

Areas of Signaling in GO to Focus on

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Gene Ontology Signaling Workshop
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http://gocwiki.geneontology.org/index.php/Signaling_Workshop_February_2010#Topics

What Needs To Be Done?

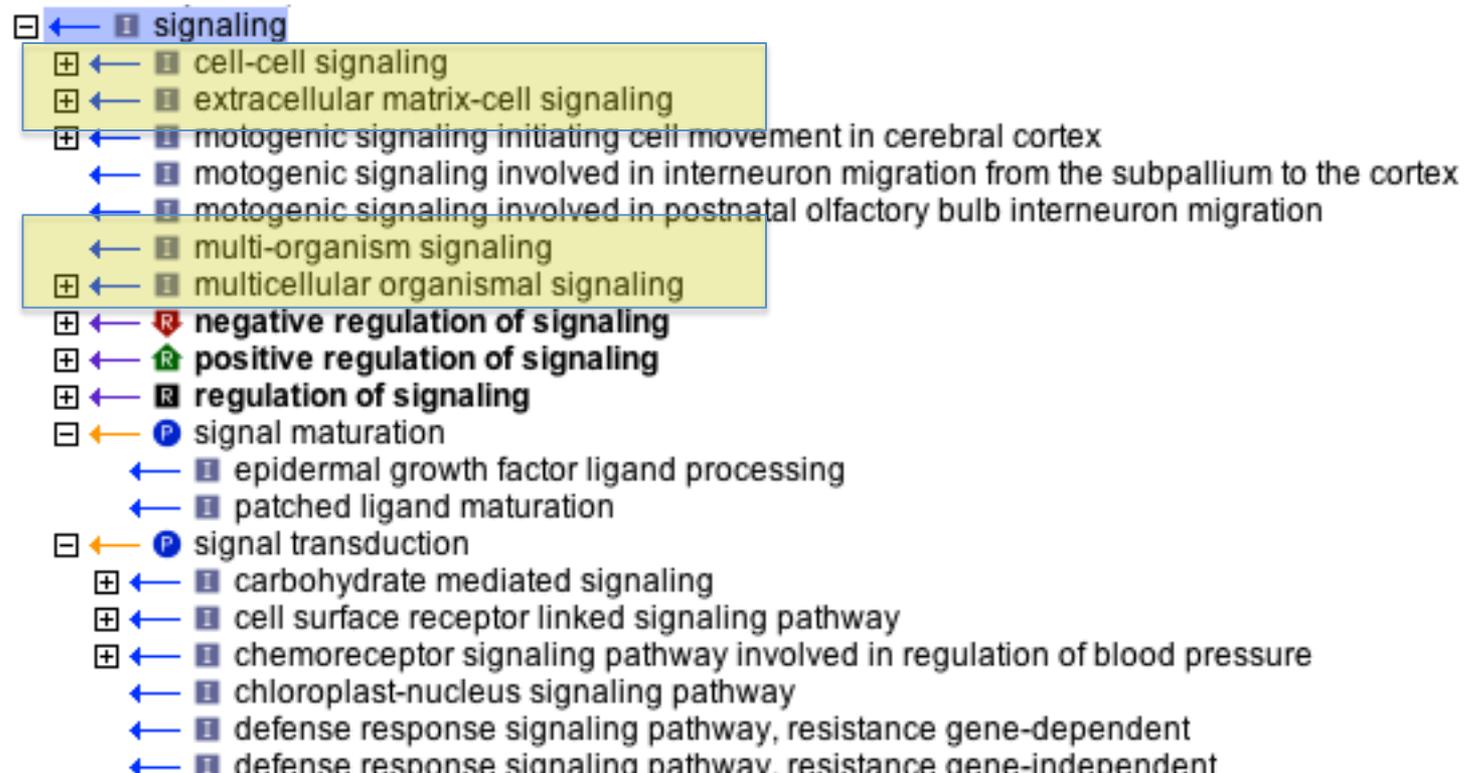
- ❖ What should and shouldn't be covered by signaling?
- ❖ Defining the start and end points of all signaling processes
 - signaling
 - generation of a signal
 - signal transduction
 - initiation of signal transduction
 - termination of signal transduction
 - signaling pathway
 - signaling cascade
 - paracrine/autocrine/endocrine signaling
- ❖ Defining a receptor
- ❖ Connecting cell-surface receptors with the intracellular signaling cassettes
- ❖ Dealing with non 1:1 ligand:receptor combinations
- ❖ How does receptor-mediated endocytosis fit with signaling?
- ❖ Is it important HOW a signal reaches the receiving cell?

