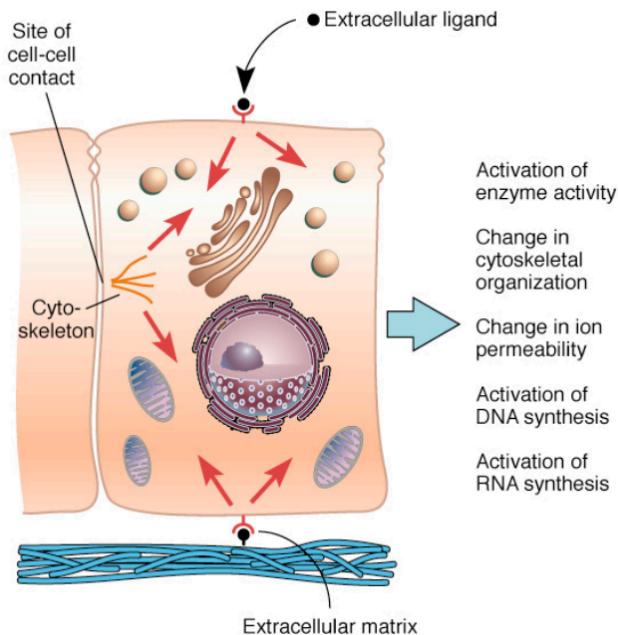


<https://www.sinobiological.com/research/signal-transduction/metabolism>

In the Avatar movie, the concept of "signal transduction" is used as a scientific explanation for how the plants on Pandora, and the Na'vi, communicate and interact, with Sigourney Weaver's character, Grace, using the term to describe this process.

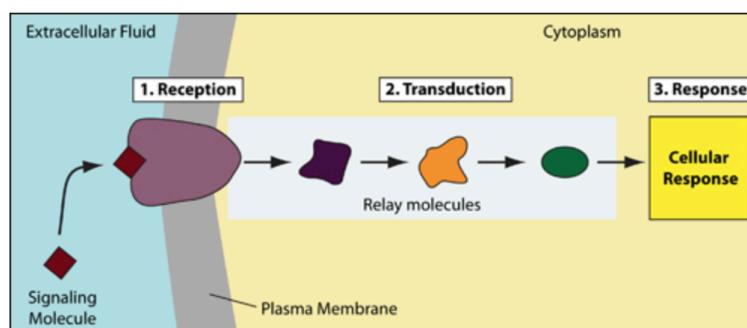


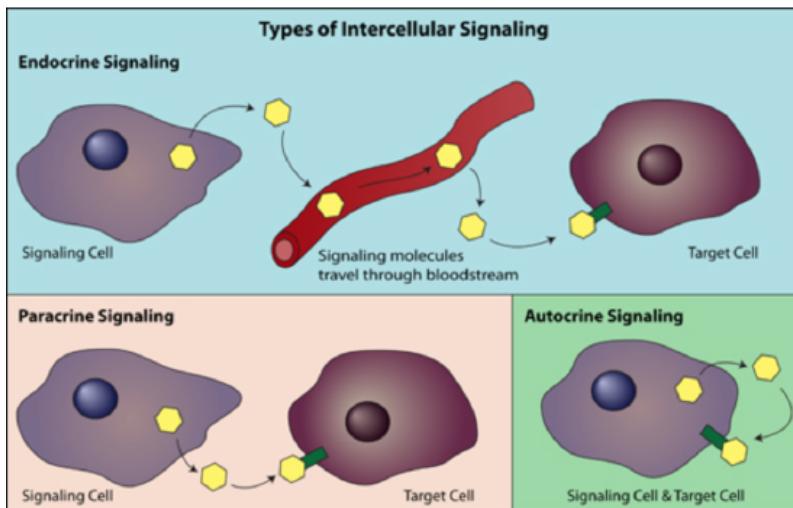
**Signal transduction** is how cells receive and respond to signals from their environment. These signals can come in the form of chemicals from nearby cells (paracrine), distant cells (endocrine), or even the same cell (autocrine). These signals often affect cell metabolism or gene expression.



Cell signaling has three stages:

1. **Reception:** The cell detects a signal when a molecule (ligand) binds to a receptor on the cell's surface or inside the cell.
2. **Transduction:** Binding of the signal changes the receptor, triggering a pathway of reactions that relay the signal inside the cell.
3. **Response:** The signal activates a specific cellular response, like gene expression or changes in metabolism.



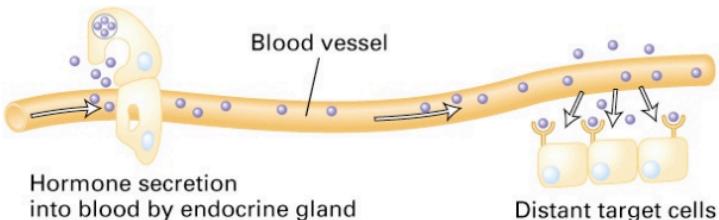


### I A - Types of Signaling

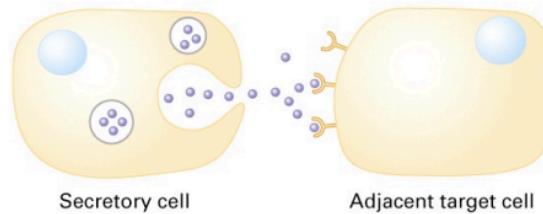
Cells communicate by means of extracellular **signaling molecules** that are produced and released by **signaling cells**. These molecules recognize and bind to **receptors** on the surface of **target cells** where they cause a cellular response by means of a **signal transduction** pathway.

Depending on the distance that the signaling molecule has to travel, we can talk about three types of signaling:

#### (a) Endocrine signaling

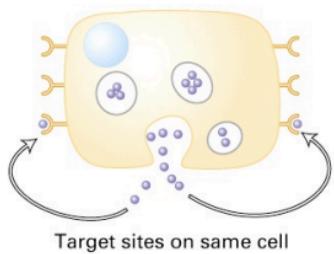


#### (b) Paracrine signaling



In **paracrine signaling** the signaling molecule affects only target cells in the proximity of the signaling cell. An example is the conduction of an electric signal from one nerve cell to another or to a muscle cell. In this case the signaling molecule is a neurotransmitter.

#### (c) Autocrine signaling

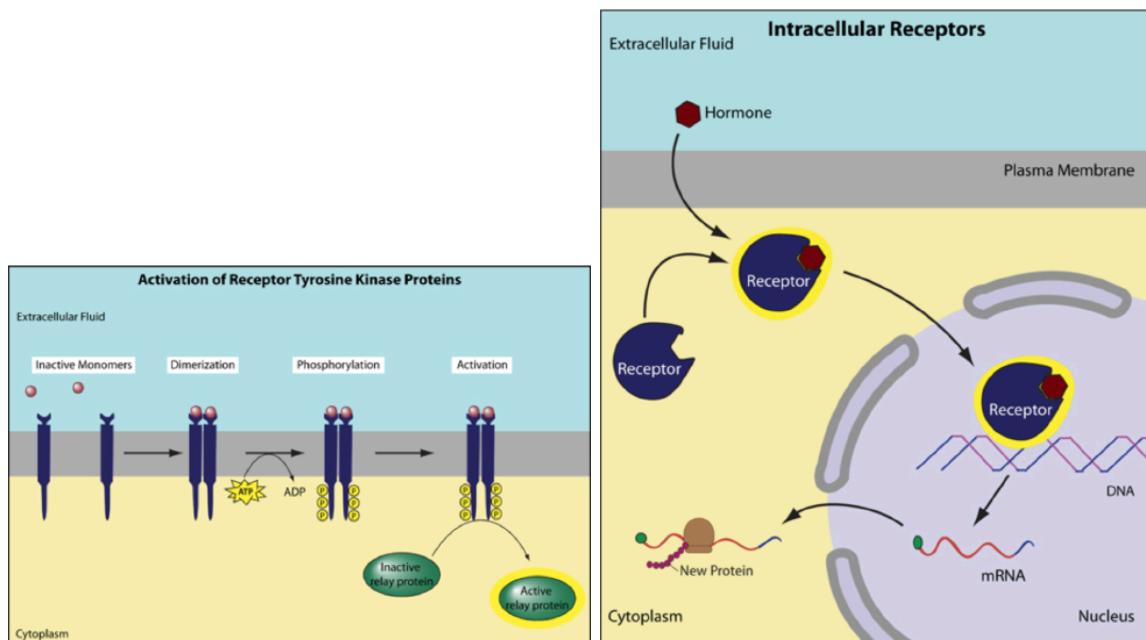


Key:

- Extracellular signal
- Receptor
- Membrane-attached signal

In **autocrine signaling** cells respond to molecules they produce themselves. Examples include many growth factors. Prostaglandines, lipophilic hormones that bind to membrane receptors, are often used in paracrine and autocrine signaling. They generally modulate the effect of other hormones.

