Introduction to Systems Biology
Lecture 3 Part B -1

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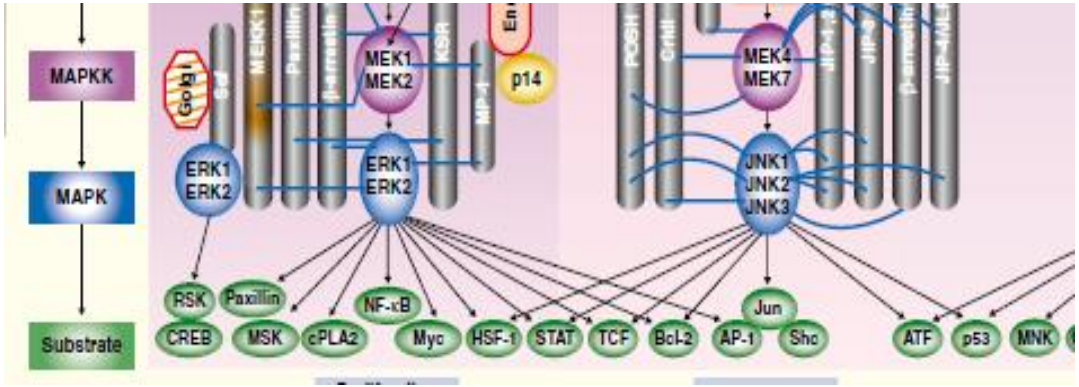
Connecting Pathways to form Networks

Signaling proteins with mutual chemical specificity due to secondary and tertiary structure enable connectivity

bidirectional specificity -- needed for formation of pathways

cross pathway specificity -- enables networking



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

Introduction to Systems Biology
Lecture 3 Part B -2

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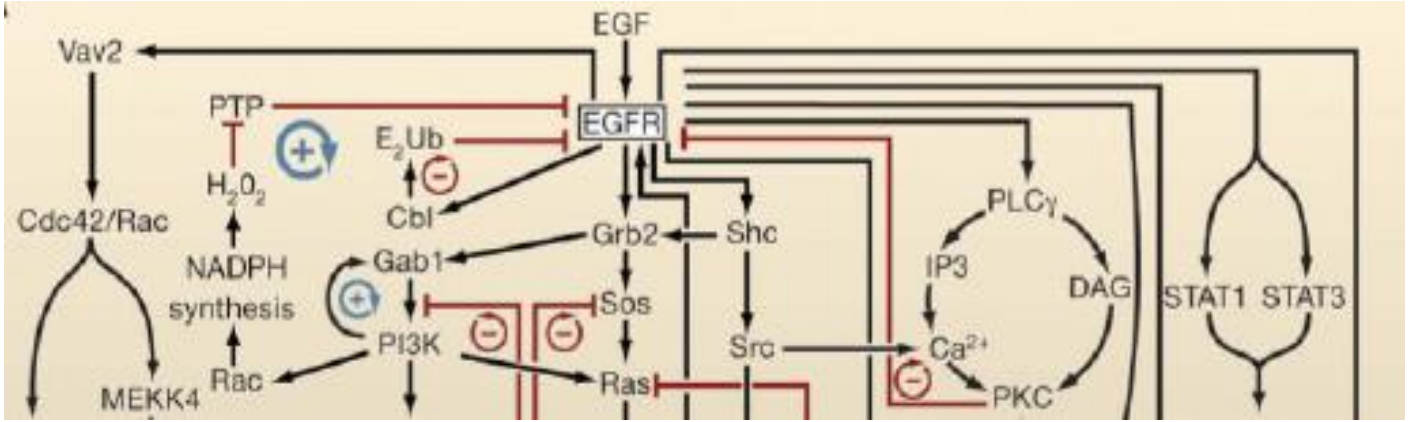
For many growth factor receptors like EGFR (epidermal growth factor receptor)
The ability to interact with multiple effectors Grb2/SOS/RAS, PI3Kinase, PLCγ, STATs
allow the receptor to regulate a large network of effectors



