

Unit 2: Cell Signaling

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2.1 Intercellular signaling: how cells talk to each other

A multicellular organism is a conversation. **Intercellular signaling** is classified by the distance the message travels:

Mode	Distance	Examples
Endocrine	Long, carried in the blood	Insulin, thyroid hormone, cortisol reaching distant organs
Paracrine	Short, to neighbouring cells	Histamine, prostaglandins, growth factors in a wound
Autocrine	The cell signals itself	Growth factors secreted by tumour cells that feed their own growth
Juxtacrine	Direct contact, membrane bound signal	Notch signaling between adjacent cells in development
Synaptic	Across a specialised junction, very fast	Neurotransmitters at nerve terminals

The signal molecule, the **first messenger**, may be a hormone, neurotransmitter, cytokine, growth factor, gas (nitric oxide) or even a photon or ion flux; what matters is that a receptor exists to read it. Hydrophilic messengers cannot cross the membrane and bind receptors on the cell surface; lipophilic messengers (steroid and thyroid hormones, vitamin D) cross and bind intracellular receptors. That single chemical fact organises the whole of the next four sections.

2.2 Intracellular signaling: the logic of the pathway

Once a surface receptor is occupied, the message must be converted into action inside the cell: **intracellular signaling**, or signal transduction. Nearly every pathway is built from the same kit of parts. The receptor acts as a **transducer**, changing shape to activate intracellular proteins. **Second messengers** are small diffusible molecules that spread the signal through the cytosol and **amplify** it: each enzyme in a cascade activates many molecules of the next, so a handful of hormone molecules can release millions of product molecules, the classic example being adrenaline mobilising glucose from glycogen. **Effector proteins**, most often protein kinases that phosphorylate targets and phosphatases that reverse them, change the activity of enzymes, channels and transcription factors, producing the cellular response. Signaling is also actively **terminated**: messengers are destroyed, receptors are desensitised and internalised, and phosphatases reset the switches. Loss of termination is disease (cholera toxin locks a G protein on, section 2.8), and most pathway drugs work by pressing on an accelerator or restoring a brake.

Intracellular Signaling: The Universal Plan

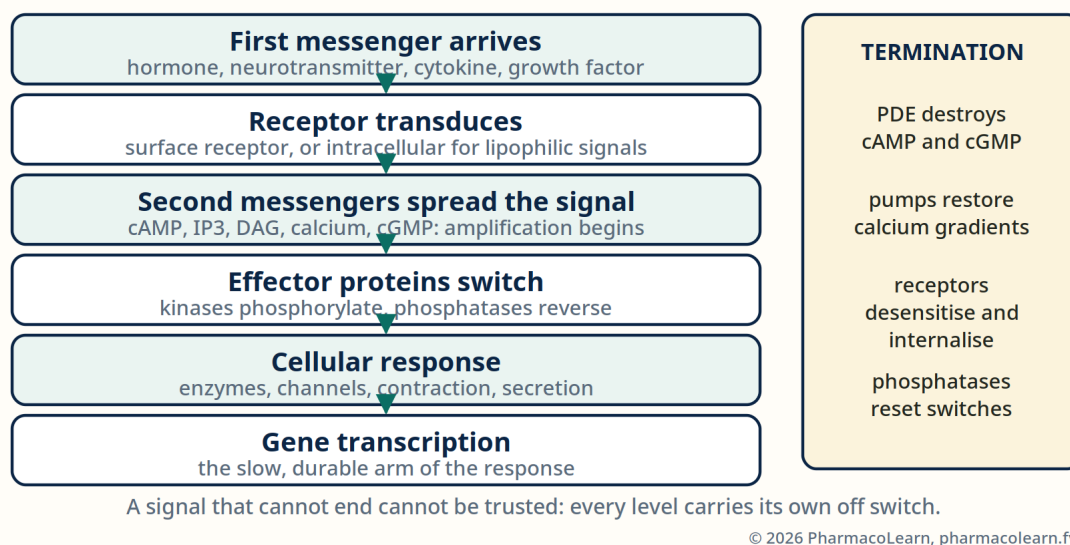


Figure: The universal plan of intracellular signaling. Receptor, transducer, second messenger, effector, response, and the off switches without which no signal can be trusted.