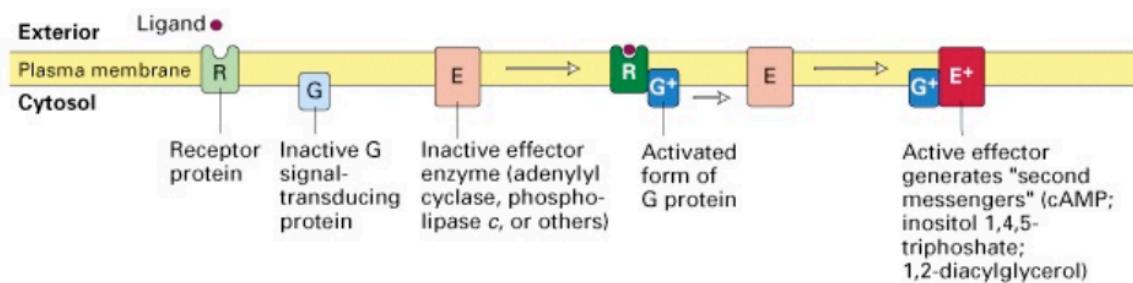
Membrane receptors often produce secondary signals inside the cell. Transduction pathways can amplify signals, often involving protein kinases and phosphatases, which add or remove phosphate groups to regulate proteins. Ultimately, signaling controls processes like gene expression, cell division, or apoptosis.



### I B - Types of Receptors

There are a number of receptor classes that are used in different signaling pathways. The two more predominant are:

#### (a) G protein-coupled receptors (epinephrine, glucagon, serotonin)

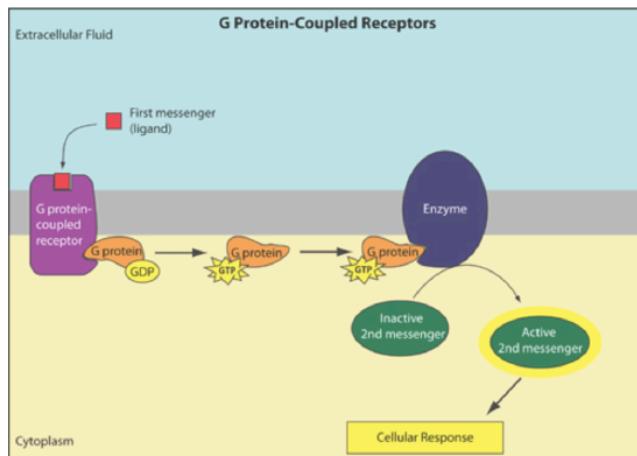


**G-protein-coupled receptors (GPCRs)** are the largest group of membrane receptors in eukaryotes, involved in detecting signals like light, nutrients, and messages from other cells. They are essential for many functions in the body, and many drugs work by binding to GPCRs.

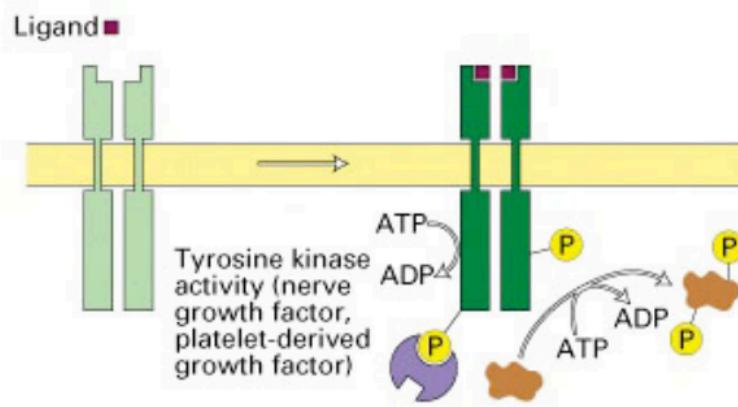
GPCRs are composed of a single protein that spans the cell membrane seven times. When a signaling molecule binds to a GPCR, it activates a nearby G protein by exchanging GDP

for GTP. This triggers the G protein to split into two parts, which then interact with other molecules inside the cell to relay the signal.

GPCRs activate second messengers (like cAMP or IP<sub>3</sub>), which help trigger cellular responses such as enzyme activation or ion channel opening. These pathways control important processes like hormone responses, nerve transmission, and blood clotting.



(b) **Receptors with intrinsic enzymatic activity** (Tyrosine kinases)



These receptors have a catalytic activity that is activated by binding of the ligand. An example are **tyrosine-kinase receptors**. Binding of an often dimeric ligand induces dimerization of the receptors that leads to cross **phosphorylation** of the cytosolic domains and phosphorylation of other proteins.

## 2. Components of Cell Signaling

### 2.1. Ligands or Signals:

Cell signaling mainly involves chemical signals that can be mechanical, electrical, or chemical in nature. These signals inform cells about their environment, like nutrients or growth factors. There are different types of signaling, such as endocrine (long-distance), paracrine (short-distance), and autocrine (acting on the same cell). Ligands include small

molecules like lipids, proteins (e.g., hormones, growth factors), and even sugars or nucleic acids. These signals bind to receptors, either on the cell surface or inside the cell.

## **2.2. Receptors:**

Receptors are proteins that receive signals. They are either cell-surface receptors (which span the plasma membrane) or intracellular receptors (located in the cytoplasm or cell organelles). Cell-surface receptors include G-protein coupled receptors, ion channels, and receptor tyrosine kinases. These receptors change shape when bound by a ligand, triggering further signaling inside the cell.

## **2.3. Specificity in Signaling:**

Receptors are highly specific, meaning each type binds only to certain ligands (e.g., insulin binds only to its receptor). Different cell types have varying types and numbers of receptors, affecting how they respond to signals. Receptor clustering can enhance signal strength, as seen in immune cells where specific receptors group together to start immune responses.

### **2.3.1. Lipids in Signaling:**

Lipids and lipid-based microdomains in the membrane also play a key role in signaling. These lipid rafts help organize signaling components, ensuring that they interact correctly and preventing interference. These microdomains can mediate processes like receptor clustering and redox signaling. Lipid-derived molecules like phosphoinositides are crucial for pathways that control cell survival, growth, and differentiation.

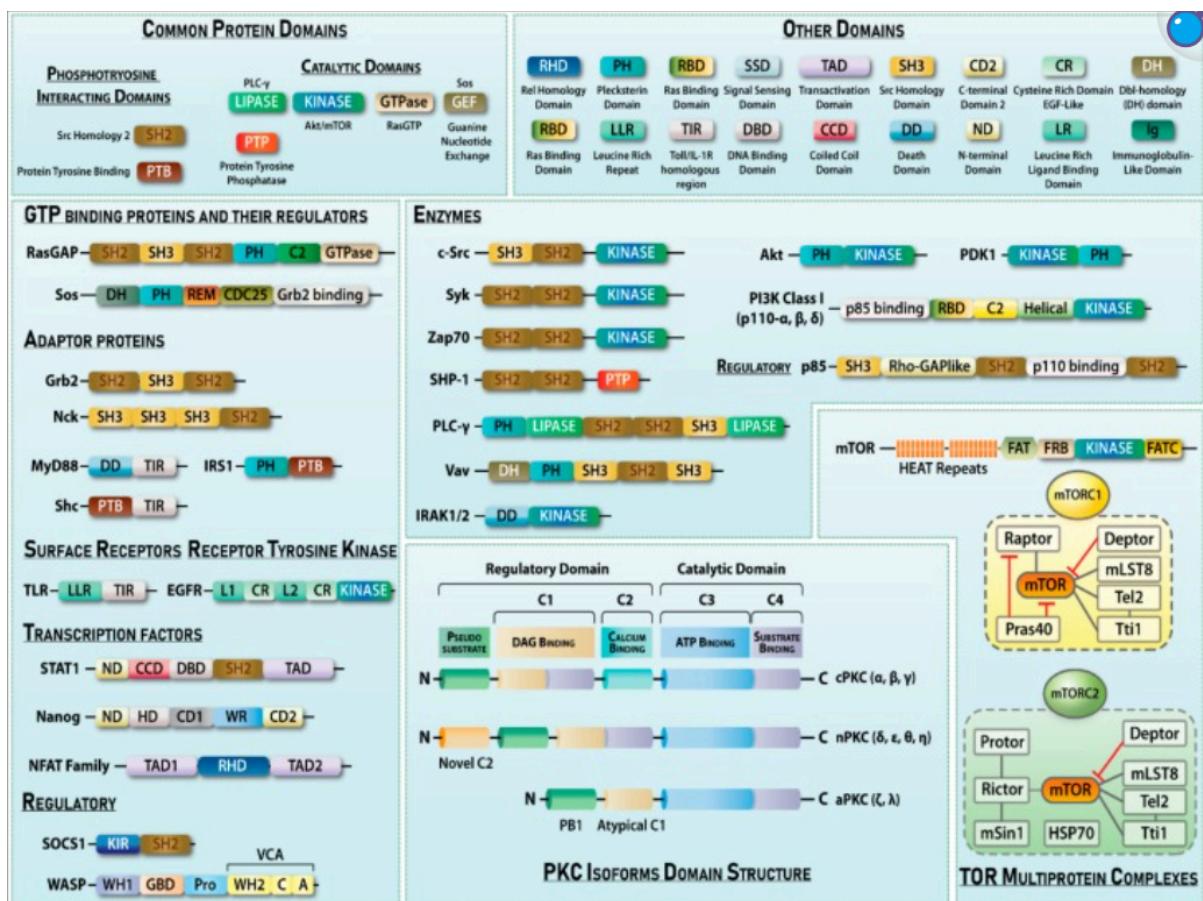
### **2.3.2. Signaling Domains**

Protein signaling specificity is influenced by its domain structure. A domain is a distinct folded section of a protein that imparts a specific function and enables the protein to interact in various signaling pathways. Domains can vary in length and can be swapped between proteins to create chimeras or mutants, diversifying protein functions. Examples of important signaling domains include EF-hand in Calmodulin and the SH3 and SH2 domains, which mediate protein-protein interactions and recognize phosphotyrosine residues. Other domains, like Pleckstrin homology (PH) and death effector domains (DED), play roles in intracellular signaling and cell death. Domains are also involved in the regulation of protein folding and function.

