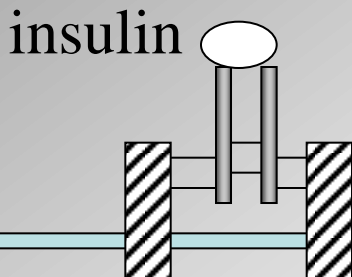


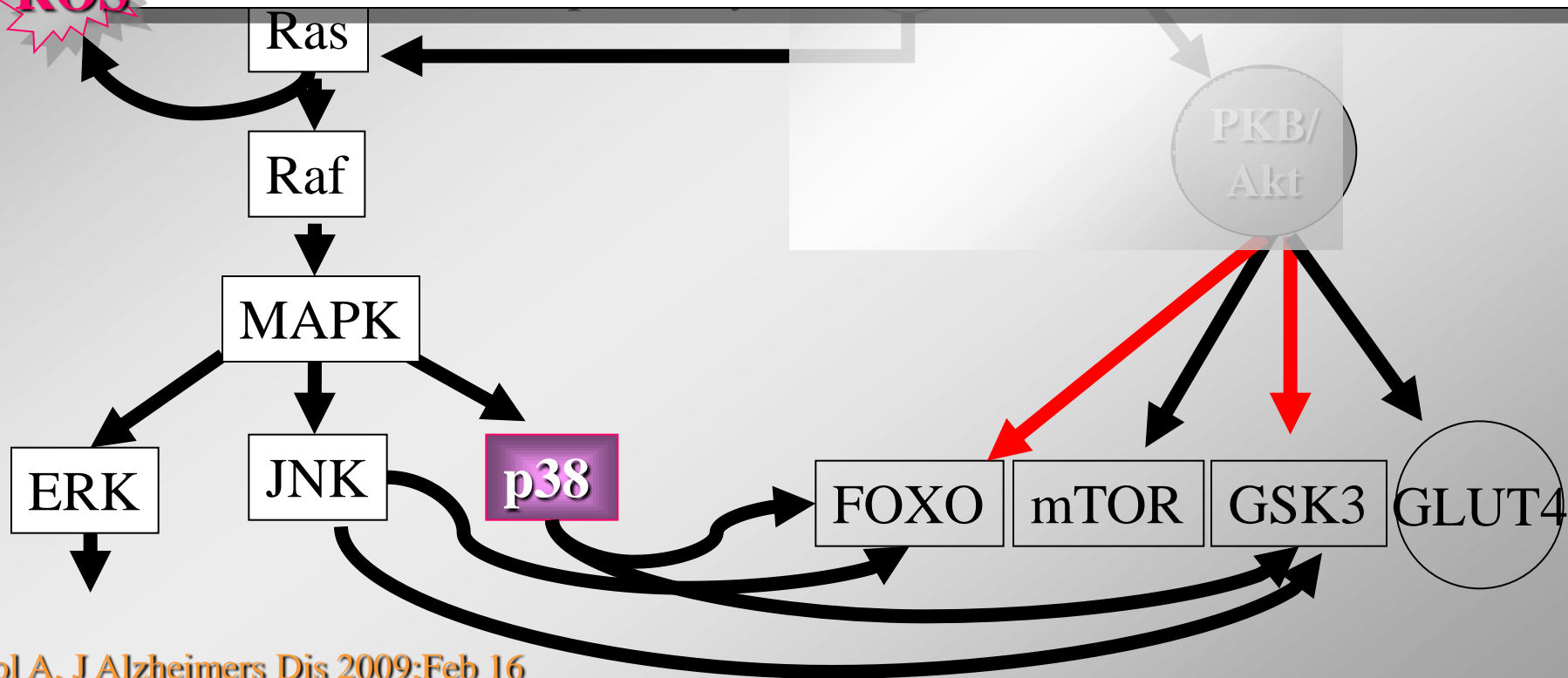
**Metabolically-induced
paradoxical cell cycle activity in
astrocytes and neurons linked to
neurodegeneration**

Adnan Erol MD.