2.3 Ligand gated ion channels: molecular structure

Ligand gated ion channels are receptors that are themselves channels: ligand binding opens a pore and ions flow within microseconds, making these the fastest receptors in the body. The best understood family, the pentameric or Cys loop receptors, assembles **five subunits** around a central pore. The muscle type **nicotinic acetylcholine receptor** carries two alpha subunits (which bind acetylcholine) with beta, gamma or epsilon and delta subunits; opening lets sodium and potassium pass and depolarises the muscle fibre. The same architecture serves the inhibitory GABA-A and glycine receptors (chloride channels, targets of benzodiazepines and barbiturates) and the excitatory 5-HT₃ receptor (the target of ondansetron). A second family, the ionotropic glutamate receptors (NMDA, AMPA and kainate), is tetrameric; the NMDA receptor is doubly gated, needing both glutamate and removal of a magnesium block by depolarisation, a molecular coincidence detector central to learning and to excitotoxicity. A third small family, the P2X receptors for ATP, is trimeric. Drugs act on these channels as agonists, antagonists, channel blockers and allosteric modulators at sites distinct from the ligand pocket.

2.4 G protein coupled receptors: molecular structure

G protein coupled receptors (GPCRs) are the largest receptor family and the largest single class of drug targets: about a third of marketed medicines act through them. The molecular structure is a single polypeptide folded into **seven transmembrane alpha helices**, with an extracellular N terminus and an intracellular C terminus; the ligand binds in a pocket among the helices or at the N terminus, and the intracellular loops engage the partner **G protein**, a heterotrimer of alpha, beta and gamma subunits anchored to the membrane. At rest the alpha subunit holds GDP and the trimer is assembled. Agonist binding makes the receptor act as an exchange factor: GDP leaves, GTP binds, and the alpha GTP and beta gamma parts separate to regulate effectors until the alpha subunit hydrolyses its own GTP back to GDP and the trimer reforms. The alpha subunit defines the family:

G protein	Main effector	Second messenger change	Example receptors
Gs	Adenylyl cyclase stimulated	cAMP rises	Beta adrenoceptors, H2, dopamine D1
Gi/o	Adenylyl cyclase inhibited, potassium channels opened	cAMP falls	Alpha2, muscarinic M2, opioid, dopamine D2
Gq/11	Phospholipase C beta stimulated	IP3 and diacylglycerol rise, calcium released	Alpha1, muscarinic M3, AT1, H1
G12/13	Rho kinase pathway	Cytoskeleton and contraction changes	Thrombin, lysophospholipid receptors

Signaling is tuned by a control system of its own: GPCR kinases phosphorylate the active receptor, **arrestins** bind and uncouple it (desensitisation) and route it to internalisation. Arrestins can also start signals of their own, the basis of biased agonism, where a drug favours one output of a receptor over another.

2.5 Tyrosine kinase receptors: molecular structure

Receptor tyrosine kinases are single pass membrane proteins with an extracellular ligand binding domain and an intracellular **tyrosine kinase** domain. Growth factors such as EGF, VEGF, PDGF and nerve growth factor bind as dimers or drive the receptors together; the paired kinase domains phosphorylate each other on tyrosine residues (**autophosphorylation**), and the phosphotyrosines become docking sites for proteins carrying SH2 domains. The adaptor Grb2 docks and brings SOS, which starts the MAP kinase cascade of section 2.11. The **insulin receptor** is the pharmacological exemplar: a preformed dimer whose activation runs through IRS proteins into the PI3 kinase and Akt pathway, ending in translocation of GLUT4 glucose transporters to the membrane of muscle and fat cells, the molecular basis of insulin stimulated glucose uptake measured in the assay of Unit 5.10. Because these receptors drive growth, their overactivity is oncogenic, and the kinase pocket is druggable: gefitinib and erlotinib block the EGF receptor kinase in lung cancer, imatinib blocks the related intracellular kinases BCR-ABL, KIT and PDGF receptor, and the antibody trastuzumab blocks the HER2 receptor from outside.