### **2.3.3. Common Signaling Domains**

- **SH3 Domain:** Mediates protein-protein interactions, often involved in cytoskeletal regulation and signaling.
- **SH2 Domain:** Recognizes phosphorylated tyrosine residues, playing a key role in kinase signaling.
- **PH Domain:** Binds phospholipids (like PIP3/PIP2) and is involved in signaling and cytoskeletal function.
- **DED Domain:** Involved in apoptosis by activating caspases.
- **bZIP Domain:** Common in DNA-binding proteins.

- **Immunoglobulin-like Domain:** Important in cell adhesion and immune response.



## 2.4. Signal Transducers

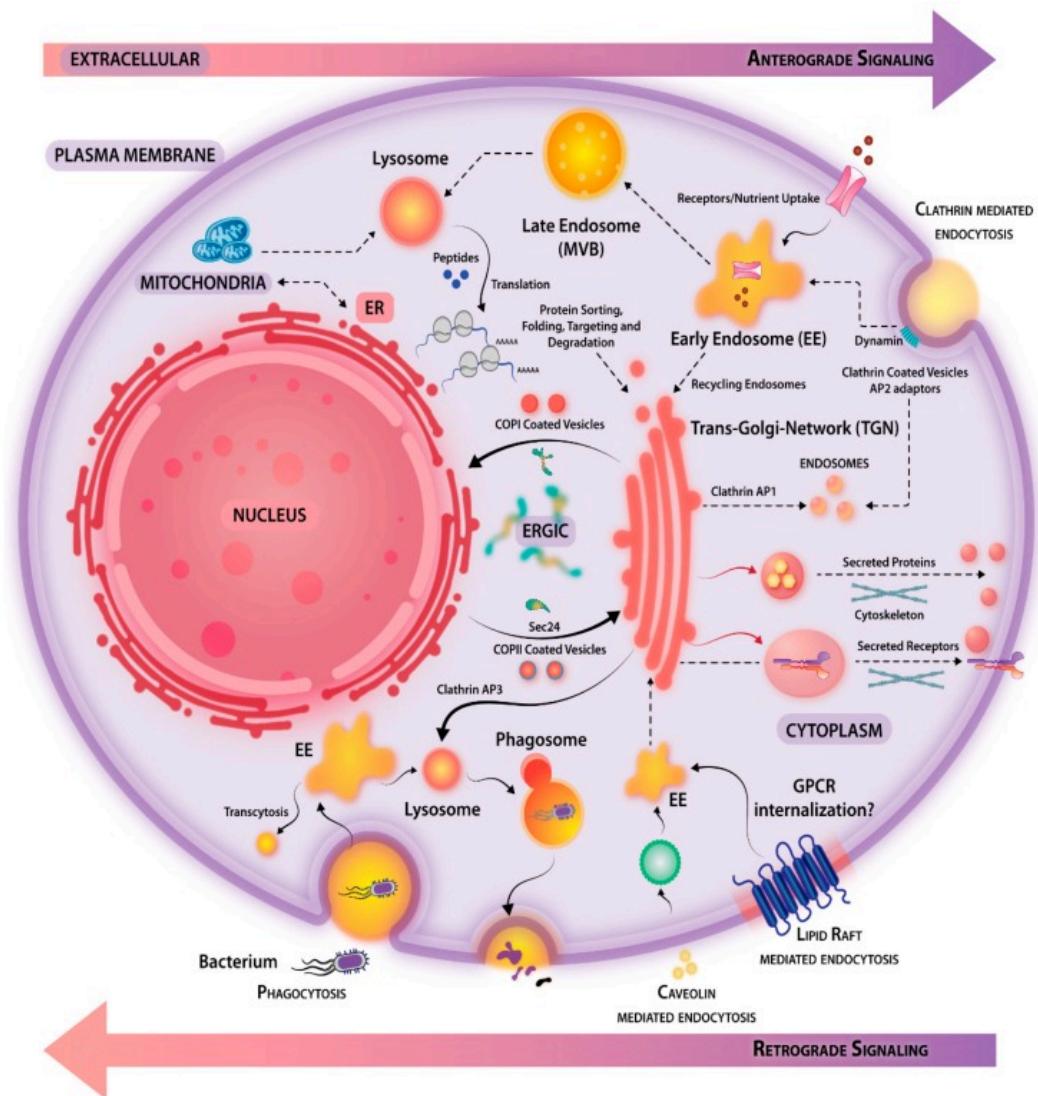
Receptor activation leads to conformational changes in transducer proteins. In GPCRs, ligand binding activates G proteins ( $G\alpha$  and  $G\beta\gamma$ ), triggering various second messengers like cAMP and phospholipase C. Other monomeric GTPases, such as Ras and Rho, also serve as key transducers. Enzyme-linked receptors, like receptor tyrosine kinases (RTKs), undergo dimerization upon ligand binding, leading to phosphorylation and activation of downstream signaling pathways. Ionotropic receptors, such as ligand-gated ion channels, allow ions like  $Na^+$ ,  $K^+$ , and  $Ca^{2+}$  to enter the cell, contributing to signal propagation.

## 2.5. Second Messengers

Second messengers like cAMP, calcium ( $Ca^{2+}$ ), and diacylglycerol (DAG) are crucial in signaling. cAMP is generated by adenylyl cyclase and regulates various cellular processes, with its levels tightly controlled by phosphodiesterases.  $Ca^{2+}$  is a versatile second messenger that influences processes like cell division, metabolism, and immune responses. Other messengers like DAG and inositol triphosphate (IP3) are involved in intracellular signaling, including activation of protein kinases like PKC, which are critical for T cell activation and immune responses.

## Transcription Factors & Signaling Pathways

1. **Transcription Factors:** Signaling pathways target transcription factors that regulate gene expression, leading to changes in cellular activity. Some transcription factors are regulated by allosteric effectors that influence gene expression. Key examples include E2F family members, MeCP2, and CSL. Transcription factors can be classified into:
  - Steroid receptors (e.g., RXR, PPARs)
  - Transcription factors activated by internal signals (e.g., p53, SREBP)
  - Cell surface receptor-activated factors (e.g., CREBs, NF-κB, STATs).
2. **Directionality of Signaling:** Signal transduction does not only originate from the plasma membrane but also from various organelles. Signaling proteins are transported via cytoskeletal networks, allowing specific compartmentalized signals in the cell. This spatial segregation helps regulate various functions, such as protein synthesis, immune response, and mitochondrial dynamics. Scaffolding proteins like AKAPs play a role in organizing signals in specific cell regions.
3. **Retrograde & Anterograde Signaling:**
  - **Retrograde signaling:** Organelles like mitochondria and chloroplasts send signals to the nucleus to adjust gene expression, especially under stress or dysfunction.
  - **Anterograde signaling:** The nucleus sends signals to organelles to regulate their gene expression.
4. **Compartmentalized Signaling:** Cells have distinct compartments (e.g., ER, Golgi, lysosomes) that help segregate signaling pathways. Vesicular trafficking between compartments, guided by coat proteins and SNAREs, ensures proper molecule delivery, recycling, or degradation within the cell.
5. **Cell Adhesion & Membrane Protrusion:** Cell migration involves the formation of focal adhesion junctions and actin-driven membrane protrusions. This process is regulated by signaling proteins like dynamin, which mediates endocytosis, and contributes to cellular remodeling, nutrient scavenging, and signaling across compartments.



## Simplified Version:

### 4. Complexity in Signaling

Cell signaling is a complex system where different signaling pathways interact with each other. These interactions happen when cells are exposed to multiple signals (like cytokines, growth factors, and pathogens), while still ensuring the proper output of signals.

#### 4.1. Interactions Between Pathways

The complexity of signaling comes from how different pathways work together or "cross-talk." These interactions help cells generate diverse responses when multiple pathways are activated at the same time. Some models for these interactions include:

- **Coincident Detector Mechanism:** Two pathways can meet at a "detector," which integrates their signals and produces a combined response. For example, a receptor's activation can lead to a response only when two signals are present at the same time.

- **Gated Mechanism:** One pathway can modify the response of another. For example, cAMP can affect various cellular responses, sometimes blocking or activating different proteins based on the cell type.
- **Feedback Mechanism:** This can either amplify or reduce a signal. Positive feedback strengthens a signal, while negative feedback dampens it. For example, the light-sensing process in the eye involves feedback that modulates protein activity in response to light.

## 4.2. Post-Translational Modifications (PTMs)

PTMs are changes made to proteins after they are produced, which affect their function. These changes include processes like phosphorylation, acetylation, and ubiquitination. Phosphorylation, for instance, can rapidly change a protein's activity or location within the cell. PTMs help control protein function, stability, and turnover and are important for maintaining circadian rhythms and cellular diversity.

## 4.3. Engagement of Different Signaling Modules

Signaling is not only controlled by pathways at the cell surface but also involves various cellular compartments. Different signaling components are organized in compartments or “signalosomes,” and their interactions decide the outcome of signaling. For example, a receptor may trigger different responses depending on which pathway it activates. Different cell types can also respond to the same signal in different ways, depending on the cell’s specific factors.