Insulin resistance is characterized by specific impairment in PI3K-dependent signaling pathway, whereas Ras/MAPK-dependent pathway is unaffected

ROS

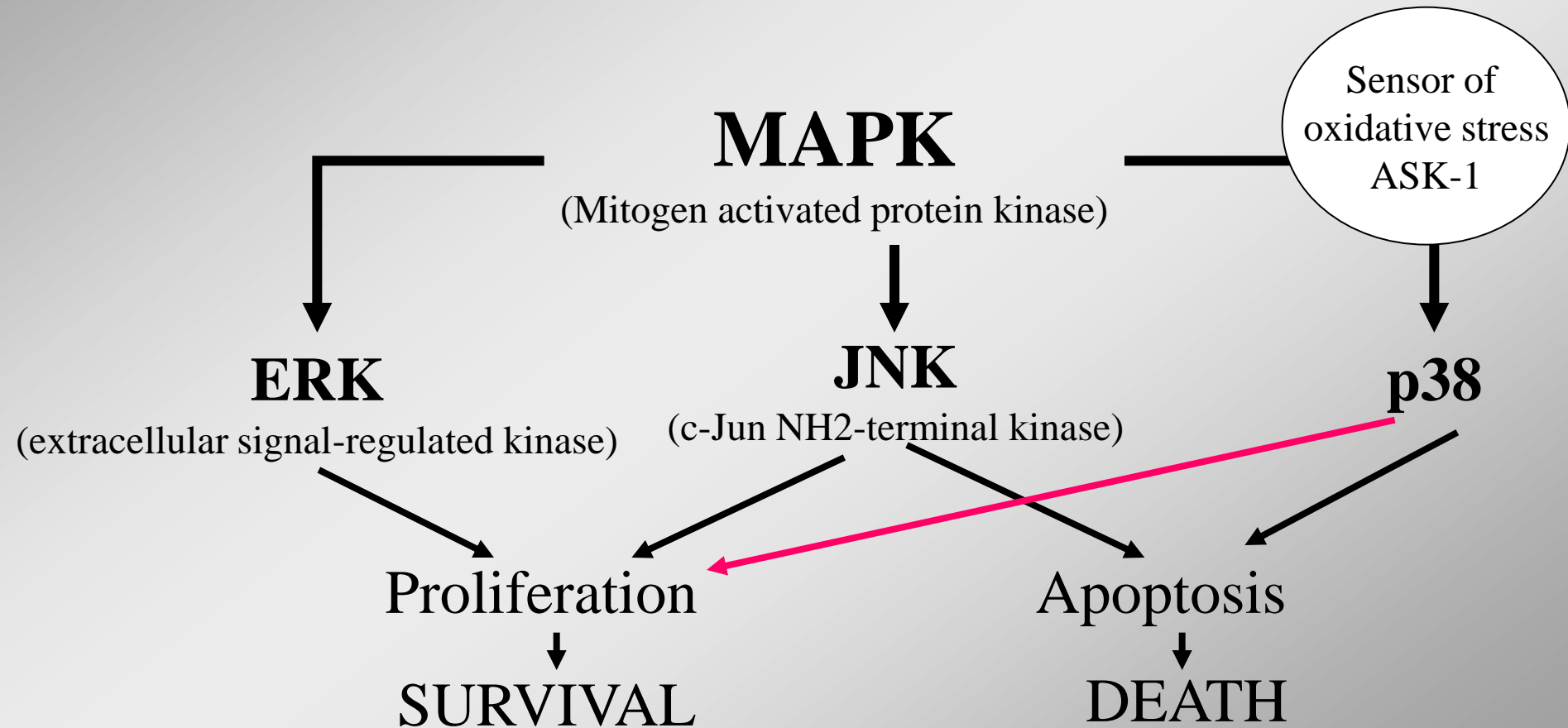


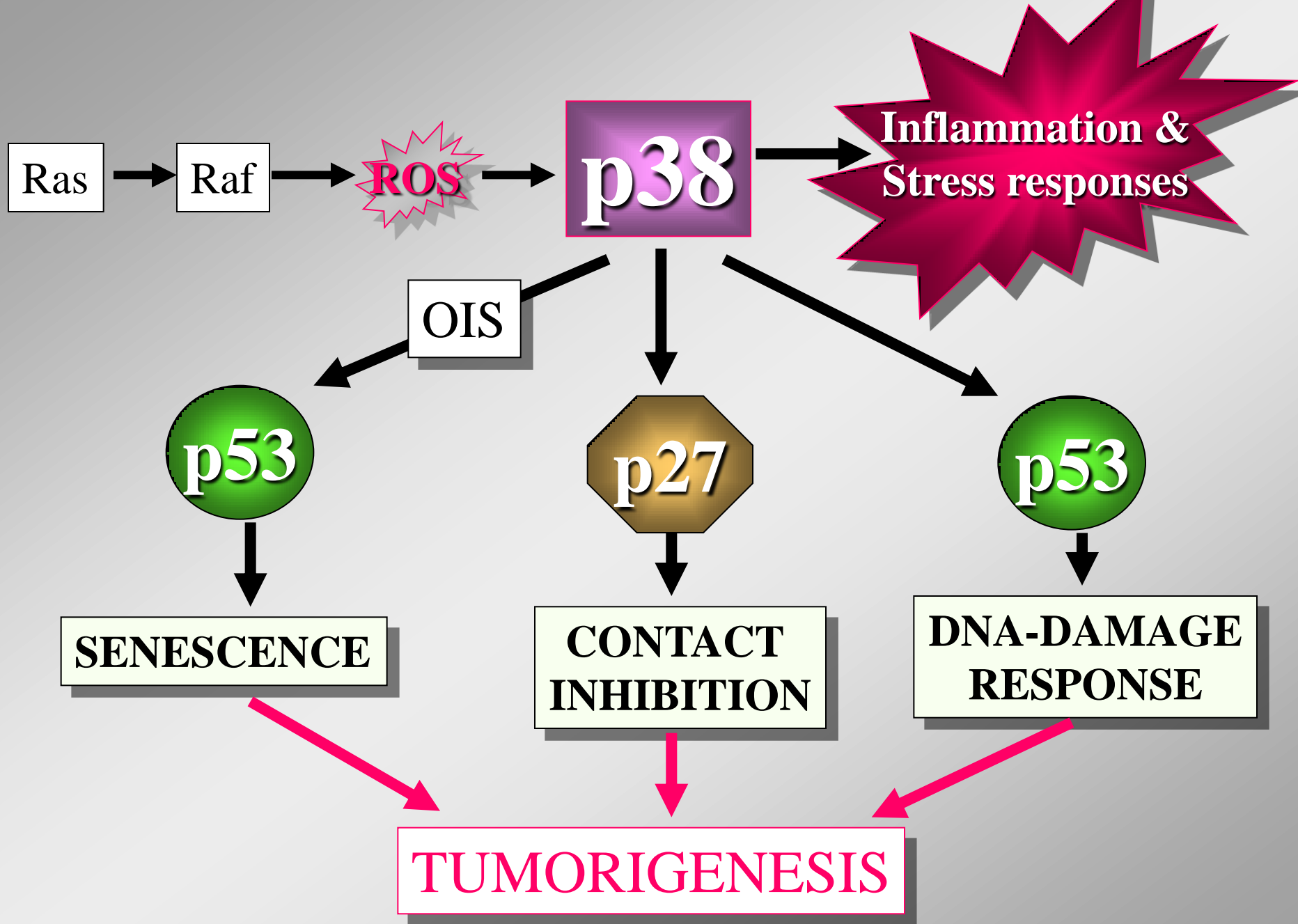
Erol A. J Alzheimers Dis 2009;Feb 16

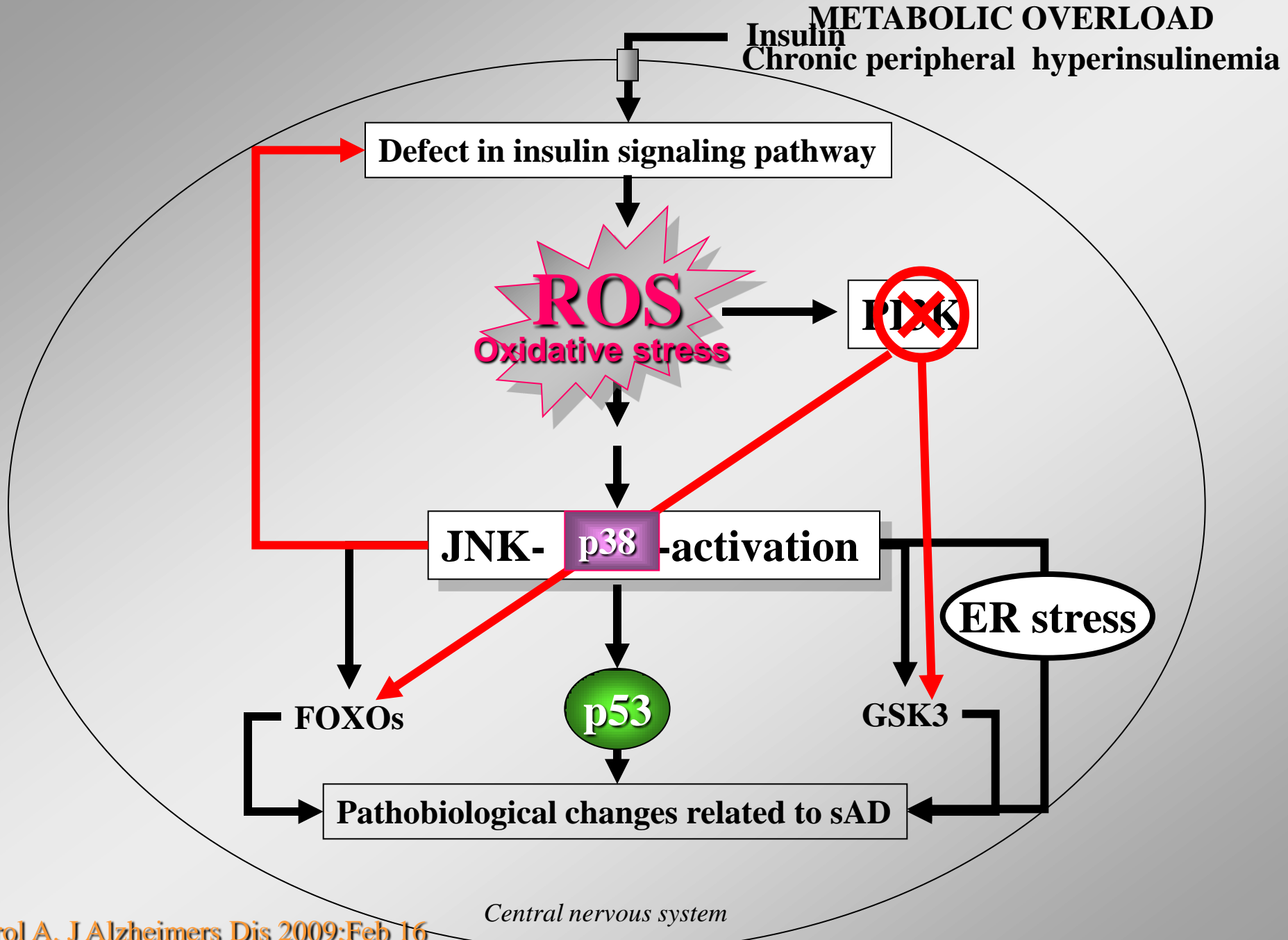
