The Virtual Free Radical School

Cell Signaling by Oxidants: Mitogen-Activated Protein Kinases (MAPK) and Activator Protein – 1 (AP-1)

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Cell Signaling by Oxidants

Society For Free Radical Biology and Medicine

Overview

Oxidants can modulate cell signaling events by modifying cell surface receptors, phosphatases and protein phosphorylation, *etc*. These phenomena are important in transactivation of transcription factors and activation/inactivation of gene transcription that may regulate steps in the development of disease. At least two classical signaling pathways, the Mitogen-Activated Protein Kinases (MAPK) and signaling leading to activation of NF-κB, are activated by oxidants. Physiological oxidant stresses, such as asbestos, induce primarily the extracellular signal-regulated kinases (ERKs) whereas H_2O_2 causes activation of all three MAPK cascades. A consequence of MAPK activation is formation of Activator Protein–1 (AP-1), which binds to the promoter regions of intermediate response genes governing cell proliferation, differentiation, *etc*.

Importance of Cell Signaling in the Development of Proliferative Diseases such as Cancer or Fibrosis

Cell Signaling → (In)Activation of Gene Transcription →

Gene Product → Biological Effect → Disease

- Protein
- Transcription Factor

- Cell Proliferation
- Cell Transformation
- Cell Death/Apoptosis

Two Classical Signaling Pathways/Transcription Factors are Associated with Exposure to Oxidants:

- MAPK/AP-1 (Activator Protein-1)

Proliferation

Survival

Apoptosis/Death

- NF-κB * (Nuclear Factor – κB)