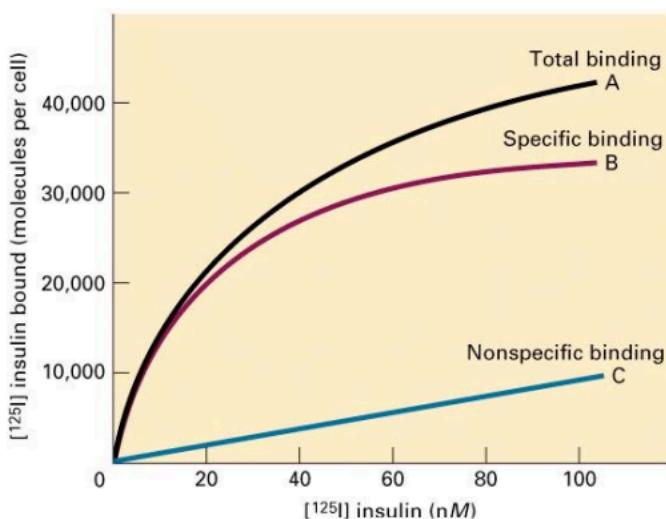
## 5. Translational Value of Understanding Signal Transduction

Understanding signaling pathways is crucial for drug development because disruptions in signaling can lead to diseases like cancer. Targeting signaling components with drugs or small molecules can help treat diseases by blocking abnormal signaling. For example, drugs targeting the Ras pathway are being developed for cancer treatment. Inhibitors of proteins like mTOR can also be used to treat drug-resistant cancers. Comprehensive knowledge of signaling pathways helps design drugs that are more effective and have fewer side effects.

Life began with simple unicellular organisms, and early cell signaling was less complex. As multicellular organisms evolved, more genes and proteins were added, making signaling networks more intricate. For example, signaling proteins in animals differ from plants and lower organisms, leading to diverse responses to the same stimuli. Studies show that signaling proteins play a key role in the diversity of eukaryotes. Receptor tyrosine kinases, crucial for multicellular organisms, appeared before multicellularity. Communication, like quorum sensing in bacteria, helped organisms survive by regulating behaviors such as antibiotic production and virulence. The evolution of signaling pathways is shaped by natural selection, and there are theories about how receptor-ligand interactions evolved, either by chance or through co-evolution. Despite the complexity of signaling, a few conserved pathways (like RTK, JAK/STAT, and Wnt) are crucial for cellular and developmental diversity. These pathways provide the plasticity needed for different biological outcomes.

## Identification and Purification of Cell-Surface Receptors

Hormone receptors are difficult to identify and purify because they are present in very low abundance and they have to be solubilized with nonionic detergents. Given their **high specificity** and **high affinity** for their ligands, the presence of a certain receptor in a cell can be detected and quantified by their binding to radioactively-labeled hormones. The binding of the hormone to a cell suspensions increases with hormone concentration until it reaches receptor saturation. Specific binding is obtained by measuring both the total and the non-specific binding (which is obtained by using a large excess on unlabeled hormone).



Intracellular signal transduction is the process by which signals from the cell surface are transmitted to various targets inside the cell, typically amplifying the signal. This process often involves enzymes like protein kinases that regulate gene expression and other cellular responses. Once a receptor binds to a signal, it triggers an intracellular signaling cascade. This often involves second messengers like cyclic AMP (cAMP), which amplify the signal inside the cell, activating enzymes like protein kinases. These enzymes add phosphate groups to proteins, which can activate or inhibit their function, influencing various cellular processes.

Signal transduction is a complex network where pathways intersect, allowing the cell to integrate multiple signals and adapt its function accordingly.

Key second messengers like cyclic AMP (cAMP) and cyclic GMP (cGMP) play crucial roles in this process by activating protein kinases that modify other proteins. For example, cAMP activates protein kinase A (PKA), which regulates glycogen breakdown and gene expression. Similarly, cGMP is involved in processes like blood vessel dilation and vision.

In addition to these pathways, signals can also be relayed through phospholipids, such as phosphatidylinositol 4,5-bisphosphate (PIP2), which produces second messengers like diacylglycerol and inositol trisphosphate, activating protein kinase C and releasing calcium ions. These pathways influence diverse cellular functions such as metabolism, survival, and gene expression.

Intracellular signaling pathways are essential for cellular communication, and second messengers like cAMP, cGMP, and calcium ions play central roles in activating key enzymes that regulate various cellular processes.

The ERK MAP kinase pathway is activated by growth factor receptors, leading to Ras activation, which then activates the Raf protein kinase. Raf triggers a cascade involving MEK and ERK, resulting in various cellular responses like gene expression changes. Ras, a small GTP-binding protein, alternates between active (GTP-bound) and inactive (GDP-bound) forms and plays a central role in cell growth. Mutations in Ras can cause continuous cell proliferation, contributing to cancer.

The activation of Ras is facilitated by receptor protein-tyrosine kinases through the Grb2-Sos complex. Active Ras activates Raf, which then phosphorylates MEK and ERK. ERK translocates to the nucleus to activate transcription factors, like Elk-1, influencing gene expression. This pathway controls vital cellular processes such as growth, survival, and differentiation.

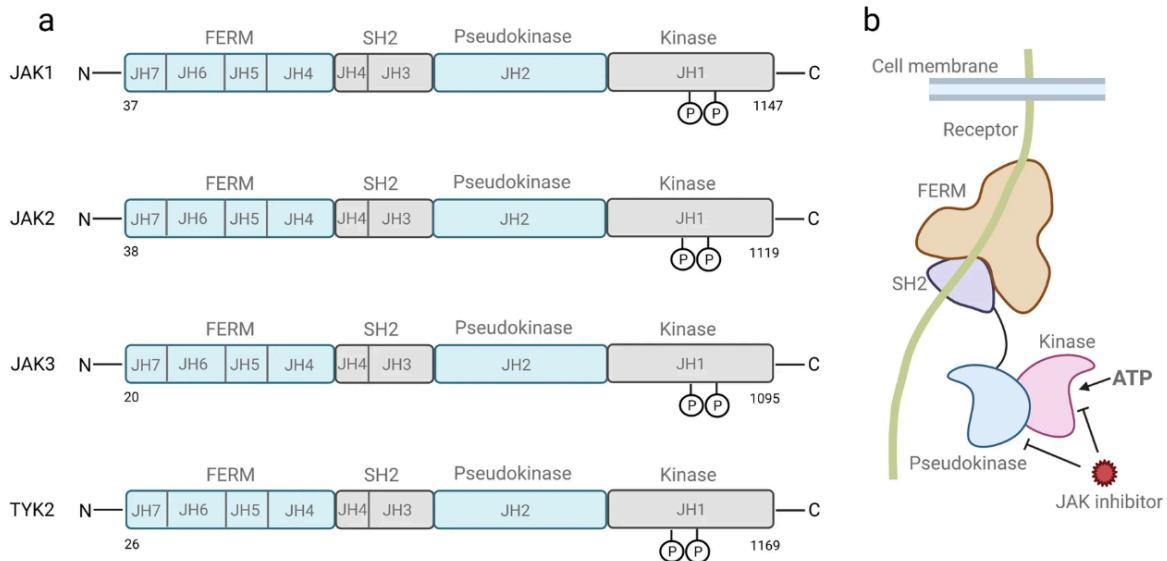
Additionally, other **MAP kinase pathways** like **JNK and p38 regulate** responses to stress and inflammation, with each pathway influencing cellular behavior differently. The **JAK/STAT** pathway, another key signaling pathway, directly links receptor activation to gene transcription via the STAT transcription factors. These pathways are crucial in regulating cellular responses to external signals, contributing to processes such as cancer development.

<https://www.ncbi.nlm.nih.gov/books/NBK9870/>

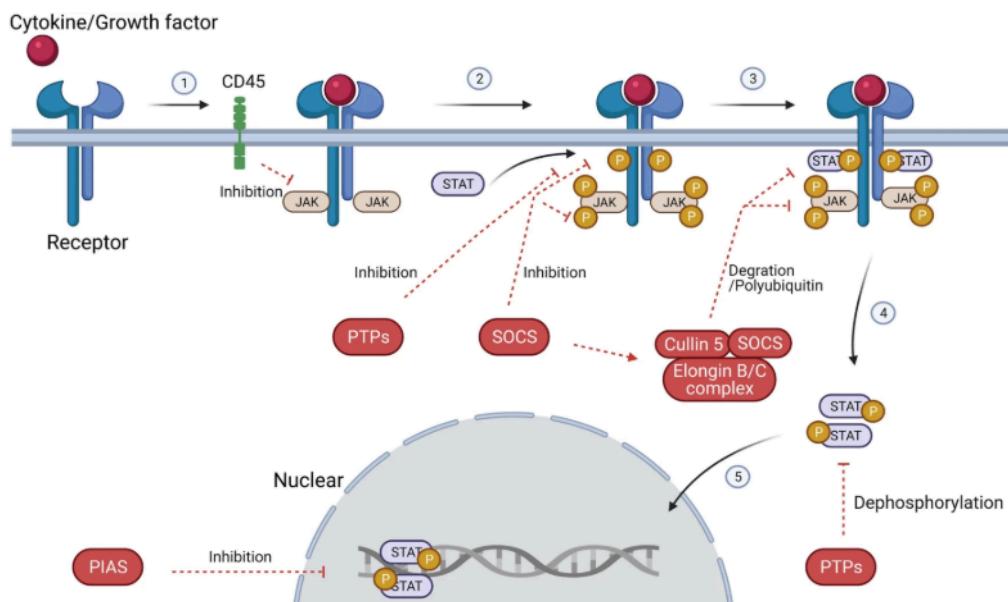
<https://dosequis.colorado.edu/Courses/MCDB3145/Docs/Karp-617-660.pdf>