Erol A. Bioessays 2007;29:811-818

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

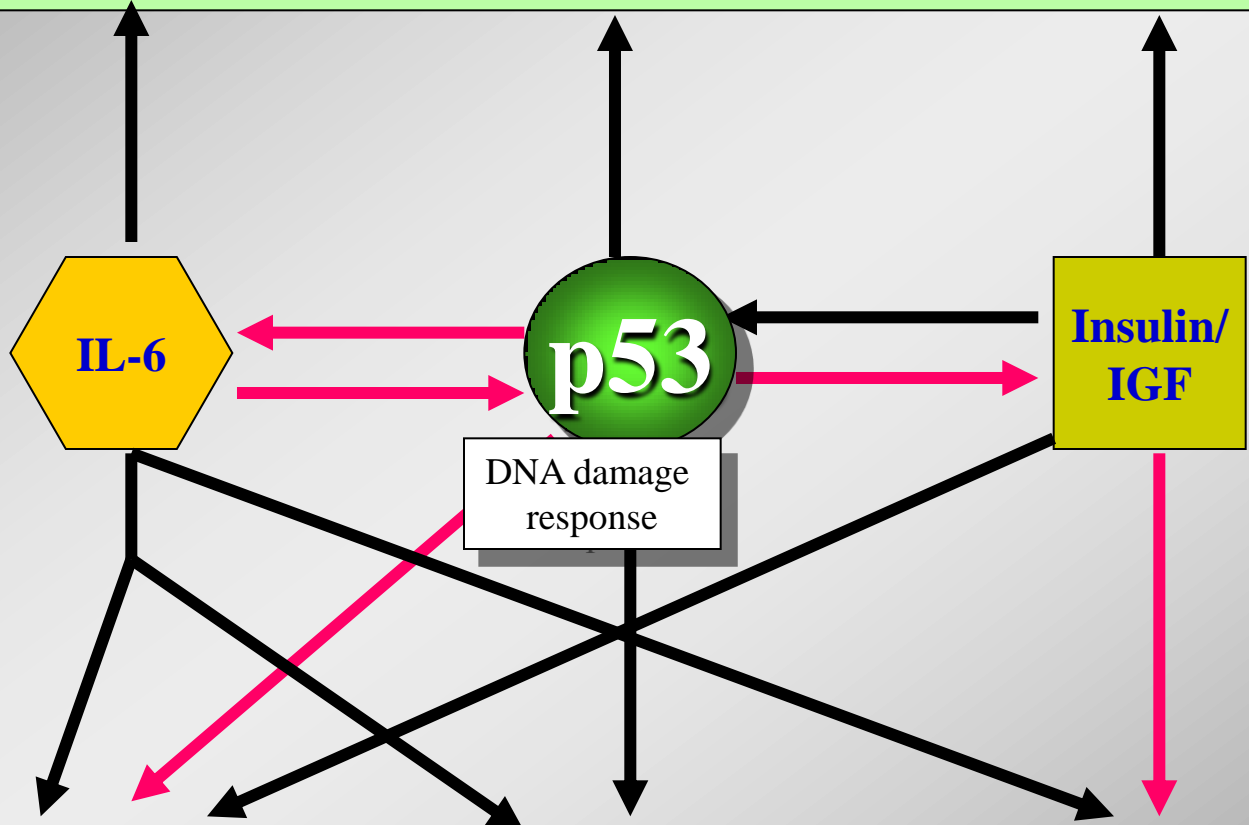
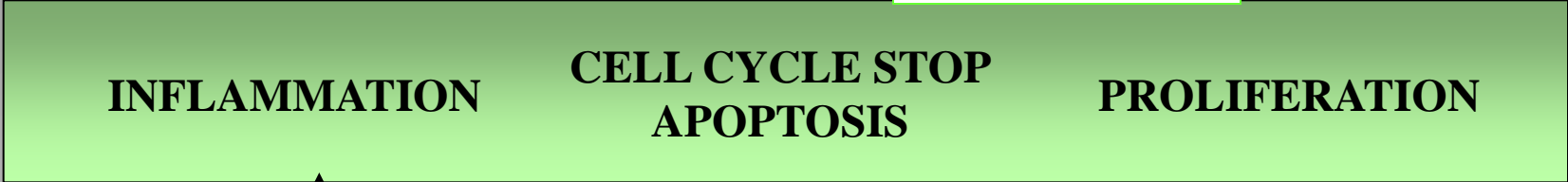






Erol A. J Alzheimers Dis 2009;Feb 16
 Smith MA, Perry G, et al. Mech Ageing Dev 2001;123-39-46

