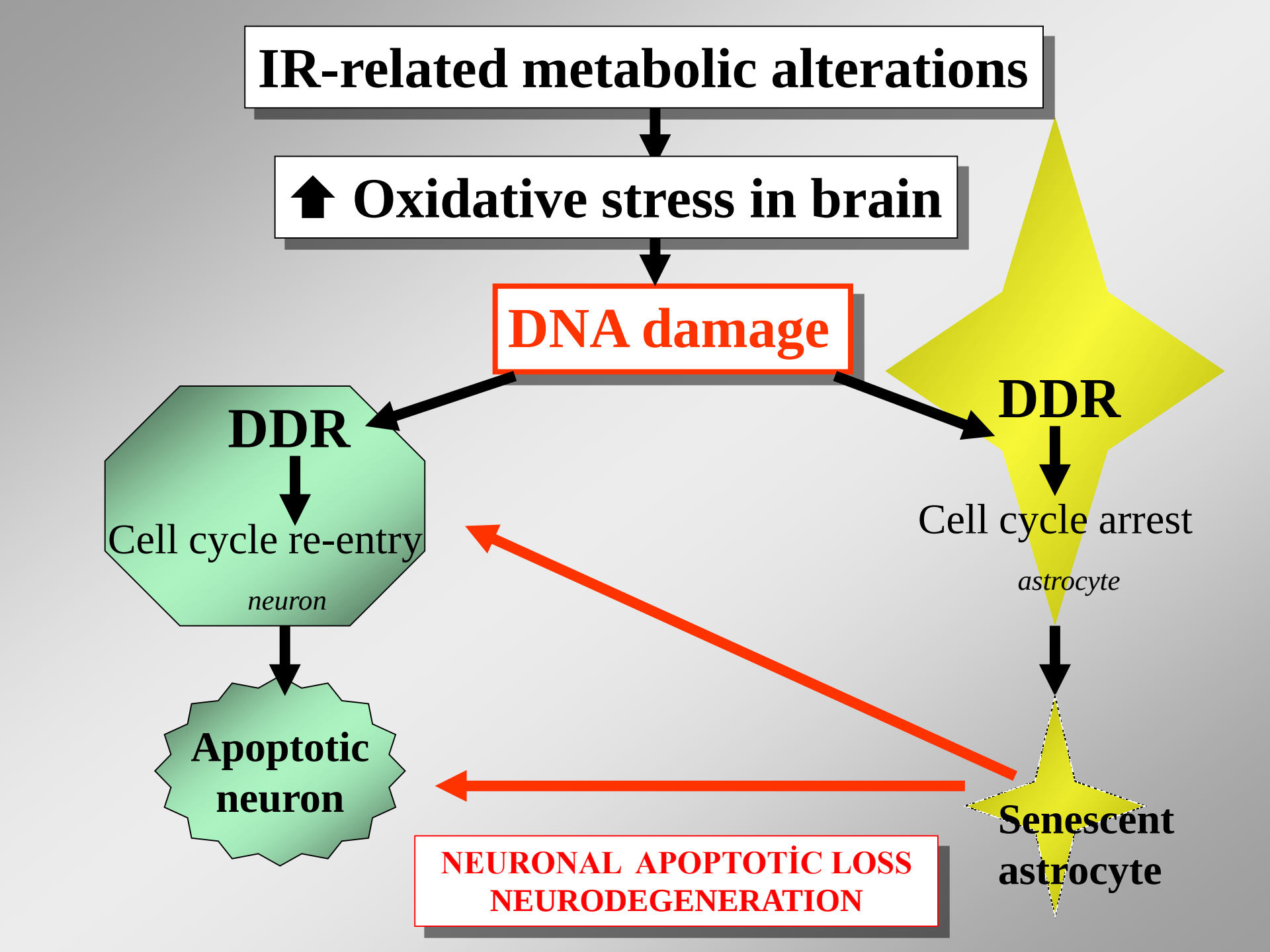
- Growth factor deficiency
- Synaptic loss
- **Amyloid beta**
- **Cellular redox changes**