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

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Lecture 3 Part B -3

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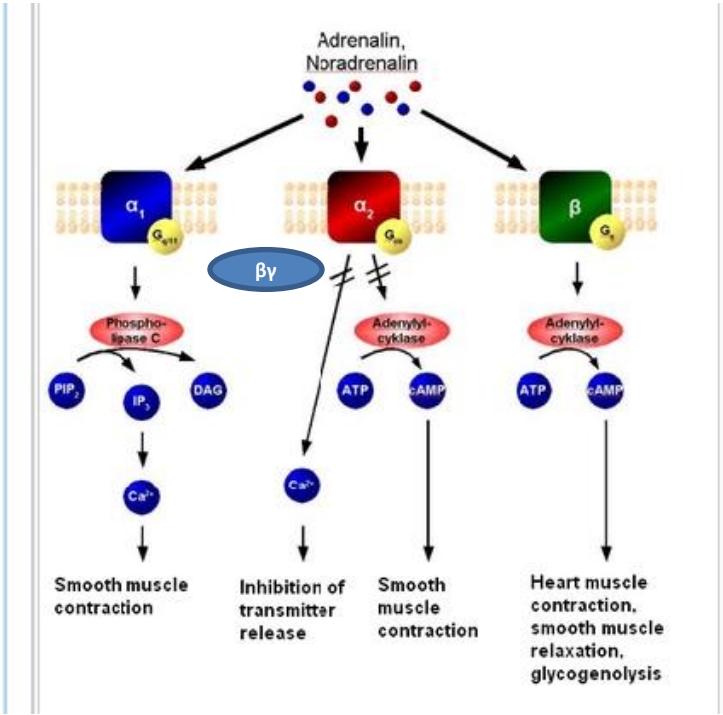

From Wikipedia - Adrenergic Receptor

Epinephrine & Norepinephrine
(Adrenaline and Noradrenaline)
can couple through
α_1- adrenergic receptors to G_q
α_2 – adrenergic receptors to $G_{i/o}$
β – adrenergic receptor to G_s
Leading to activation of
different pathways

Norepinephrine is largely in the brain and
epinephrine is in the periphery ,
and each type of receptor has several isoforms such as
β1 and β2 adrenergic receptors that have different affinities
for epinephrine and norepinephrine
(more details and more complexity)

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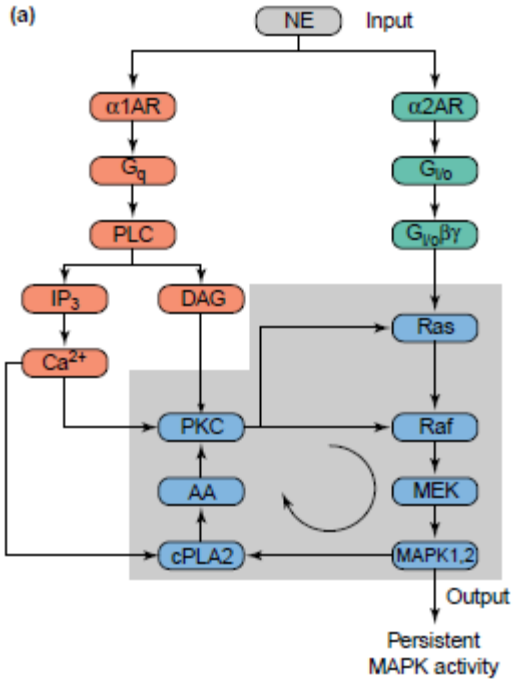

A single ligand (hormone) through multiple receptors can engage a network due to cross connectivity

Eungdamrong and Iyengar *Trends Cell Biol.* 14(12):661-9 (2004)

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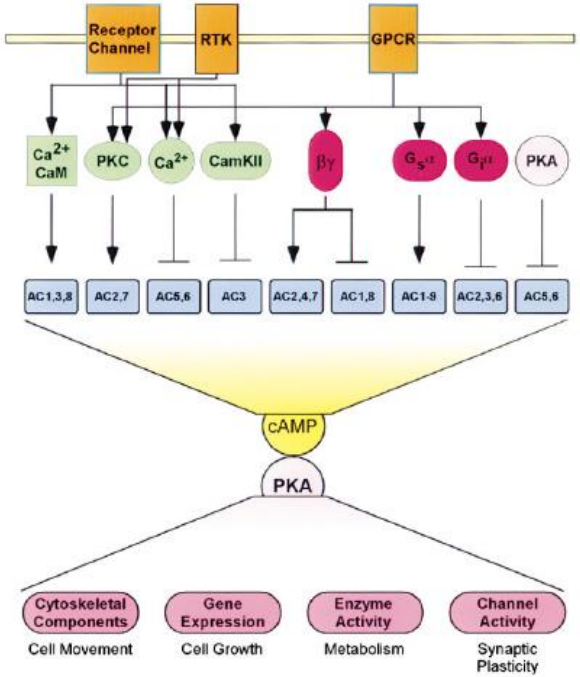

Isoforms of signaling components such as the different isoforms of mammalian adenylyl cyclases enable networking through mix and match connectivity

Note the *bowtie configuration* of the network through cAMP/PKA

Jordan, Landau, Iyengar *Cell* 103(2):193-200 (2000)