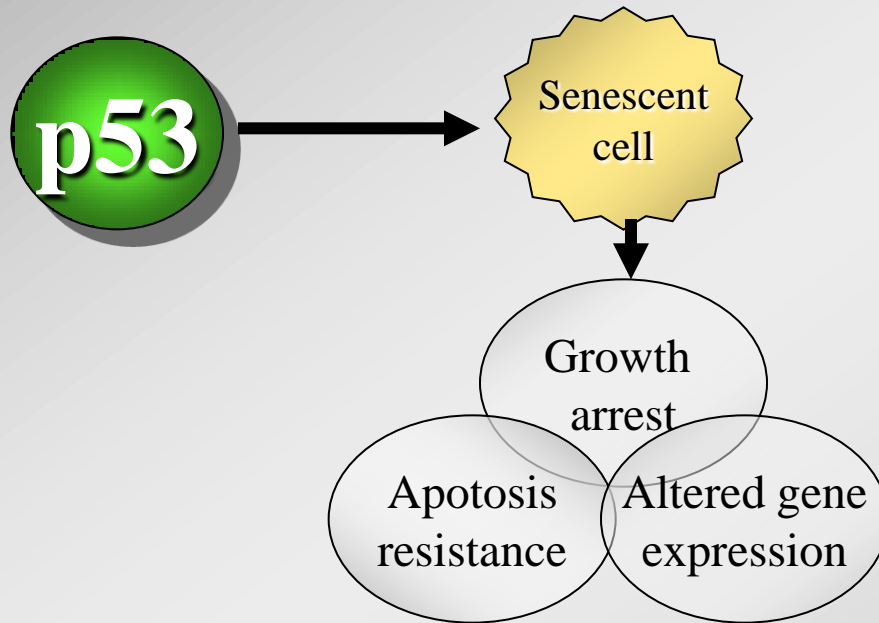
PHYSIOLOGY



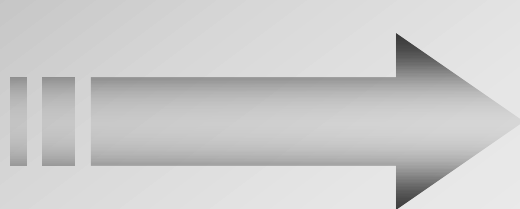
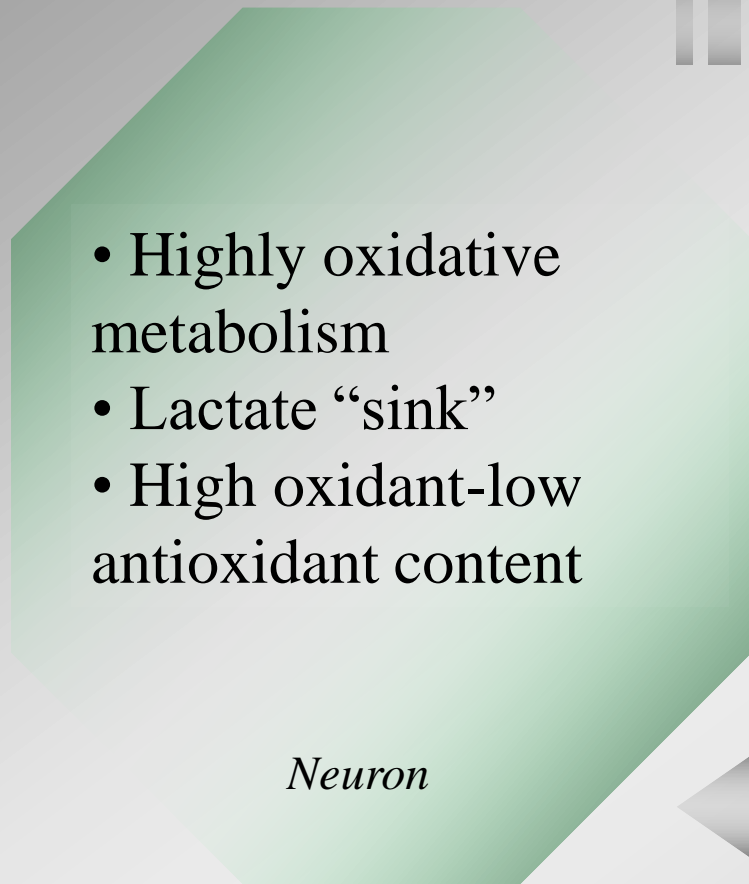
PATHOLOGY