Inflammation

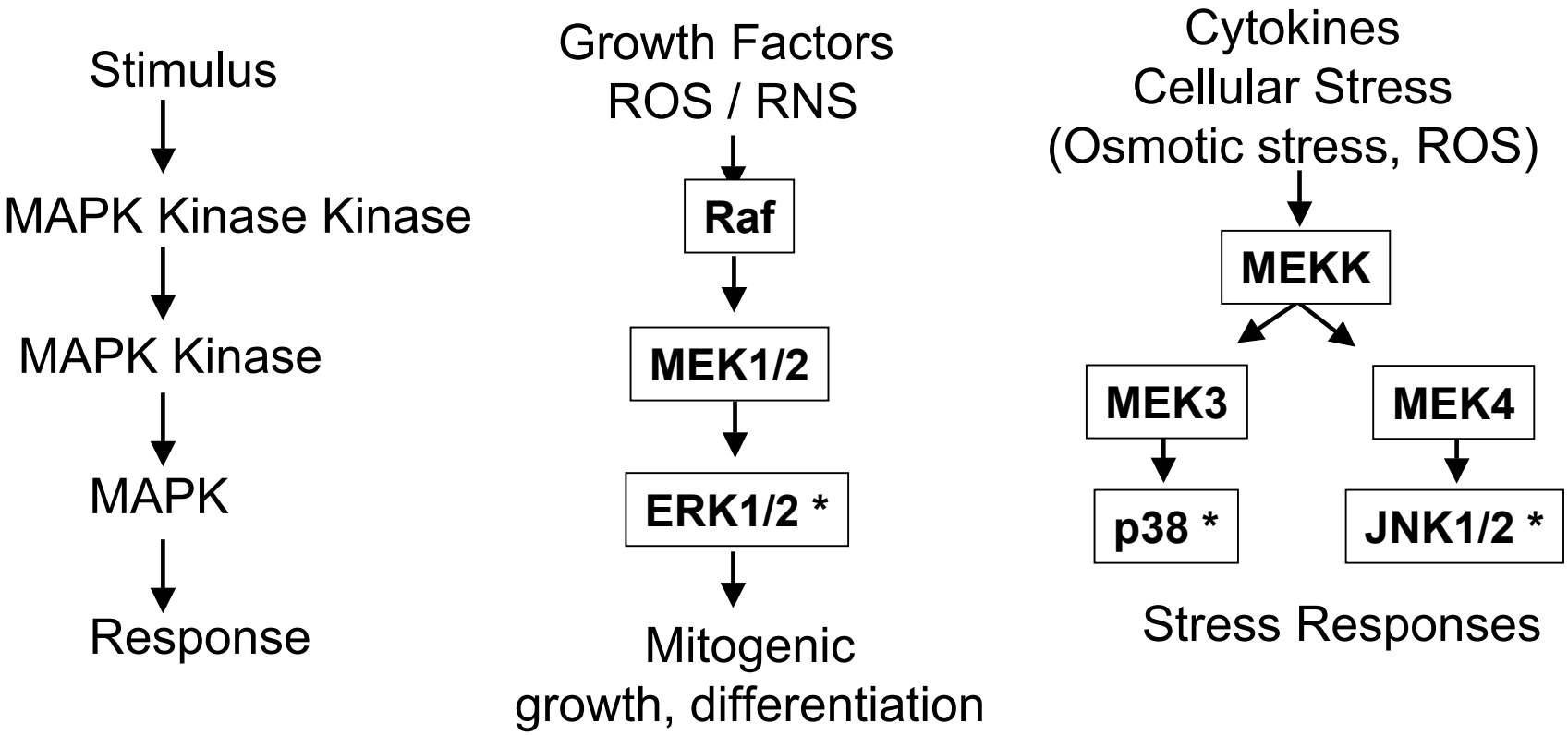
Survival

Cell Cycle Control

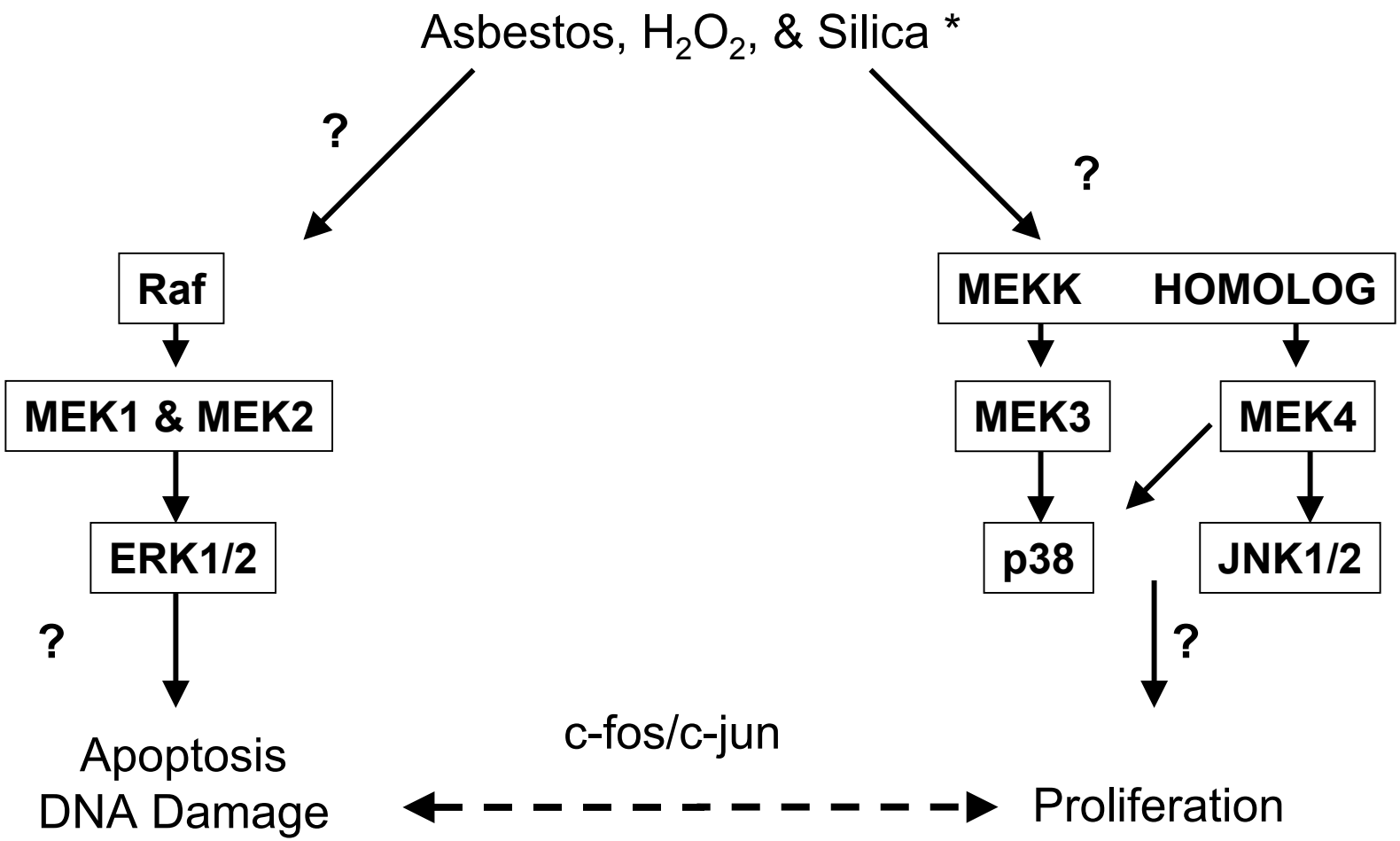
* See Janssen-Heininger *et al., Free Rad. Biol. Med*. 28: 1317 – 27, 2000.

