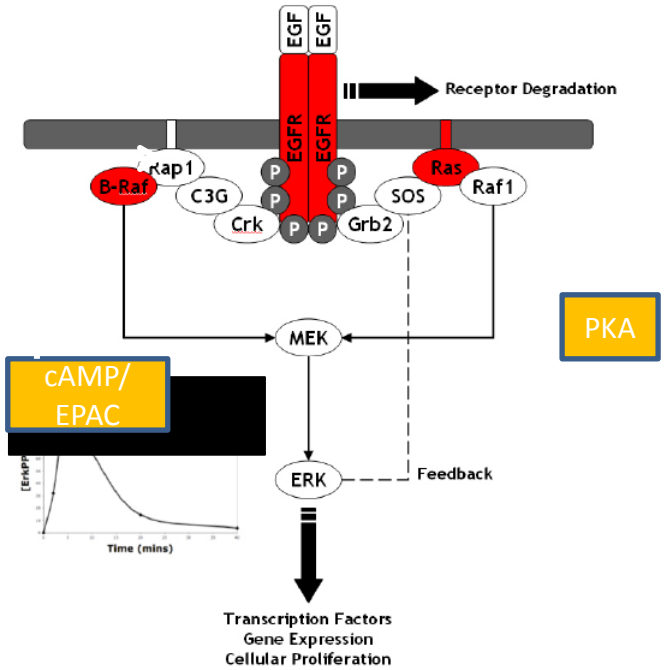
Introduction to Systems Biology
Lecture 3 - Part A-1

Iyengar

Bottom-up Approaches : Pathways to Networks : the MAP-kinase pathways/network



PKA

Pathways become networks when components of one pathway interact with and regulate components of another pathway

Example: interactions between the cAMP and MAPK pathways

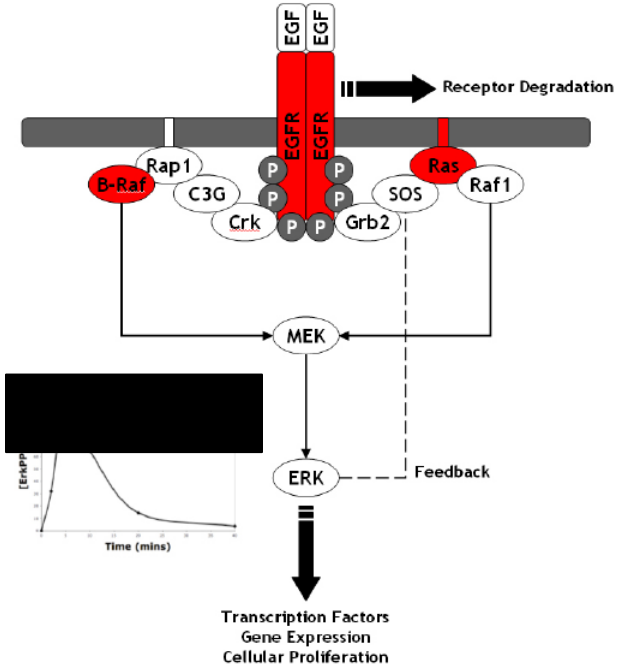
cAMP through the GEF called EPAC activates the GTPase Rap

PKA phosphorylates and inhibits the protein kinase Raf 1

Adapted from Orton RJ et al *BMC Syst Biol.* 3:100 (2009)