JAK STAT Pathway

<https://www.youtube.com/watch?v=tIM8XNLSG6I>

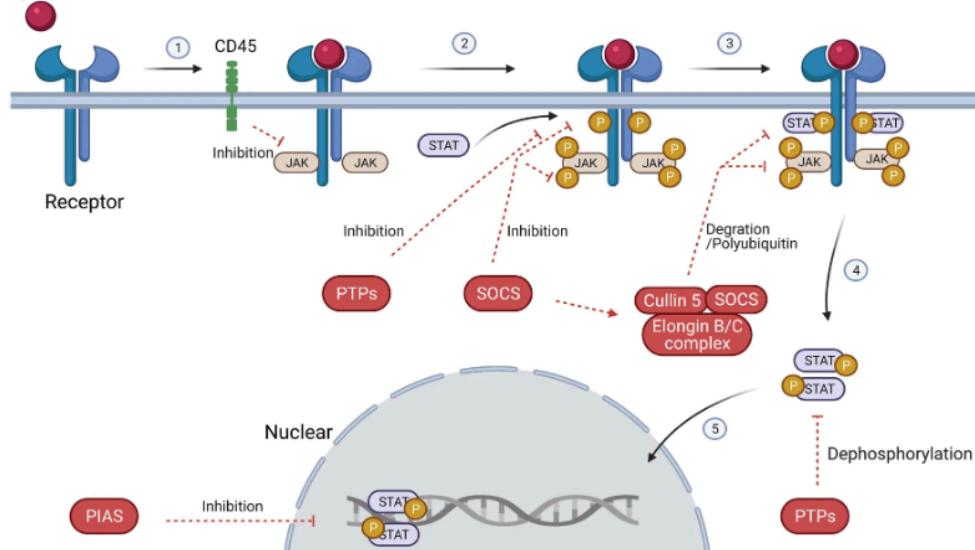


Structure of JAKs. **a** Structure and conserved phosphorylation sites of the JAK family. The JAK family has four main members: JAK1, JAK2, JAK3, and TYK2. Each is composed of seven homology domains (JH), of which JH1 constitutes the kinase domain; JH2 constitutes the pseudokinase domain; a part of JH3 and JH4 together constitute the SH2 domain; and the FERM domain is composed of the JH5, JH6, and part of the JH4 domains. The conserved tyrosine phosphorylation sites in JAK1 are Y<sup>1038</sup>/Y<sup>1039</sup>; the conserved tyrosine phosphorylation sites in JAK2 are Y<sup>1007</sup>/Y<sup>1008</sup>; the conserved tyrosine phosphorylation sites in JAK3 are Y<sup>980</sup>/Y<sup>981</sup>; the conserved tyrosine phosphorylation sites in Tyk2 are Y<sup>1054</sup>/Y<sup>1055</sup>. **b** Structure of JAKs and targeting sites of JAK inhibitors.

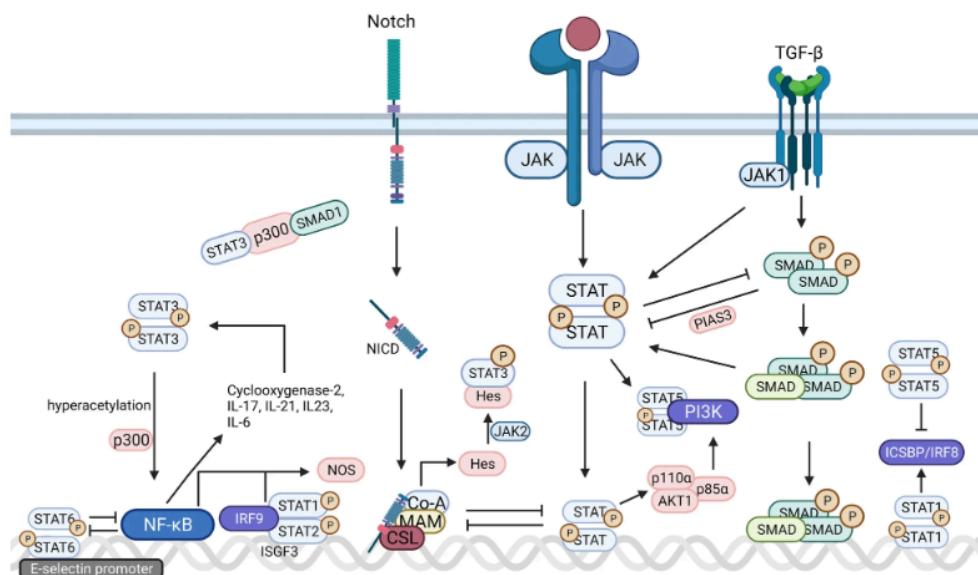


Activation and negative regulation of JAK/STAT signaling pathways. Black arrows indicate the activation process. Red dotted arrows indicated negative regulation. Activation of the JAK/STAT signaling pathway: (1) cytokines and growth factors bind to their corresponding receptors, leading to receptor dimerization and recruitment of related JAKs; (2) JAK activation leads to tyrosine phosphorylation of the receptors and formation of docking sites for STAT; (3) STATs are phosphorylated by tyrosine; (4) STATs dissociate from the receptor to form homodimers or heterodimers; (5) STAT dimers enter the nucleus, bind to DNA, and regulate transcription. Negative regulation of the JAK/STAT signaling pathway: There are three main types of proteins involved in the negative regulation of the JAK/STAT signaling pathway: the PIAS (protein inhibitor of activated STAT), CIS/SOCS (suppressor of cytokine signaling) family, and PTPs (protein tyrosine phosphatase). PIAS mainly interacts with STAT dimers to inhibit STAT binding to DNA, thereby blocking JAK/STAT signal transduction. The CIS/SOCS family negatively regulates the JAK/STAT pathway in three ways: (1) binding to a tyrosine kinase receptor to block the recruitment of STAT; (2) binding directly to JAK to inhibit its kinase activity; (3) forming an elongin B/C-cullin5 complex that degrades JAK or STAT bound to the SOCS protein through polyubiquitination and proteasome degradation. PTPs inhibit the JAK/STAT pathway by interacting with JAK, STAT, or receptors to (1) dephosphorylate the STAT dimer; (2) interact with the receptor to dephosphorylate the related JAK; and (3) in the case of CD45 (a transmembrane PTP) inhibits the phosphorylation of JAK. Created with BioRender.com

### Cytokine/Growth factor

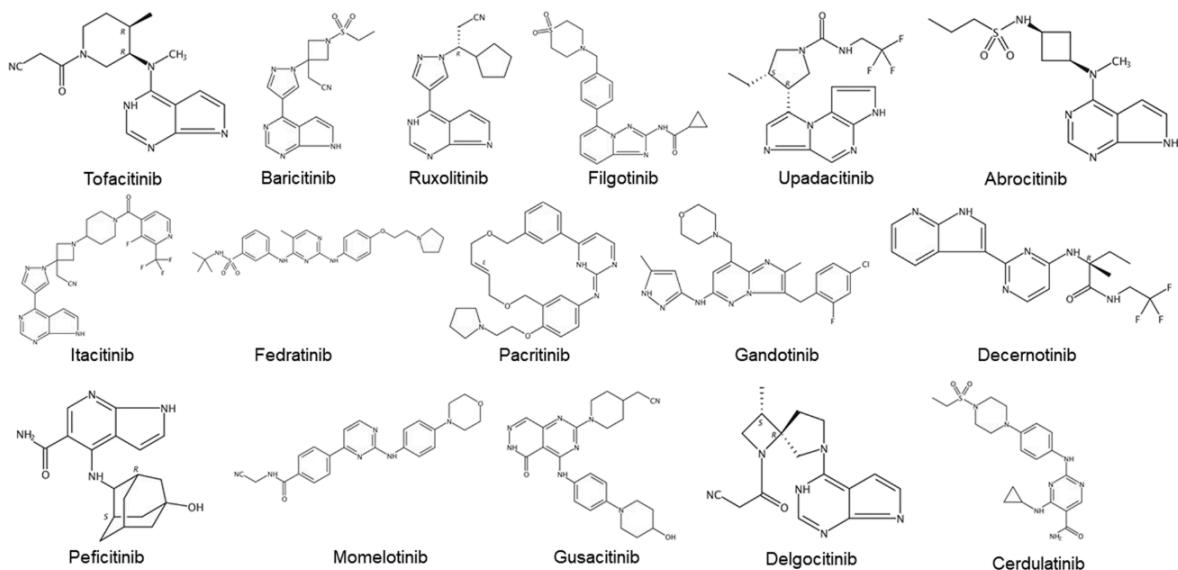


Activation and negative regulation of JAK/STAT signaling pathways. Black arrows indicate the activation process. Red dotted arrows indicated negative regulation. Activation of the JAK/STAT signaling pathway: (1) cytokines and growth factors bind to their corresponding receptors, leading to receptor dimerization and recruitment of related JAKs; (2) JAK activation leads to tyrosine phosphorylation of the receptors and formation of docking sites for STAT; (3) STATs are phosphorylated by tyrosine; (4) STATs dissociate from the receptor to form homodimers or heterodimers; (5) STAT dimers enter the nucleus, bind to DNA, and regulate transcription. Negative regulation of the JAK/STAT signaling pathway: There are three main types of proteins involved in the negative regulation of the JAK/STAT signaling pathway: the PIAS (protein inhibitor of activated STAT), CIS/SOCS (suppressor of cytokine signaling) family, and PTPs (protein tyrosine phosphatase). PIAS mainly interacts with STAT dimers to inhibit STAT binding to DNA, thereby blocking JAK/STAT signal transduction. The CIS/SOCS family negatively regulates the JAK/STAT pathway in three ways: (1) binding to a tyrosine kinase receptor to block the recruitment of STAT; (2) binding directly to JAK to inhibit its kinase activity; (3) forming an elongin B/C-cullin5 complex that degrades JAK or STAT bound to the SOCS protein through polyubiquitination and proteasome degradation. PTPs inhibit the JAK/STAT pathway by interacting with JAK, STAT, or receptors to (1) dephosphorylate the STAT dimer; (2) interact with the receptor to dephosphorylate the related JAK; and (3) in the case of CD45 (a transmembrane PTP) inhibits the phosphorylation of JAK. Created with BioRender.com