TOP LEVEL TERM: SIGNALING

DEFINITION AND SCOPE OF SIGNALING

❖ signaling ; GO:0023052

- Current Def: *The entirety of a process whereby information is transmitted. This process begins with the initiation of the signal and ends when a response has been triggered.*



Cellular vs. multicellular vs. multi-organism

- ❖ BACKGROUND: GO process has 3 broad DISJOINT grouping terms among its children. The disjoint means that child terms can only be is_a to ONE of the three grouping terms. They can be connected to the other terms via part_of relationships, if needed. *The signaling node was split in the same way.*
- ◆ multi-organism process ; GO:0051704
 - *Current Def: Any process in which an organism has an effect on another organism of the same or different species*
- ◆ multicellular organismal process ; GO:0032501
 - *Current Def: Any biological process, occurring at the level of a multicellular organism, pertinent to its function.*
- ◆ cellular process ; GO:0009987
 - *Current Def: Any process that is carried out at the cellular level, but not necessarily restricted to a single cell. For example, cell communication occurs among more than one cell, but occurs at the cellular level.*

DEFINITION AND SCOPE OF SIGNALING

signaling ; GO:0023052

- Current Def: *The entirety of a process whereby information is transmitted. This process begins with the initiation of the signal and ends when a response has been triggered.*

Q1: Where does initiation of the signal begin?

- transcription of the ligand?
 - translation of the ligand?
 - post-translational modifications to the ligand?
 - (what about where the ligand isn't a protein (e.g. external nutrient, photon...)?
-
- ❖ The difference between 'signaling' and 'signal transduction': signal transduction is limited to molecular events in the receiving cell, where the signal is received and passed on. Signaling is a grouping term.

DEFINITION AND SCOPE OF SIGNALING

Q: Should we put ligand metabolism terms under signaling?

Q: Should we put ligand transport terms (transport from signaling to receiving cells) under signaling?

Q: Should we put receptor metabolism terms under 'signaling'?

- generation of the receptor
- (ligand-independent) processing of the receptor
- Transport of the receptor to its site of activity (E.g. cell surface)

Q: Is there anything we have included under signaling that **shouldn't** be there?

Q: Is there anything we haven't included under signaling that **should** be there?

- NB: The old term 'behavioral signaling' was merged into 'behavioral interaction between organisms', so that GO:0023052 now represents molecular signaling.

autocrine vs. paracrine

Q: Should we distinguish between 'endocrine' and 'paracrine' signaling in GO?

endocrine signaling ; GO:NEW

Def: The transfer of information from one cell to another, where an endocrine hormone is transported from the signal-producing cell to the receiving cell via the circulatory system (via blood, lymph or cerebrospinal fluid). The signaling cell and the receiving cell are often distant to each other.

is_a: cell-cell signaling ; GO:0007267

part_of: endocrine process ; GO:0050886

part_of: multicellular organismal signaling ; GO:0035637

ISBN:3527303782, ISBN:0199264678

paracrine signaling ; GO:NEW

Def: The transfer of information from one cell to another, where the signal travels from the signal-producing cell to the receiving cell by passive diffusion or bulk flow in intercellular fluid. The signaling cell and the receiving cell are usually in the vicinity of each other.

ISBN:3527303782

is_a: cell-cell signaling ; GO:0007267

('paracrine signaling' is currently a narrow synonym of cell-cell signaling ; GO:0007267)

SIGNALING

Q: Any other high-level problems people have come across?

DEFINING THE START AND END POINTS OF EACH PROCESS

GENERATION OF A SIGNAL

DEFINITION: 'GENERATION OF A SIGNAL'

- ❖ **generation of a signal involved in cell-cell signaling ; GO:0003001**
 - *Current Def: The cellular process that creates a physical entity or change in state, i.e. a signal, that originates in one cell and is used to transfer information to another cell. This process begins with the initial formation of the signal and ends with the mature form and placement of the signal.*
 - *Broad synonym: Formation of a signal*

Q: Where does 'initial formation of the signal' begin... ?

- Transcription of the gene encoding the ligand?
- Translation of the ligand?
- Post-translational modifications of the ligand?

(this also affects the definition of signaling ; GO:0023052)