General Schema for Mitogen-Activated Protein Kinase (MAPK) Cascade

* ERK=Extracellular Signal-Regulated Kinase
* JNK=c-Jun N-terminal Kinase
* p38

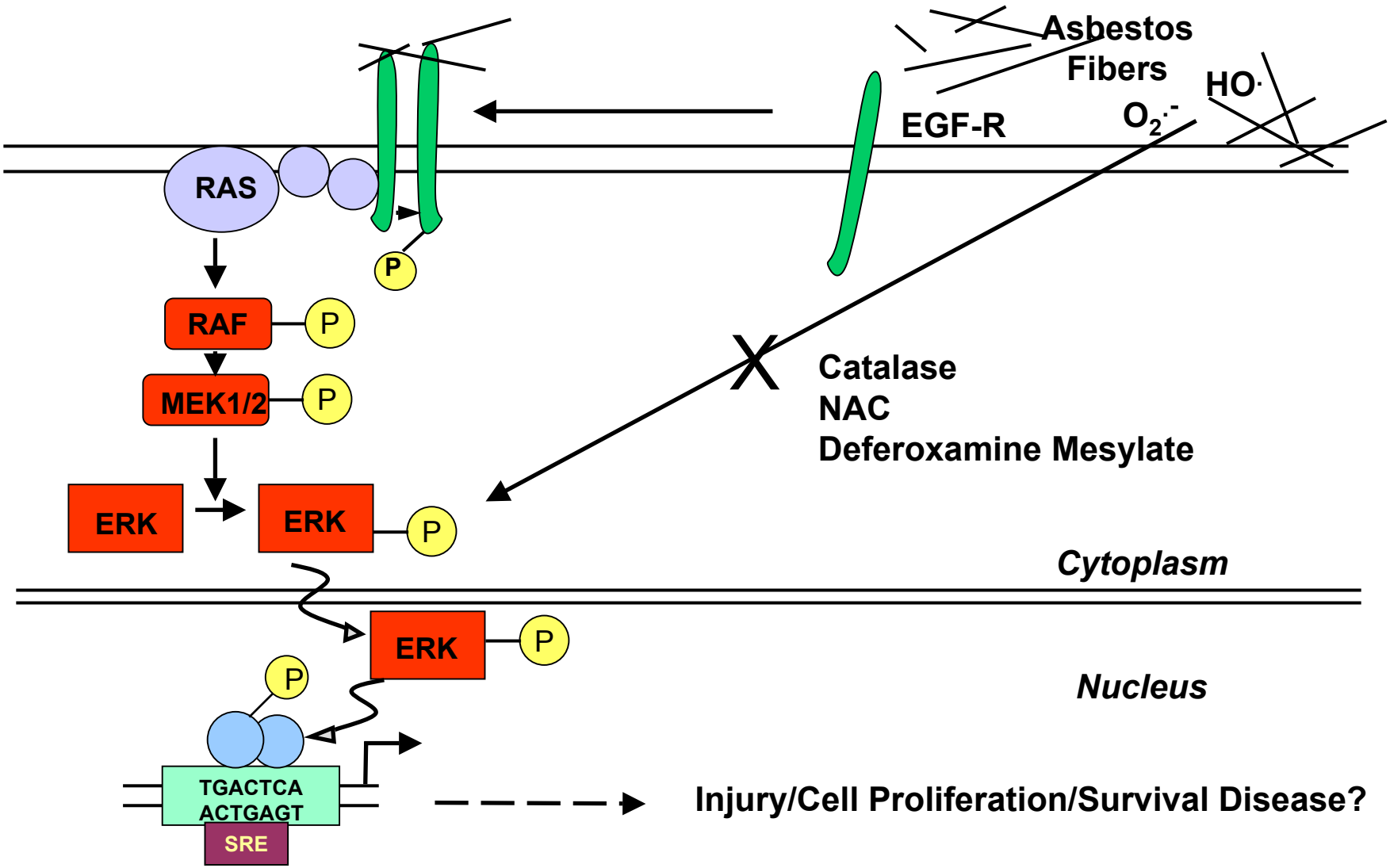