2.6 Nuclear receptors: molecular structure

Nuclear receptors are transcription factors with a built in ligand pocket, so receptor and effector are one molecule. The structure has four working parts: a variable N terminal region, a highly conserved **DNA binding domain** built around two zinc fingers that grip specific DNA sequences called hormone response elements, a hinge, and a **ligand binding domain** that carries the main activation surface. Lipophilic ligands cross the membrane to reach them. In the classic **type I** pattern (glucocorticoid, oestrogen, progesterone and androgen receptors), the unliganded receptor sits in the cytoplasm held by heat shock proteins; ligand binding releases the chaperones, the receptor dimerises, enters the nucleus and switches gene transcription on or off, recruiting coactivator or corepressor proteins that remodel chromatin. In the **type II** pattern (thyroid hormone, retinoic acid, vitamin D and PPAR receptors), the receptor already sits on DNA as a heterodimer with the retinoid X receptor, silencing genes until the ligand arrives. Responses take hours to days but last, because they are written into protein synthesis. The drug list is long and central: corticosteroids, sex steroids and their antagonists, the selective oestrogen receptor modulator tamoxifen, thiazolidinediones at PPAR gamma, fibrates at PPAR alpha and calcitriol at the vitamin D receptor.

2.7 Second messengers: the intracellular currency

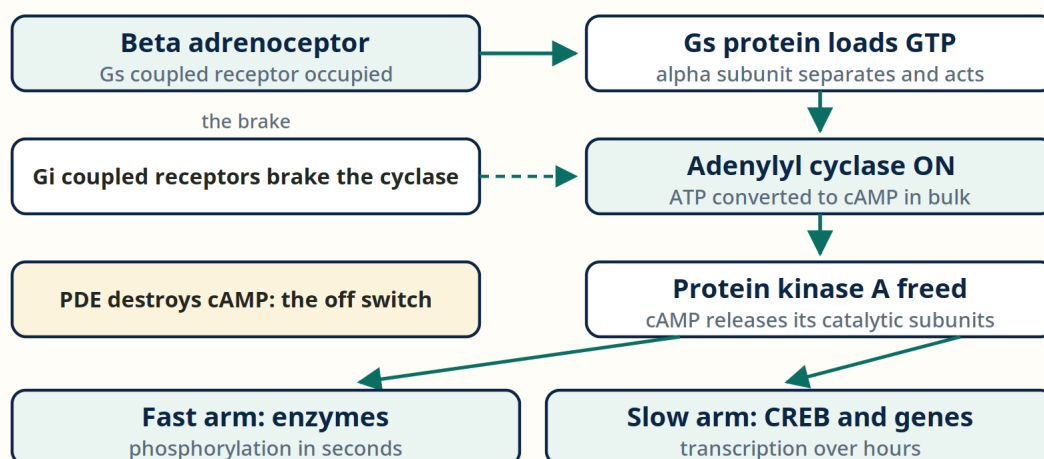
Second messengers share a design: made on demand in large amounts, small and diffusible, read by specific effector proteins, and destroyed quickly so the signal can end.

Messenger	Made by	Read by	Ends by
Cyclic AMP (cAMP)	Adenylyl cyclase from ATP (Gs on, Gi off)	Protein kinase A, Epac, cyclic nucleotide gated channels	Phosphodiesterases hydrolyse it to AMP
Cyclic GMP (cGMP)	Guanylyl cyclase (soluble form switched on by NO)	Protein kinase G, channels	Phosphodiesterases, including PDE5
Inositol trisphosphate (IP3)	Phospholipase C cutting PIP2	IP3 receptors on the endoplasmic reticulum, releasing calcium	Dephosphorylation, recycled to inositol
Diacylglycerol (DAG)	Phospholipase C cutting PIP2 (same cut as IP3)	Protein kinase C (with calcium and phospholipid)	Phosphorylation to phosphatidic acid
Calcium ion (Ca ²⁺)	Enters through channels or is released from the endoplasmic reticulum	Calmodulin and its kinases, troponin, many enzymes	Pumps (SERCA, plasma membrane Ca ATPase) and exchangers restore low cytosolic levels
Nitric oxide (NO)	Nitric oxide synthase from arginine	Soluble guanylyl cyclase (it is the ligand)	Scavenged by haemoglobin, oxidised within seconds