Signaling cross-talk between JAK/STAT and other pathways. (1) STAT3-p300- SMAD1 forms a complex to induce astrocyte differentiation; (2) JAK1 binds to TGFBR1 and activates STAT3; (3) TGF-β also activates STAT3 via SMAD-dependent manner. (4) STAT3 inhibits SMAD3-SMAD4 complex formation and suppress SMAD3-DNA binding; (5) SMAD3 inhibits STAT3 activation via recruiting PIAS3 to STAT3; (6) TGF-β blocks IL-12 mediated JAK2 and TYK2 tyrosine phosphorylation; (7) Notch signaling suppresses JAK/STAT activation by interfering with STAT translocation to the DNA domain, and signals of JAK/STAT inhibited Notch signaling conversely. (8) Hes proteins directly bind to STAT3 and induce phosphorylation by recruiting JAK2; (9) STAT5 direct interacts with PI3K; (10) STAT5 upregulates the expression of p85α (PI3r31), p110α (PI3cα), and AKT1; (11) STAT3 drives the hyperacetylation of RelA via interacting with p300; (12) cyclooxygenase-2, IL-17, IL-21, and IL-23 encoded by NF-κB activate STAT3; (13) NF-κB preceded ISGF3 (a complex containing STAT1, STAT2, and IRF9 subunits) at the Nos2 promoter, thus regulating nitric oxide synthase expression; (14) IRF9-STAT1-STAT2 trimeric complex induces gene expression; (15) STAT1 regulates IRF8 synthesis; (16) STAT5 suppresses IRF8 activity; (17) STAT1 and IRF1 synergistic induce IFNy-induced gene transcription; (18) IRF8 increases IFNy-induced gene transcription mediated by STAT1 and IRF1. Created with BioRender.com

From: [The JAK/STAT signaling pathway: from bench to clinic](#)



Chemical structures of JAK inhibitors.

The **JAK-STAT pathway** is crucial for immune cell signaling and inflammation control. Its **dysregulation** is linked to diseases like **autoimmune disorders, cancer, COVID-19, and neurodegeneration**. **JAK inhibitors** are being used or explored as treatments for these conditions by targeting the pathway to reduce inflammation and abnormal cell growth.

<https://www.kegg.jp/entry/K11217> -JAK1 pathway



## ORTHOLOGY: K11217

[Help](#)

Entry	K11217	KO
Symbol	JAK1	
Name	Janus kinase 1 [EC:2.7.10.2]	
Pathway	map01521 EGFR tyrosine kinase inhibitor resistance map04151 PI3K-Akt signaling pathway map04217 Necroptosis map04380 Osteoclast differentiation map04550 Signaling pathways regulating pluripotency of stem cells map04620 Toll-like receptor signaling pathway map04621 NOD-like receptor signaling pathway map04630 JAK-STAT signaling pathway map04658 Th1 and Th2 cell differentiation map04659 Th17 cell differentiation map05140 Leishmaniasis map05145 Toxoplasmosis map05152 Tuberculosis map05160 Hepatitis C map05161 Hepatitis B map05162 Measles map05163 Human cytomegalovirus infection map05164 Influenza A map05165 Human papillomavirus infection map05166 Human T-cell leukemia virus 1 infection map05167 Kaposi sarcoma-associated herpesvirus infection map05168 Herpes simplex virus 1 infection map05169 Epstein-Barr virus infection map05171 Coronavirus disease - COVID-19 map05200 Pathways in cancer map05203 Viral carcinogenesis map05212 Pancreatic cancer map05235 PD-L1 expression and PD-1 checkpoint pathway in cancer	

<https://www.kegg.jp/pathway/map05171+K11217> Covid 19 & pathways involved

Go down to get the genes involved, their inhibitors, targets:  
<https://www.kegg.jp/entry/hsa:3716>

<http://bioinformatics.sdsstate.edu/go/>

<https://www.bioinformatics.com.cn/en>

To get **Fold Change (FC)** values for a **KEGG pathway**, you **don't calculate a single FC for the entire pathway** — instead, you analyze **gene-level FC values** (often as **log2FC**) and **map those to KEGG pathways** to find **enriched biological themes**. Here's how it works step-by-step:

---

### Step-by-Step: Getting FC Values for a KEGG Pathway

## Step 1: Perform Differential Gene Expression (DGE) Analysis

- Use your RNA-Seq data (or microarray) and tools like:
  - **DESeq2** (R)
  - **edgeR** (R)
  - **limma**
- Output: A table with genes, **log2FC**, **p-value**, **adjusted p-value (FDR)**.

Gene	log2FC	p-value	FDR
GeneA	2.1	0.001	0.01
GeneB	-1.8	0.005	0.04
GeneC	0.3	0.9	0.98

---

## Step 2: Identify Differentially Expressed Genes (DEGs)

- Use thresholds:
  - $|\text{log2FC}| > 1.5$  or  $> 2$
  - **adjusted p-value (FDR) < 0.05**
- This gives you the list of genes significantly up/downregulated.

---

## Step 3: Map DEGs to KEGG Pathways

- Use tools like:
  - **Enrichr**

- **ClusterProfiler (R package)**
- **GSEA (Gene Set Enrichment Analysis)**
- **DAVID**
- **KEGG Mapper**
- **Pathview (for visualization)**

These tools match your DEGs (with log2FC values) to KEGG-defined gene sets (pathways), and calculate:

- Which pathways are **enriched**
  - How many genes are up/down in each pathway
  - The **average FC or log2FC** of genes within each pathway (optional summarization)
- 

### **Optional: Get "Pathway-Level FC"**

While KEGG pathways don't have a direct FC value:

- Some analyses compute **mean log2FC** of all DEGs in a pathway
- Or visualize each gene's FC on the pathway map using **Pathview**

Pathway	Genes Involved	Avg log2FC
p53 Signaling Pathway	TP53, CDKN1A, MDM2	1.7
Cytokine-cytokine interaction	IL6, TNF, IL10	-2.0

---

### **In Summary:**

- **FC values are calculated per gene.**

- You use gene FC (or log2FC) to identify DEGs.
  - Then, you map DEGs to KEGG pathways to find which pathways are affected.
  - Some tools visualize or calculate average pathway FC, but this is derived **from individual gene FCs**, not a separate measurement.
- 

## Want to try it out?

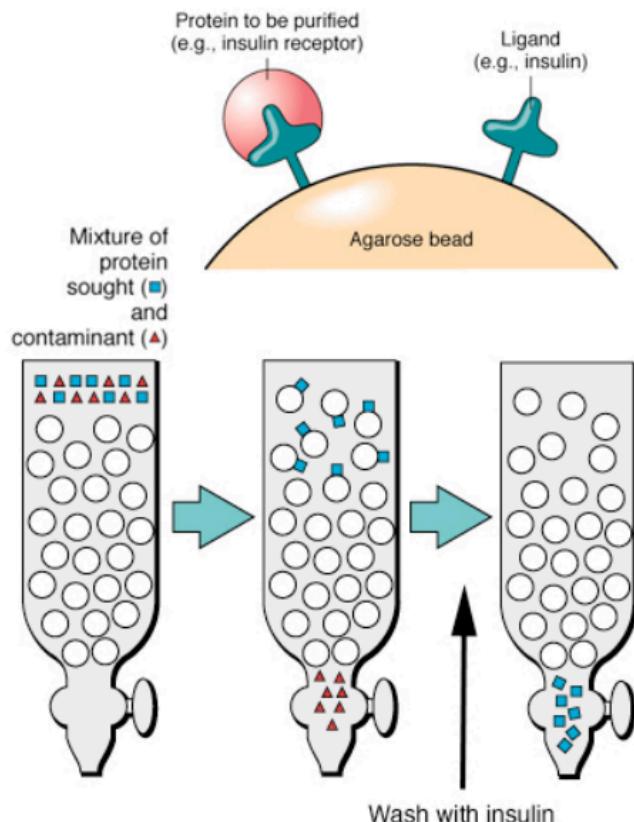
If you have a CSV of gene expression values or log2FC results, I can help you:

- Filter DEGs
- Perform basic KEGG pathway mapping
- Even simulate how genes appear on a KEGG map (e.g., color-coded by up/downregulation)

Just upload your file and let me know what you'd like to see!