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

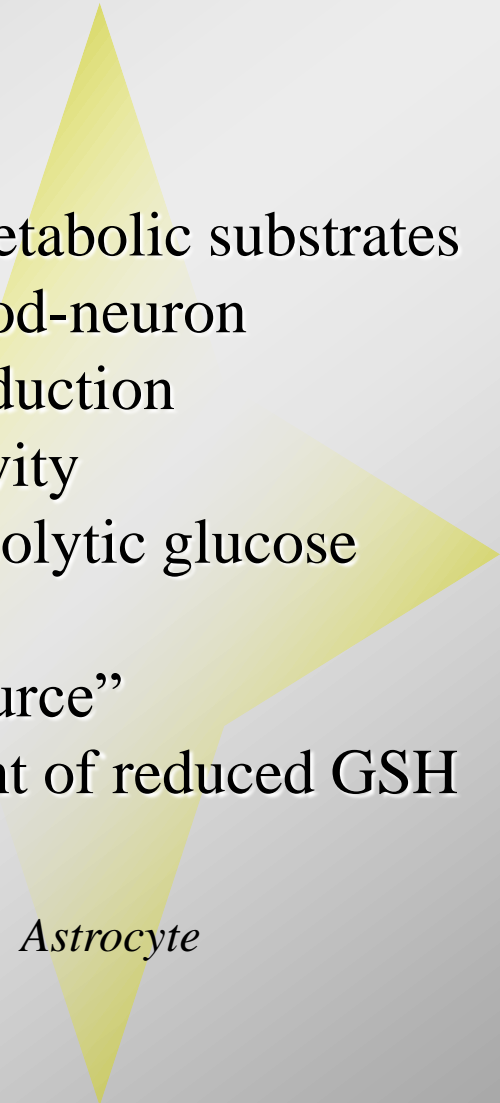
SENESCENCE
Metabolically viable cell cycle arrest
with persistent DNA damage
signaling



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



- Channel metabolic substrates between blood-neuron
- ketone production
- nNOS activity
- highly glycolytic glucose metabolism
- Lactate “source”
- High content of reduced GSH



“Cell cycle activation occurs in Alzheimer’s Brain”

Abstract: The mechanism(s) leading to widespread hyperphosphorylation 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 neuroblastoma cells that are in the M phase of cell division.

...and immunoblotting to neuroblastoma cells, the appearance of the PHF/MC phospho-epitopes coincides with activation of mitotic protein kinases with the activity of the neuronal specific cyclin-dependent kinase, cdk5. These data suggest that the phospho-epitopes are conserved mitotic phospho-epitopes produced as a result of increased mitotic kinase activity. To investigate this possibility in AD, we exam-

“Two-hit hypothesis”

First hit

- Activation of the mitotic processes
- Induction of oxidative stress

Second hit

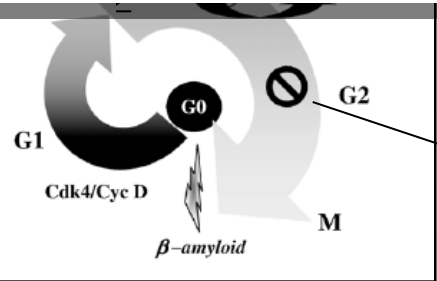
- Increased oxidative stress
- **Activation of cell cycle**

Neuronal adaptive changes

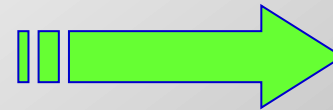
Apoptotic neuronal loss & neurodegeneration

- 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 APOPTOTIC LOSS
NEURODEGENERATION**