2.8 The cyclic AMP signaling pathway in detail

The **cAMP pathway** is the prototype against which all others are taught. A Gs coupled receptor (the beta adrenoceptor is the classic) activates adenylyl cyclase, cAMP accumulates, and cAMP binds the regulatory subunits of **protein kinase A**, freeing its catalytic subunits to phosphorylate target proteins on serine and threonine residues: metabolic enzymes within seconds, and, when PKA enters the nucleus, the transcription factor **CREB**, whose phosphorylation switches on genes carrying cAMP response elements, giving the pathway a fast and a slow arm. Gi coupled receptors brake the same cyclase. Termination is by phosphodiesterases (PDEs), which hydrolyse cAMP, and by phosphatases. The pathway explains several textbook drug and toxin stories. **Cholera toxin** permanently ADP ribosylates the Gs alpha subunit, locking it on; intestinal cAMP stays high, chloride and water pour into the gut, and the result is the lethal secretory diarrhoea of cholera. **Pertussis toxin** disables Gi, removing the brake. **Forskolin** activates the cyclase directly and is a laboratory standard. PDE inhibitors raise cAMP by blocking its destruction: caffeine and theophylline weakly and non selectively, milrinone (PDE3) in acute heart failure, and roflumilast (PDE4) in severe COPD.

The Cyclic AMP Signaling Pathway



Cholera toxin locks Gs on; PDE inhibitors (milrinone, roflumilast) hold the off switch open.

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Figure: The cAMP pathway end to end. One receptor, one cyclase, millions of cAMP molecules, two speeds of response: enzymes now, genes later.

2.9 The phosphoinositide pathway: IP₃, diacylglycerol and calcium

Gq coupled receptors (alpha1 adrenoceptors, muscarinic M3, angiotensin AT1) activate **phospholipase C beta**, which cuts the membrane lipid PIP₂ into two messengers at once. **IP₃** diffuses to the endoplasmic reticulum and opens its calcium channels, releasing a pulse of **calcium** into the cytosol. **Diacylglycerol** stays in the membrane and, together with the calcium pulse, activates **protein kinase C**. Calcium itself is a complete signaling system: at rest the cytosol holds it near 100 nanomolar against a millimolar exterior, so opening any calcium channel, in the plasma membrane or the ER, produces a steep local signal. Calcium is read by **calmodulin**, which wraps around four calcium ions and then activates kinases (including myosin light chain kinase, the trigger of smooth muscle contraction), phosphatases and nitric oxide synthase. Pumps and exchangers then restore the gradient and the store refills. The pathway is the working mechanism of vasoconstriction, glandular secretion and platelet activation, and it gives one famous psychiatric drug clue: **lithium** inhibits inositol monophosphatase, the enzyme that recycles inositol, which may damp overactive phosphoinositide signaling in bipolar disorder.

2.10 Cyclic GMP and nitric oxide signaling

Nitric oxide is a messenger that ignores the usual rules: a gas, made on demand by nitric oxide synthase from the amino acid arginine, diffusing freely through membranes and living for seconds. Endothelial NOS and neuronal NOS are switched on by calcium calmodulin; inducible NOS, written into macrophages and smooth muscle during inflammation, produces large sustained amounts. NO enters the neighbouring smooth muscle cell and binds the haem group of **soluble guanylyl cyclase**, which makes **cyclic GMP**; cGMP activates protein kinase G, which lowers cytosolic calcium and relaxes the muscle. Every step is drugged. Glyceryl trinitrate and the organic nitrates are NO donors. **Sildenafil** blocks PDE5, the enzyme that destroys cGMP in the corpus cavernosum and the pulmonary circulation, and so prolongs the signal, the basis of its use in erectile dysfunction and pulmonary hypertension. Riociguat stimulates the cyclase directly.