Introduction to Systems Biology
Lecture 3- Part A-2

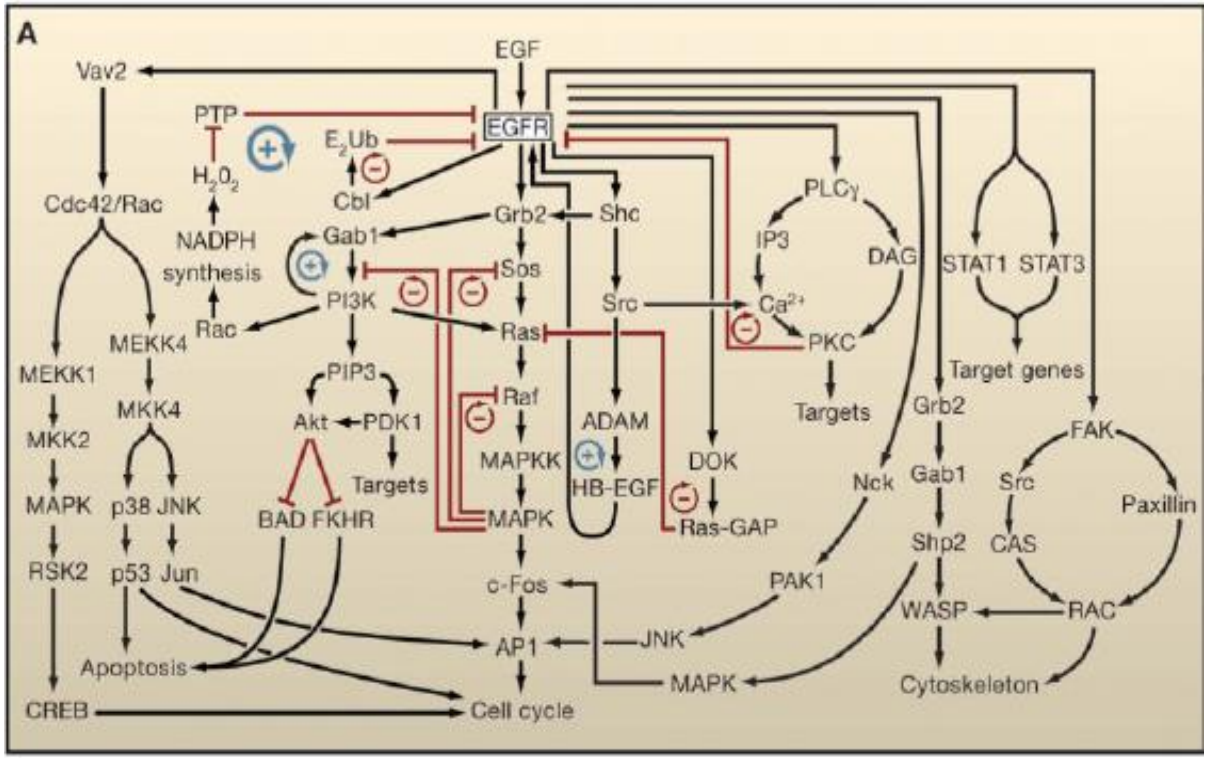
Iyengar



Orton RJ et al *BMC Syst Biol.* 3:100 (2009)

Assembling Signaling Complexes:
Adaptors such as Grb2 and Crk, and exchange factors (GEFs) such as SOS and C3G are assembled as extracellular signals such as epidermal growth factor (EGF) arrive to enable the receptor that activates the GTPases Ras or Rap

The adaptors and some GEFs use specific domains, called SH2 or SH3 domains, to achieve desired connectivity



A large network can emanate from a single receptor

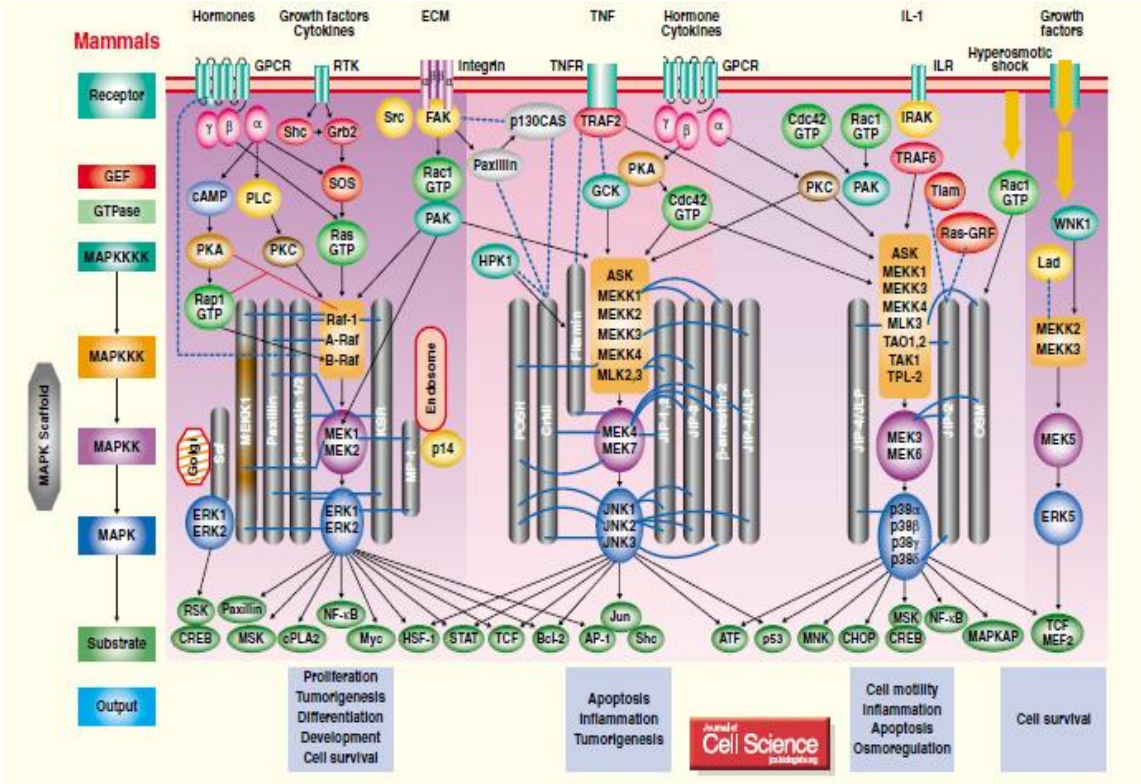
EGFR interacts with multiple effectors to engage an extensive network

