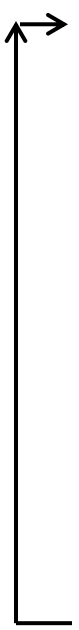
General Organization of the heterotrimeric G protein pathways



Receptors > 1000

G proteins [αβγ] (4 of classes of α subunits)
α subunits define receptor specificity and often also effector specificity

Effectors - Enzymes, Channels, or Regulators of small GTPases

Intracellular Second Messengers
cAMP, IP_3 , DAG

Protein Kinases PKA, PKC, PKB, CaMKII

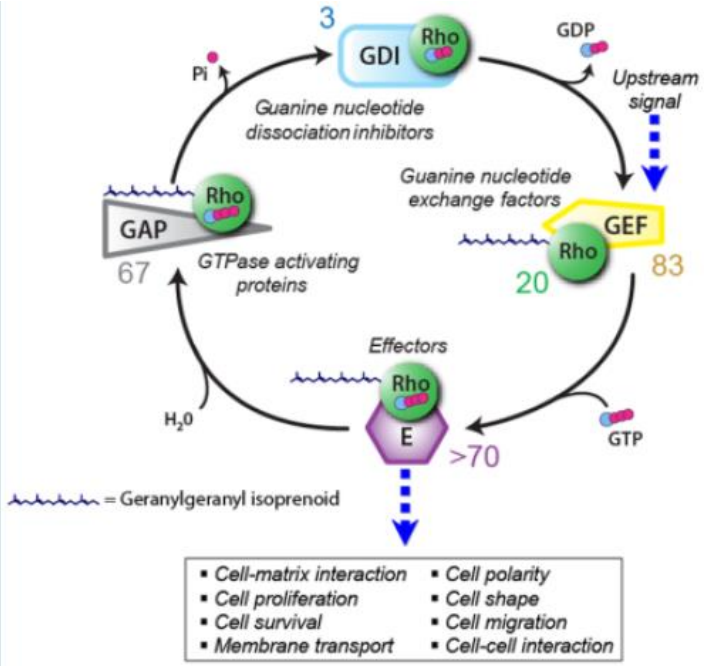
Physiological Effectors
Transcription factors, metabolic enzymes

Receptors activate G proteins by catalyzing the exchange of GDP for GTP on α subunits

Even in linear pathways there are feedback loops

Introduction to Systems Biology
Lecture 2 - Part B-2

Iyengar

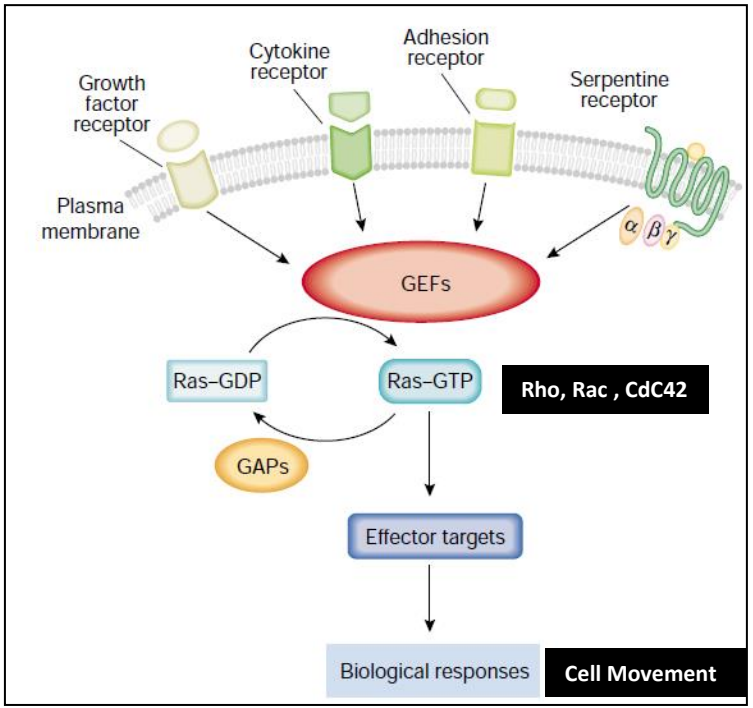


The small GTPases (21-28 kDa) another class of signal transducers that are active when GTP is bound and inactive when GDP is bound

Vigil D et al *Nat. Rev Cancer* 10(12):842-57 (2010)

Introduction to Systems Biology
Lecture 2 - Part B-3

Iyengar



Many **receptors**
Many **GEFS** and **GAPS**
Many **GTPases**
Many **protein kinases**
Interconnections go to form an extensive network