2.11 The MAP kinase signaling pathway

The **mitogen activated protein kinase (MAPK)** pathway carries growth and differentiation orders from the cell surface to the nucleus, and it is built as a three storey cascade of kinases, each storey amplifying and offering a control point. A growth factor receptor (or a GPCR reaching across) recruits Grb2 and SOS, which load GTP onto the small G protein **Ras**. Ras switches on **Raf** (the first kinase, a MAPK kinase kinase), Raf phosphorylates **MEK** (the MAPK kinase), and MEK phosphorylates **ERK1 and ERK2** (the MAPKs themselves). ERK enters the nucleus and phosphorylates transcription factors such as Elk-1, switching on the genes of cell division. Parallel arms of the family, JNK and p38, answer stress and inflammatory signals rather than growth. Because the cascade shouts "divide", its components are frequent oncogenes: activating BRAF mutations (V600E) appear in about half of melanomas and Ras mutations in a large share of pancreatic, colorectal and lung cancers. The cascade is correspondingly drugged at several levels: vemurafenib and dabrafenib block mutant BRAF, trametinib and cobimetinib block MEK, and the multikinase inhibitor sorafenib includes Raf among its targets. Resistance, usually by reactivating the cascade downstream or around the block, is the standing problem of this drug class.

The MAP Kinase Cascade

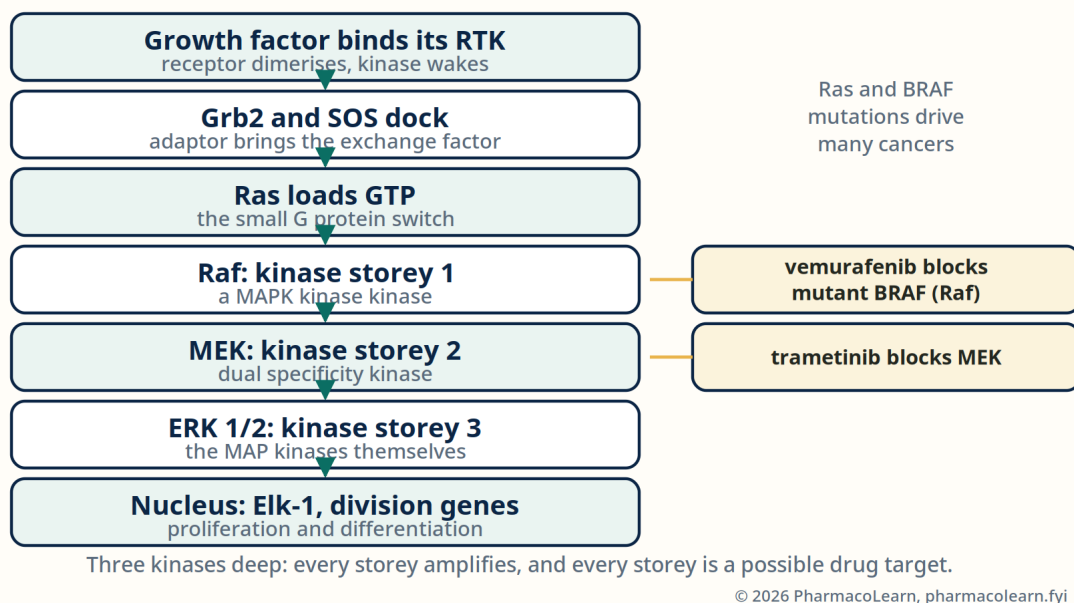


Figure: The MAPK cascade: three kinases deep, each level an amplifier and a possible drug target. BRAF and MEK inhibitors are marked where they strike.