Please note that MAPK pathway has been drawn twice in this cartoon – for visual clarity
MAPKK(2) and MKK2 are the the same.

Lemmon and Schlessinger *Cell* 141(7):1117-34 (2010)

Introduction to Systems Biology
Lecture 3- Part A-4

Iyengar



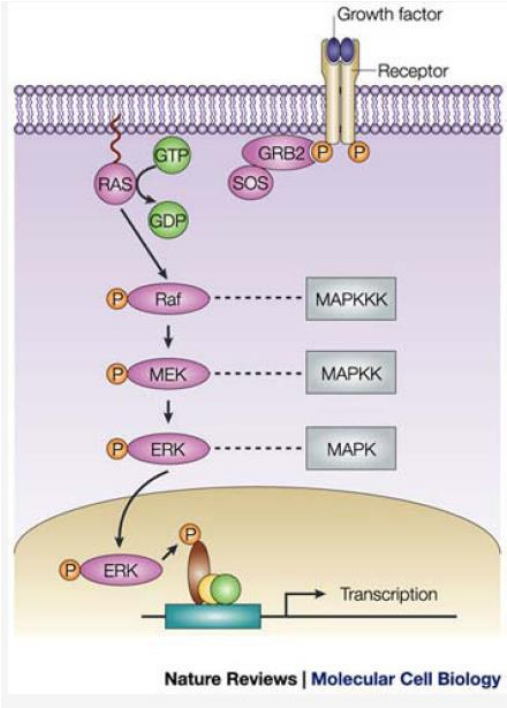
There are 3 major MAPK pathways : ERK, JNK and p38.

At the core of each pathway there are 3 protein kinases (MAPKKK, MAPKK and MAPKs) that through sequential phosphorylation transmit information
Some times there are additional protein kinases above and below this core .

Note the considerable interconnectedness

Qi and Elion *J Cell Science* 118: 3569-72 (2005)

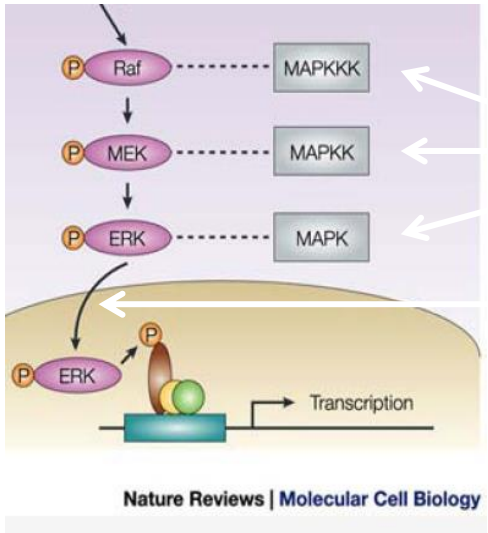
Growth factor signaling from cell surface membrane to nucleus



Information flow involves 3 cellular compartments:
Plasma membrane
Cytoplasm
Nucleus

Mathematical models often need to deal with specification of where the reactions occur, when biochemical reactions are represented as coupled differential equations

Kim & Bar Sagi *Nat Rev Mol Cell Biol*. 5(6):441-50 (2004)



Kim & Bar Sagi *Nat Rev Mol Cell Biol*. 5(6):441-50 (2004)

Representing space in mathematical models

Compartmental Models
Biochemical reactions within a compartment are represented as groups of ODEs.

Components that move between compartments have a rate associated with the movement and there is mass conservation between compartments

Partial Differential Equations (PDEs)
Based on Fick's laws of diffusion PDEs can explicitly compute both change in concentration and change in location of reactants and products