ROS - Induced Mitogen-Activated Protein Kinase (MAPK) Cascade



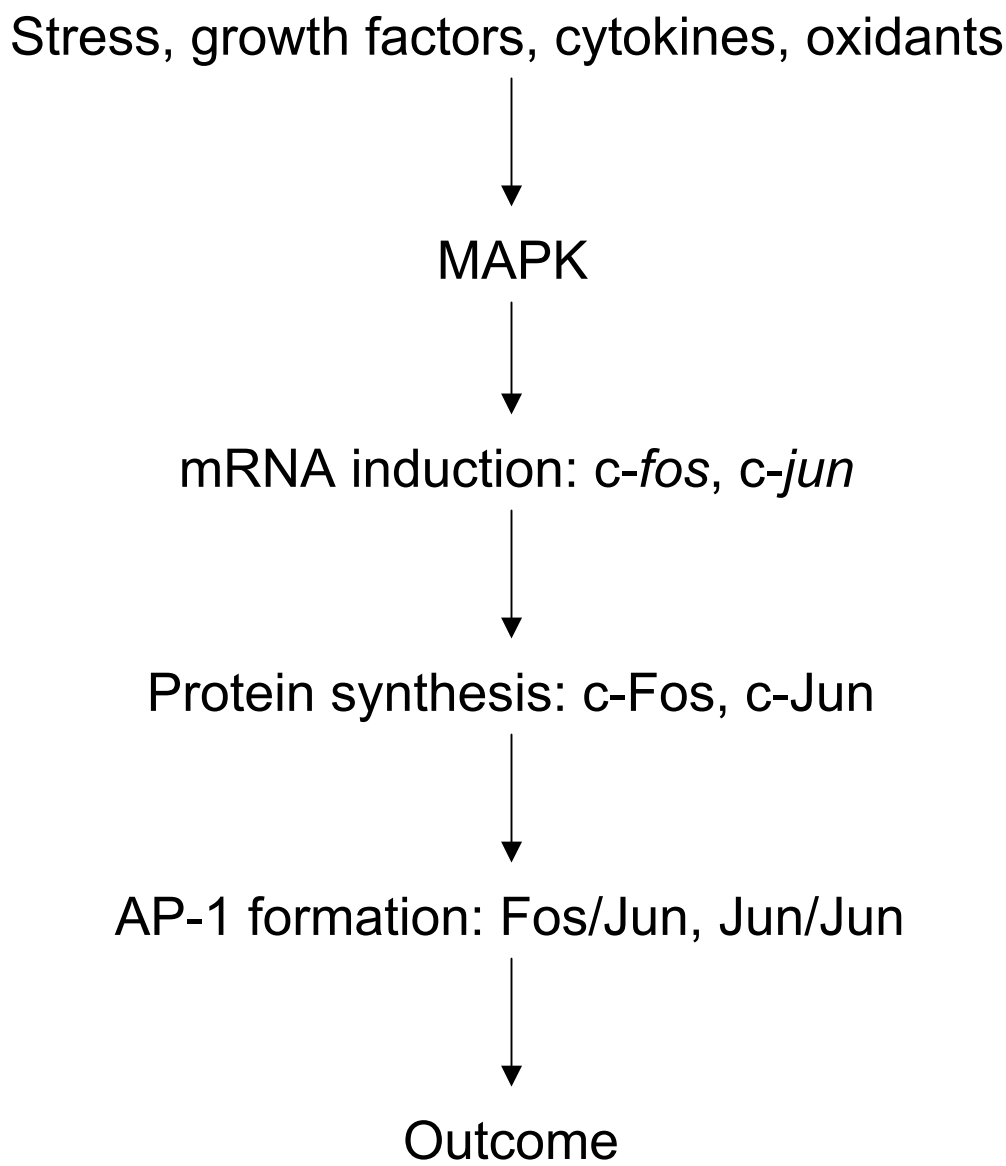
* See Ramos *et al., Molec. Cell. Biochem*. 234/235: 111-115, 2002

ROS-Induced Stimulation of Extracellular Signal Regulated Kinases (ERK1/2)