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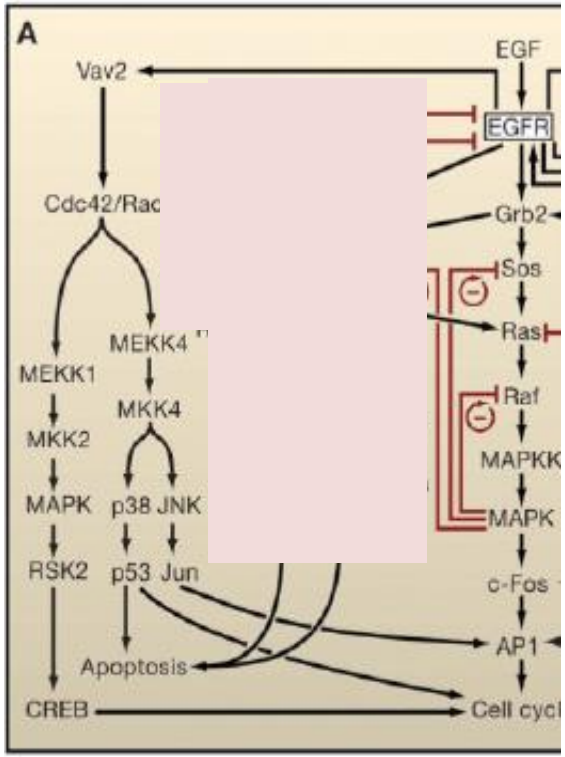

Small GTPases enable networking by acting through multiple pathways reach different effectors

Through MEKK 1 or MEKK4, Cdc42 can activate the transcription factors CREB or Jun and both CdC42 and Ras can through different paths activate the transcription factor AP1

Please note that the MAPK pathway is shown twice just for visual clarity-they are the same pathway and same components (MKK2 is MAPKK) and MAPK is also called MAPK1,2 and ERK1,2

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

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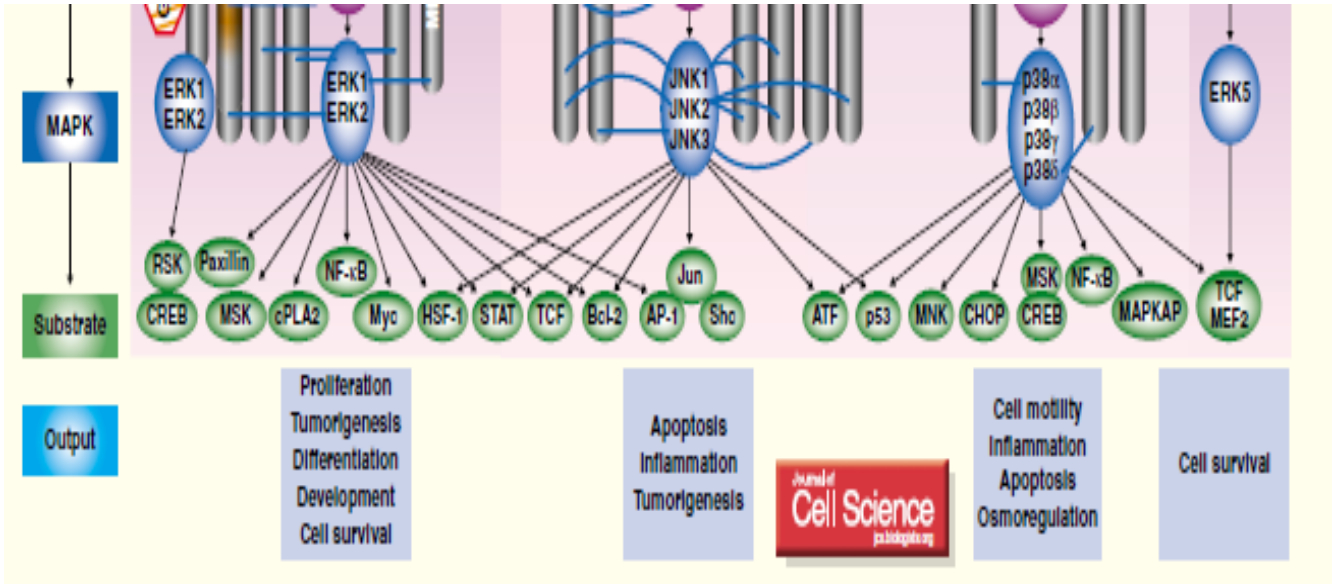
The ability of a protein kinase to phosphorylate many substrates, such as transcription factors, leads to cross–connectivity that creates extensive networking



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

Lecture 3 – Take Home Points

- Receptors as well as intracellular signaling components enable networking between signaling pathways
- Pathways arise due to the bidirectional biochemical specificity of signaling components
- Networks arise from the ability of components of one signaling pathway to selectively interact with and regulate components of another pathway