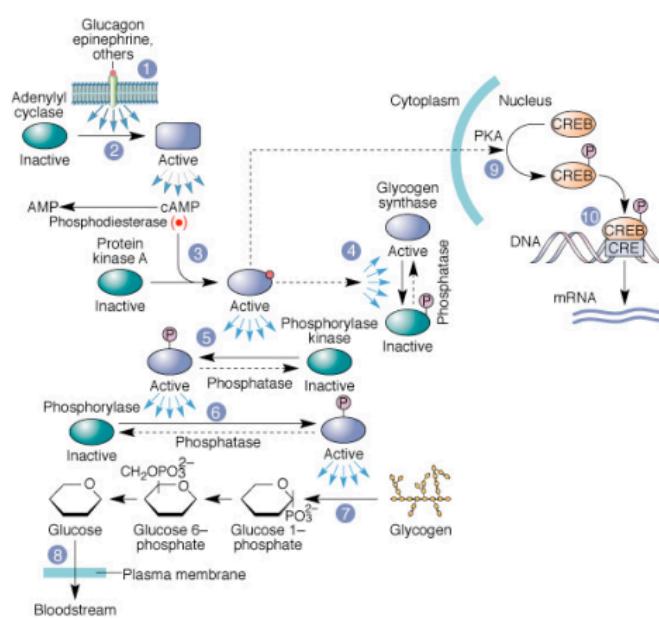
<https://www.bioinformatics.com.cn/en?keywords=enrichment>

The receptor can be purified in some cases by means of **affinity chromatography**: the hormone is linked to agarose beads. Crude, solubilized membranes are passed through a column with these beads, which will retain only their specific receptor. The receptor is later released by passing excess hormone through the column. A single pass can produce a 100,000 fold enrichment.



### Glucose Mobilization

- Glucose is stored in animal cells as glycogen, an insoluble polymer.
- The enzyme phosphorylase catalyzes glycogen breakdown, while glycogen synthase catalyzes polymerization.
- Regulation is achieved by several hormones, such as glucagon (from the pancreas) and epinephrine (from the adrenal medulla).

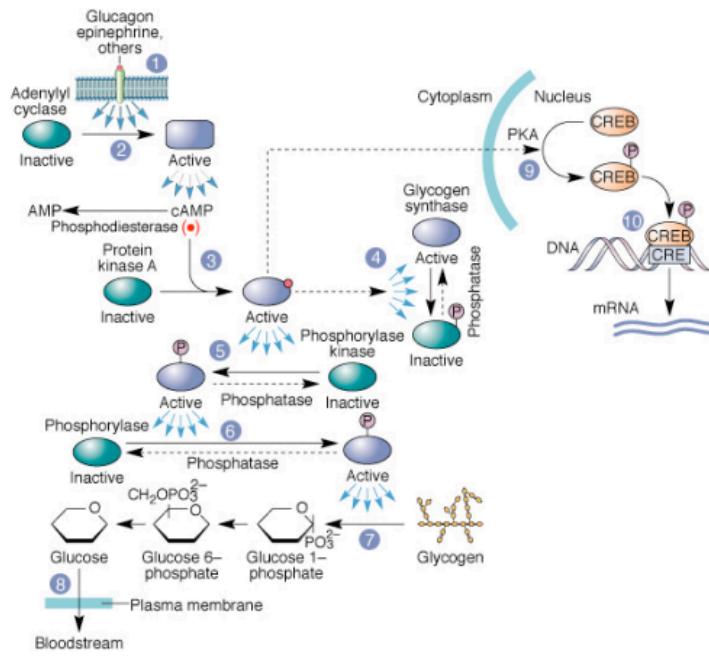


- Binding of epinephrine or glucagon to their receptors activates adenyl cyclase.
- cAMP binds to the regulatory subunit of protein kinase A (PKA) causing the release of the catalytic subunit.
- PKA phosphorylates and inhibits glycogen synthase.
- PKA phosphorylates and activates phosphorylase kinase, which then phosphorylates and activates phosphorylase.
- PKA also translocates to the nucleus where it phosphorylates the transcription factor CREB. Phosphorylated CREB binds to the CRE enhancer activating genes involved in gluconeogenesis.

## Amplification

Because the concentration of hormones in the blood is very low ( $<10^{-8}$  M), the signal has to be amplified:

- binding of a single ligand stimulates a large number of adenylyl cyclases,
- each producing a large number of cAMPs.
- each two cAMPs activates a PKA,
- which in turn phosphorylates a number of other proteins, and so on.



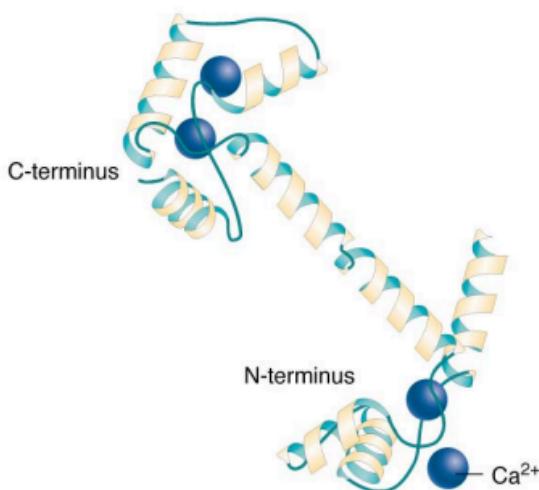
## Termination

Termination of the signal involves phosphatase-1, which removes phosphate groups from the different enzymes. Its activity is regulated by inhibitor-1, which itself is activated by PKA. Because cAMP is continually degraded, when the hormone dissociates from its receptor and adenylyl cyclase is shut down, cAMP levels quickly drop. This inactivates PKA and thus inhibitor-1, leading to the activation of phosphatase-1.

$\text{Ca}^{++}$  effects includes exocytosis of secretory vesicles, muscle contraction or the induction of mitosis in fertilized eggs.

To trigger these responses calcium affects a number of cellular effectors. In most cases it does it in conjunction with the calcium-binding protein **calmodulin**. This protein is found in all eukaryotes and is widely conserved in sequence among species.

When the concentration of  $\text{Ca}^{++}$  increases calmodulin binds 4  $\text{Ca}^{++}$  ions. This results in a large conformational change in the protein that increases its affinity for a number of effector proteins.

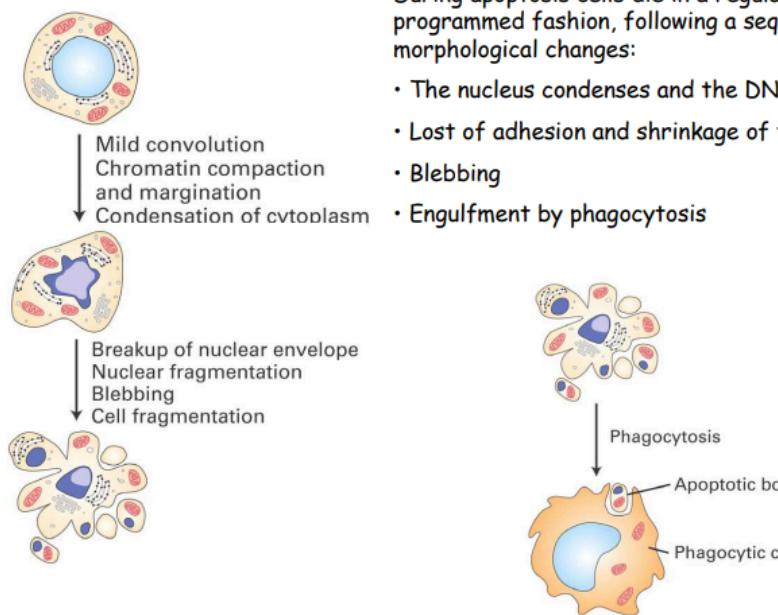


Summarizes some protein that regulate calcium signaling in diverse cell types.

PROTEIN	CELLULAR/PHYSIOLOGICAL FUNCTION	REFERENCE
<i>Adenylyl cyclase (AC Type-1)</i>	Act as second messengers in regulatory processes in the central nervous system.	[79]
<i>Annexins</i>	Annexin I modulates cell functions by controlling intracellular $\text{Ca}^{2+}$ release.	[80]
<i><math>\text{Ca}^{2+}/\text{Calmodulin-dependent protein kinase (CaMK)}</math></i>	Wnt7a signaling promotes dendritic spine growth and synaptic strength through $\text{Ca}^{2+}/\text{Calmodulin}$ -dependent protein kinase II.	[81]
<i><math>\text{Ca}^{2+}\text{-ATPase (SERCA)}</math></i>	The sarco/endoplasmic reticulum $\text{Ca}^{2+}$ ATPase (SERCA) is the third element in capacitative calcium entry.	[82]
<i><math>\text{Ca}^{2+}</math>-dependent endonucleases</i>	$\text{Ca}^{2+}/\text{Mg}^{2+}$ -dependent endonucleases are drivers of apoptosis.	[83]
<i>Calcineurin</i>	Calcineurin is a common target of cyclophilin-cyclosporin A and FKBP-FK506 complexes.	[84]
<i>Calcium channel blockers</i>	Important roles in arterial and pulmonary hypertension.	[85]
<i>Calcium Release-Activated Channel (CRAC)</i>	STIM1 is a $\text{Ca}^{2+}$ sensor that activates CRAC channels and migrates from the $\text{Ca}^{2+}$ store to the plasma membrane.	[86]