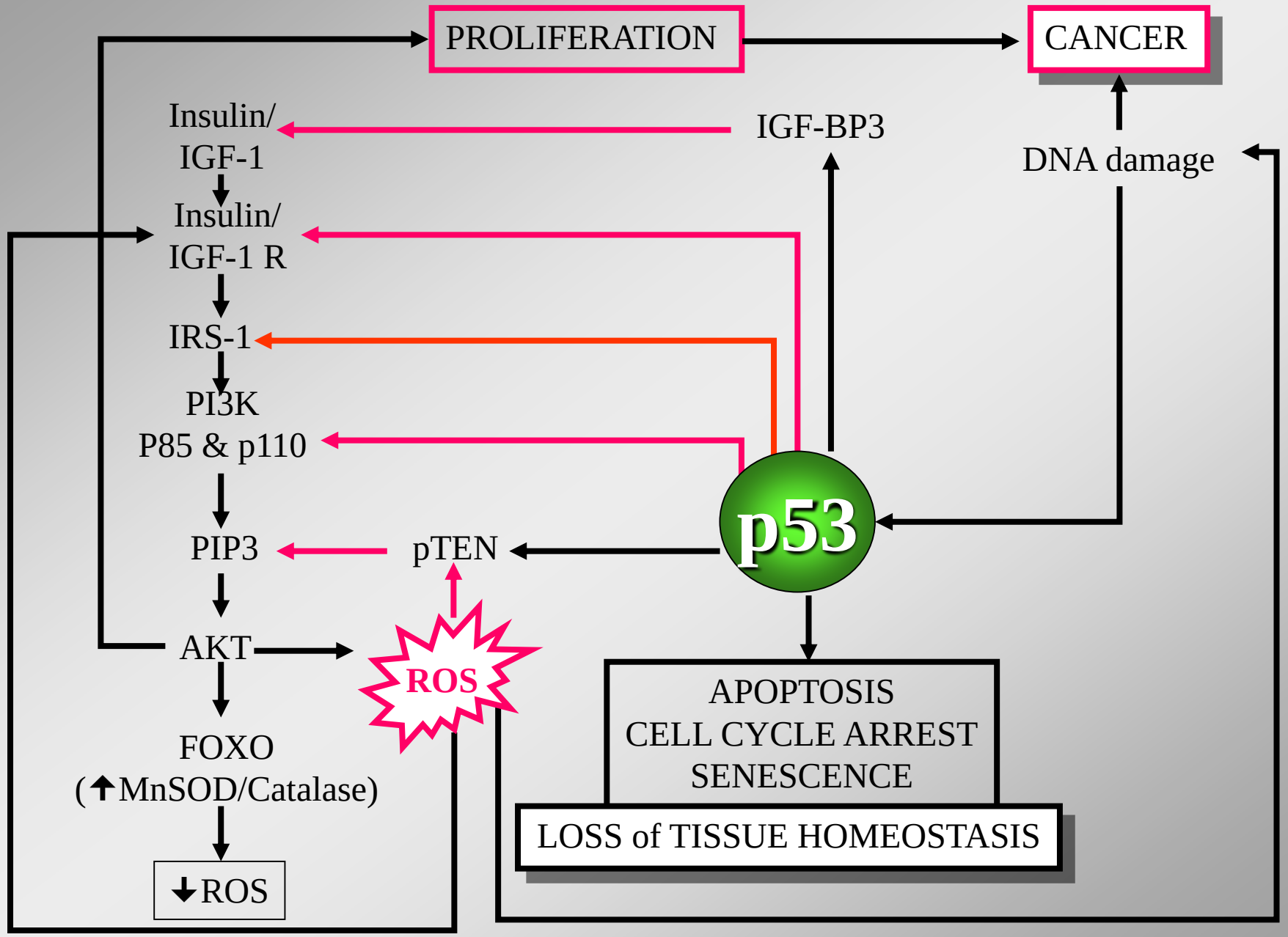
**Any events that force a mature neuron back into the cell cycle are lethal rather than mitogenic for the neuron**




**Initiation Of Cell cycle in Mature Neurons**


Lopes JP, et al. J Alzheimers Dis 2009;16:541-549
Copani A, et al. Biochim Biophys Acta 2007;1772:409-412


IR-related metabolic alterations
Oxidative stress in brain
DNA damage
DDR
Cell cycle re-entry
neuron
Apoptotic neuron
DDR
Cell cycle arrest
astrocyte
Senescent astrocyte
NEURONAL APOPTOTİC LOSS
NEURODEGENERATION




Hinkal G, Donehover LA. Mech Ageing Dev 2008;129:243-253
Dröge W, Schipper HM. Aging Cell 2007;6:361-370