2.12 The JAK/STAT signaling pathway

Many cytokine receptors have no enzyme activity of their own; they borrow one. The **Janus kinases (JAK1, JAK2, JAK3 and TYK2)** sit permanently attached to the cytoplasmic tails of receptors for erythropoietin, growth hormone, prolactin, the interferons and many interleukins. Ligand binding brings two receptor chains together, the paired JAKs phosphorylate each other and then the receptor tails, and the phosphotyrosines dock **STAT** proteins (signal transducers and activators of transcription). The JAKs phosphorylate the docked STATs, which pair up as dimers, travel to the nucleus and switch on the genes of the response: red cell production for erythropoietin, immune cell programmes for the interleukins. It is the shortest route in this unit from membrane to gene, with no second messenger at all. Control is by phosphatases and by the SOCS proteins, which the pathway itself induces as a feedback brake. One mutation shows the pathway's power: **JAK2 V617F**, a constitutively active kinase, drives the myeloproliferative neoplasms. The JAK inhibitors are now a drug family: ruxolitinib (JAK1 and JAK2) in myelofibrosis and polycythaemia vera, and tofacitinib, baricitinib and upadacitinib in rheumatoid arthritis,

ulcerative colitis and other immune diseases, traded against a class burden of infection (including herpes zoster reactivation), lipid changes and regulatory warnings on major cardiovascular events and malignancy in older patients with cardiovascular risk.

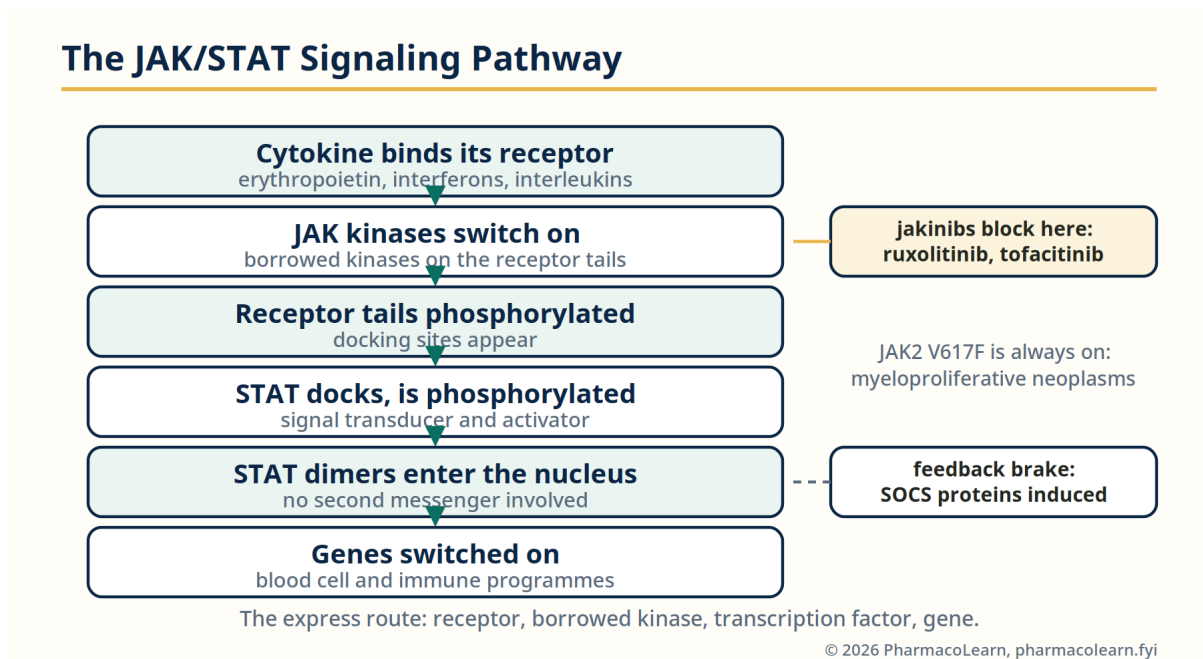


Figure: JAK/STAT: the express route from cytokine receptor to gene, with no second messenger. The jakinib drugs block the borrowed kinase at the top of the pathway.

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