More about networks in the next lecture
Now let us focus on **Receptors** -- *Major Drug Targets*

Zheng and Quilliam *EMBO Reports* 4(5):463-8 (2003)

Receptor ligands are widely used drugs

Agonists - specifically binds to receptor and initiates action
Antagonists - specifically binds to receptors – but does not initiate action
blocks the effects of agonists in disease – generally the deleterious effects

Insulin - Natural hormone Insulin receptor agonist - peptide –
mostly used to treat Type 1 Diabetes , sometimes Type2 as well

Propranolol - β adrenergic receptor antagonist – among the first antihypertensives
Cimitedine - H2 histamine receptor antagonist – blocks acid secretion
(small chemicals)

Trastuzumab - antibody antagonist against ERBB2 –
receptor used to treat certain breast cancers

Mathematical Representations of Drug Actions

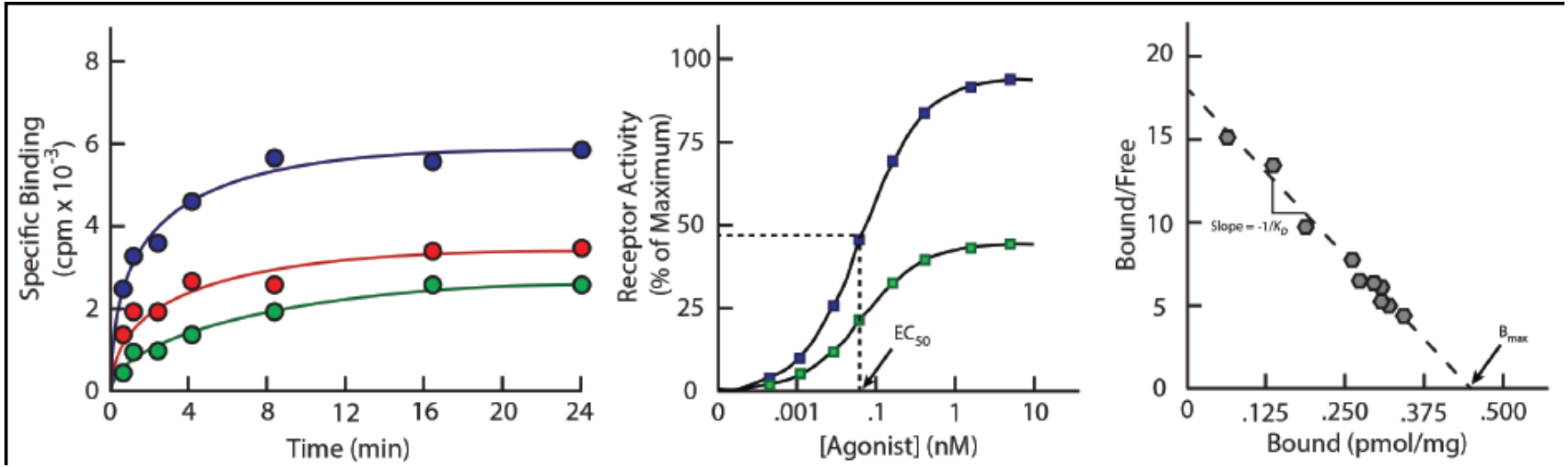
Understanding the competition between
the antagonist drug and the natural ligand (agonists)
is critical for developing potent drugs

$$[IR]+[L] \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} [L]+[R]+[I] \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} [LR]+[I]$$

$$[LR]=\frac{[R]_{TOTAL}[L]}{[L]+K_D+\frac{K_D}{K_I}[I]}$$

I - Inhibitor (antagonist)
L - ligand (agonist)

Level of [LR] determines the extent of the
physiological (or pathophysiological) response



Plots of data from ligand-receptor interaction experiments

Left - different concentrations of radioactively labeled ligand or a fixed concentration of radioactive ligand and varying concentrations of a competing drug are tested for binding

Middle - Semi-log plot of Receptor Activity (Receptor bound to agonist) as a function of agonist concentration The agonist concentration corresponding to 50% activity is called EC_{50}

Right – Scatchard Plot - a linear transformation plot. Slope is $-1/K_D$ where K_D is the affinity constant (dissociation constant) and intercept on abscissa is total receptor concentration

Lecture 2 – Take Home Points

- Signaling pathways receive information from outside the cell and change cellular physiology in response to this information

- Signaling pathways contain many components each of which receive and transmit information with bi-directional specificity

- Information flow through signaling pathways can be studied mathematically using ordinary differential equations

- Receptors, are targets of drugs used to treat various diseases