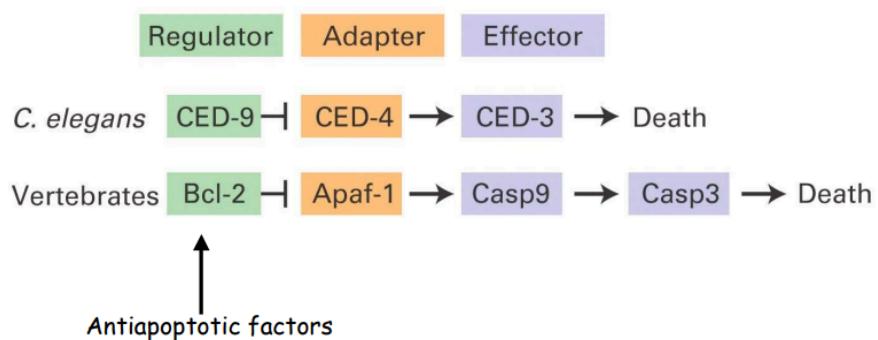
<https://pmc.ncbi.nlm.nih.gov/articles/PMC6651758/#sec2-ijms-20-03292>

## V Cell Signaling and Apoptosis



## Importance of Apoptosis

- Billions of cells in our body die by apoptosis every day.
- Apoptosis is essential during development
  - morphogenesis
  - neurons
  - T lymphocytes
- Apoptosis is used as a control against cancer development



[https://mcb.berkeley.edu/courses/mcb110spring/nogales/mcb110\\_s2008\\_4signaling.pdf](https://mcb.berkeley.edu/courses/mcb110spring/nogales/mcb110_s2008_4signaling.pdf)

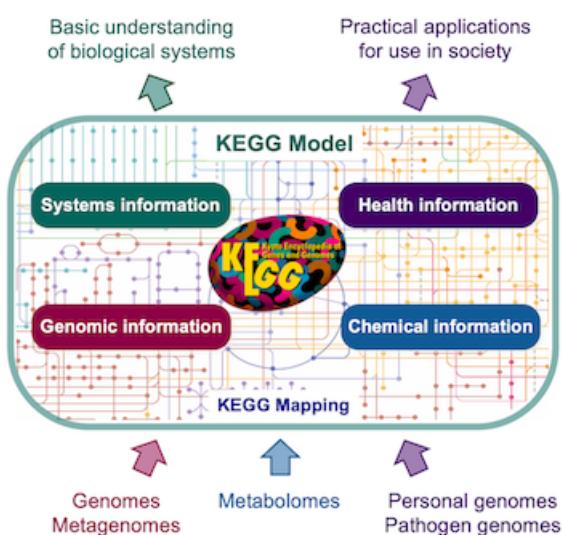
### Important websites:

<https://www.cellsignal.com/>

<https://www.ebi.ac.uk/interpro/result/InterProScan/#table>

<https://www.science.org/journal/signaling>

<https://www.genome.jp/kegg/>



<i>Flow cytometry</i>	<ul style="list-style-type: none"> <li>• Multiplex flow cytometry.</li> </ul>
<i>Chromatography</i>	<ul style="list-style-type: none"> <li>• Ion Exchange Chromatography.</li> <li>• Affinity Chromatography.</li> <li>• Gel Filtration Chromatography</li> </ul>
<i>Spectroscopy</i>	<ul style="list-style-type: none"> <li>• Circular Dichroism.</li> <li>• Optical rotatory dispersion.</li> <li>• NMR Spectroscopy.</li> </ul>
<i>Algorithms</i>	<ul style="list-style-type: none"> <li>• IQR algorithm.</li> <li>• ConCavity.</li> <li>• High-Performance Multi-Objective Evolutionary Algorithm (HPMOEA).</li> <li>• Synthetic Genetic logic circuits.</li> </ul>
<i>Transcriptomics and metabolomics characterization</i>	<ul style="list-style-type: none"> <li>• Single-cell RNA sequencing (scRNA-seq).</li> <li>• Microarray analysis.</li> <li>• NanoString Counter analysis.</li> <li>• Ingenuity Systems Pathways Analysis (IPA).</li> </ul>
<i>Protein-protein interactions</i>	<ul style="list-style-type: none"> <li>• Yeast-two-hybrid.RNA sequencing.</li> </ul>
<i>Protein-nucleic acid interactions</i>	<ul style="list-style-type: none"> <li>• Western blotting and co-immunoprecipitation.</li> <li>• In vitro phosphorylation assays.</li> <li>• Phosphoproteomics.</li> <li>• Mass spectrometry.</li> <li>• 2-D gel electrophoresis.</li> <li>• Microchannel for multiparameter analysis of proteins in a single complex" (mMAPS).</li> <li>• Structure analysis -X-ray crystallography.</li> </ul>

Here's a simplified version with colorful bullet points to make it more appealing:

- **Genomic Data Insights** 
  1. ICGC cataloged genomic data from 50 cancer types.
  2. Only a few driver genes are frequently mutated, but many less common genes also play a role.
- **The Rise of Pathway & Network Analysis** 
  1. Interest in analyzing groups of genes to uncover cancer processes.
  2. Helps identify key pathways involved in cancer.
- **Key Genetic Changes Studied** 
  1. Common alterations: **SNVs, CNAs, structural changes, fusion transcripts, epigenetic reprogramming**.
  2. Data paired with **clinical information** for deeper insights.
- **Understanding Cancer Mutation Patterns** 
  1. Cancers like prostate cancer have fewer mutations, while others (pancreatic, lung, breast) have a wider range.
  2. **Driver genes**: Often identified by positive selection, but some important genes are overlooked due to sample size limitations.
- **Pathways vs. Networks** 
  1. **Pathways**: Well-defined biological processes (e.g., signaling).
  2. **Networks**: Broad, complex gene interactions that capture cellular logic.
  3. **Networks** are harder to interpret but offer new insights.
- **Benefits of Pathway & Network Analysis** 
  1. **Aggregates** multiple gene events into meaningful biological processes.
  2. Results are easier to interpret, focusing on key processes like **cell cycle** or **apoptosis**.
  3. Helps identify **drug targets** and potential **tumor subtypes**.

- **Analyzing Cancer Data** 

1. **MUCOPA** (ICGC group) developed standard methods for analyzing cancer genomics.
2. Focuses on **somatic mutations**, but methods can apply to **CNAs**, **epigenetics**, and other changes.

- **Three Major Approaches to Analysis** 

1. **Gene Set Enrichment**: Analyzes gene sets from pathway databases.
2. **Network Construction & Clustering**: Builds networks from gene interactions.
3. **Network Modeling**: Uses advanced techniques to interpret complex interactions.

This approach helps **integrate data** (genomic, transcriptomic, proteomic) for a **unified view** of cancer biology.

Here's a simplified and more digestible version with colorful bullet points:

## Simplified Overview of Pathway & Network Analysis

### Pathway Representation (A) vs. Network Representation (B)

- **Pathway Representation** :

- Includes genes, proteins, small molecules, and their interactions.
- Genes don't directly interact but participate in reaction events (white squares).

- **Network Representation** :

- All nodes are the same biological entity (e.g., gene products).
- Bold arrows = curated pathway interactions; light lines = gene-gene interactions (like co-expression or physical interactions).

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### Approach 1: Fixed Gene Set Enrichment Analysis

- **What it is:**

- Treats pathways and networks as simple gene sets.
- Identifies over-represented genes in a given list based on chance.
- **Steps:**
  - **Define Gene List:** Filter for significant genes in a dataset.
  - **Enrichment Analysis:** Find pathways and processes enriched in the list.
- **Tools:**
  - Hypergeometric tests (e.g., Fisher's exact test) estimate statistical significance.
  - Software tools available for analysis (e.g., DAVID, g:Profiler, GSEA).
- **Challenges:**
  - Fixed gene thresholds may exclude important genes.
  - **Solutions:** Advanced tools like **g:Profiler** and **GSEA** can work with ranked gene lists, considering gene expression strength.

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## Approach 2: De Novo Network Construction & Clustering [🔗](#)

- **What it is:**
  - Builds cancer gene networks by analyzing molecular interactions.
  - Starts with mutated genes, then integrates interaction databases (e.g., BioGRID, STRING).
- **How it Works:**
  - Gene mutations interact with neighbors in a reconstructed network.
  - **Guilt by association:** Non-mutated genes linked to altered genes may play a role in cancer.
- **Tools:**
  - **GeneMANIA:** Suggests related genes based on network analysis.

- **ReactomeFIViz:** Clusters genes and relates them to tumor phenotypes.
  - **MEMo:** Studies mutual exclusivity in cancer alterations.
- **Challenges:**
    - Limited data models and lack of depth in biological interaction understanding.
- 

## Approach 3: Network-Based Modeling

- **What it is:**
    - Uses networks to infer how genetic components interact and change in cancer.
    - Helps model the activity of genes and pathways disrupted in cancer.
  - **Examples:**
    - **HotNet:** Uses heat diffusion to map gene alterations and network influences.
    - **Pathifier:** Ranks cancer samples based on biological attributes (e.g., tumor aggressiveness).
    - **SPIA:** Quantifies impacts of gene changes and ranks them hierarchically.
  - **Challenges:**
    - Requires high-resolution data that's often unavailable.
    - Models can be computationally expensive and complex.
- 

## Challenges & Future Perspectives

- **Incomplete Data:** Pathways and networks in normal and cancer cells are not fully understood.
- **Computational Costs:** High computational demands for analyzing large datasets.
- **Complex Interactions:** Mutations' roles vary depending on other mutations and cell states.

- **Clinical Application:** The challenge of integrating these methods into personalized cancer treatment.
- 

## The Big Picture

- Pathway and network analyses offer transformative potential in understanding cancer biology and treatment.
- The next step is developing better databases, refining models, and making these tools more practical for clinical use.