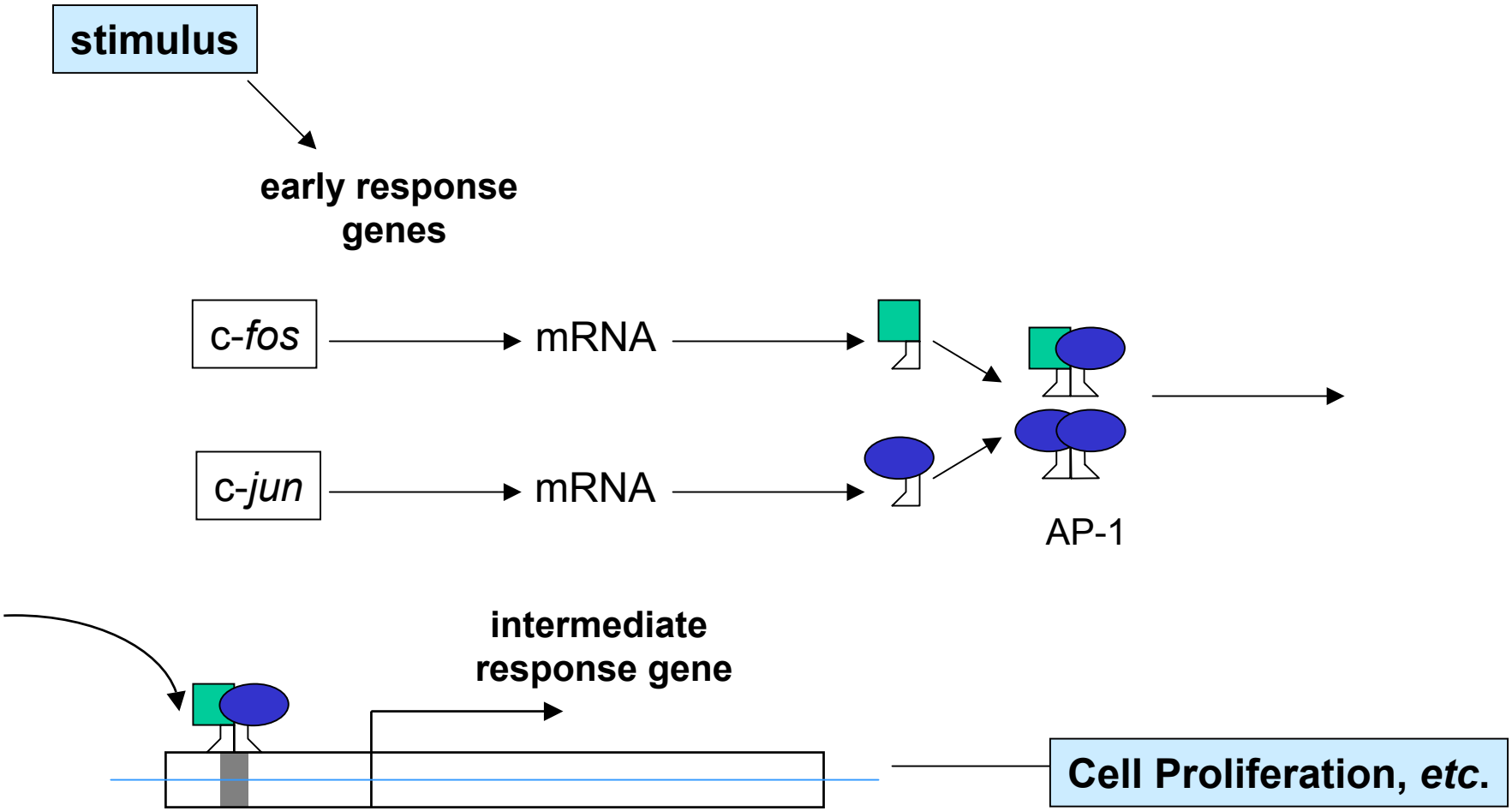


The ERK family (at least 8 isoforms) are typically activated in a series of protein phosphorylation events after phosphorylation of cell surface receptors (*i.e.* the epidermal growth factor receptor (EGFR) or other extracellular signals. Phosphorylated members of the ERK family then function to transcriptionally regulate specific subsets of genes. For example, phosphorylated ERK2 translocates to the nucleus to phosphorylate ternary complex factor (TCF) which finds to the serum response element (SRE) of c-fos.

Relationships between MAPK Activation and AP-1



Formation of Activator Protein–1 (AP-1)



Summary

- Oxidants can induce MAPK.

- The MAPKs family includes extracellular signal-regulated kinases (ERKs), which are generally activated by mitogens, and c-Jun NH_2 – terminal kinase (JNKs) and p38 MAPKs, both activated by cytokines and cellular stresses.

- Upon activation, JNKs and ERKs phosphorylate Jun and Fos proteins, *i.e.* AP-1 family members. Although p38 MAPKs do not activate AP-1 proteins directly, they can regulate jun and fos transcription by phosphorylating enhancer binding proteins (C/EBPs) binding to their promoter elements.

- By selective dimerization of AP-1 family members (Jun/Jun or Fos/Jun partners) and diverse binding specificities with the promoter regions of genes, the AP-1 transcription factor regulates gene expression important in cell injury, repair, proliferation, and differentiation.