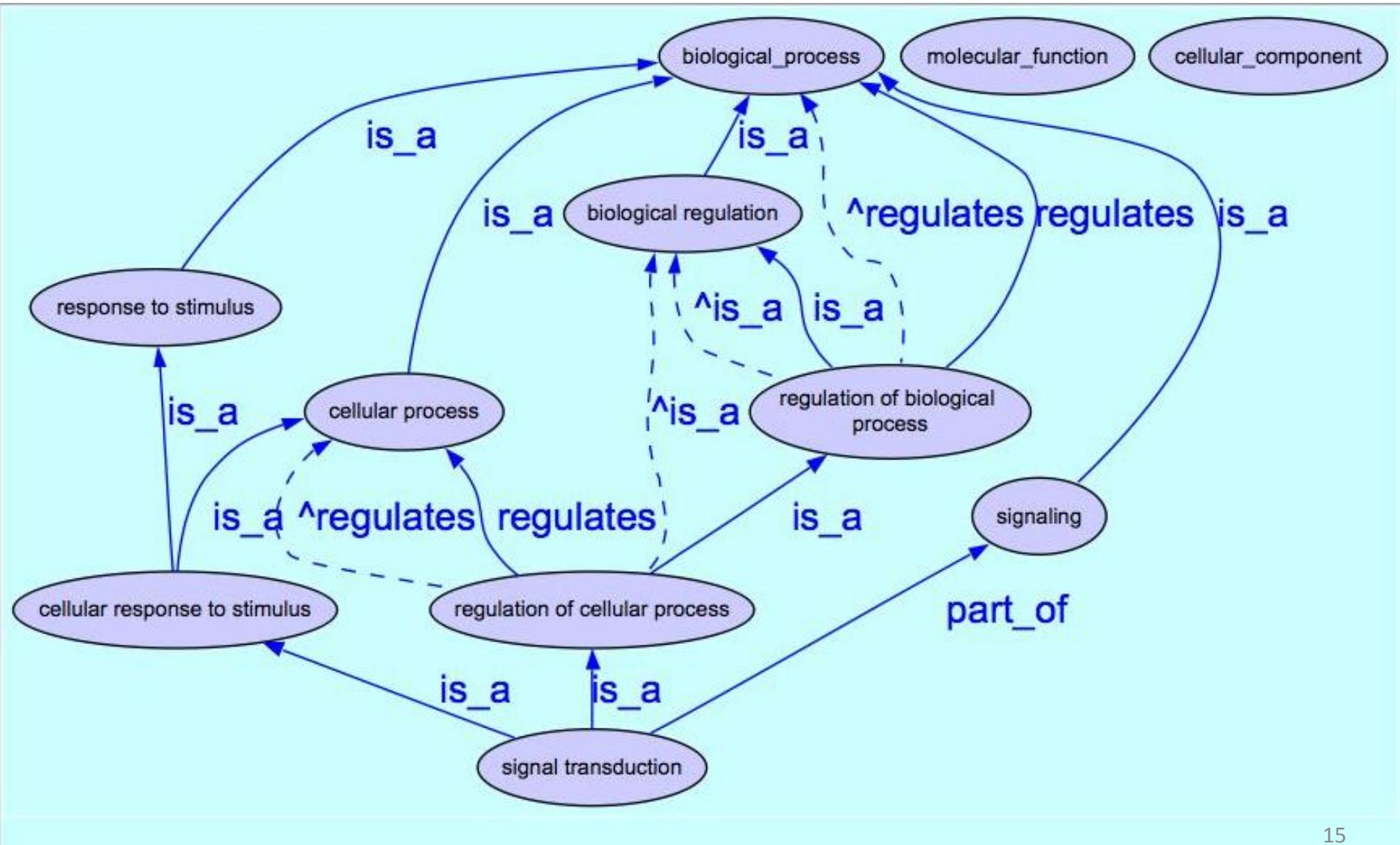
SIGNAL TRANSDUCTION

SIGNAL TRANSDUCTION

- [-] ← [I] signaling
 - [+] ← [I] cell-cell signaling
 - [+] ← [I] extracellular matrix-cell signaling
 - [+] ← [I] mitogenic signaling initiating cell movement in cerebral cortex
 - ← [I] mitogenic signaling involved in interneuron migration from the subpallium to the cortex
 - ← [I] mitogenic signaling involved in postnatal olfactory bulb interneuron migration
 - ← [I] multi-organism signaling
 - [+] ← [I] multicellular organismal signaling
 - [+] ← [R] **negative regulation of signaling**
 - [+] ← [R] **positive regulation of signaling**
 - [+] ← [R] **regulation of signaling**
 - [+] ← [P] signal maturation
 - [-] ← [P] signal transduction 
 - [+] ← [I] carbohydrate mediated signaling
 - [+] ← [I] cell surface receptor linked signaling pathway
 - [+] ← [I] chemoreceptor signaling pathway involved in regulation of blood pressure
 - ← [I] chloroplast-nucleus signaling pathway
 - ← [I] defense response signaling pathway, resistance gene-dependent
 - ← [I] defense response signaling pathway, resistance gene-independent
 - [+] ← [I] DNA replication checkpoint
 - [+] ← [I] ER-nucleus signaling pathway
 - [+] ← [I] hormone-mediated signaling pathway
 - ← [I] hydrogen peroxide mediated signaling pathway

The pathway terms have recently been moved back under signal transduction

- Signal transduction is a child of 'cellular response to stimulus' ...



DEFINITION: SIGNAL TRANSDUCTION

❖ signal transduction ; GO:0007165

- Current Def: *The process whereby a signal is passed across a cell to trigger a change in the activity or state of a cell. Signal transduction begins with reception of a signal and ends with regulation of a downstream process. Signal transduction covers signaling from receptors located on the surface of the cell, and signaling via molecules located within the cell. For signaling between cells, signal transduction is restricted to events at and within the receiving cell.*
- Defined broadly (no change in state necessary)
- Covers ligands, receptors and downstream signaling molecules

❖ signal transducer activity ; GO:0004871

- Current Def: *Conveys a signal across a cell to trigger a change in cell function or state. A signal is a physical entity or change in state that is used to transfer information in order to trigger a response.*
- Currently housing both receptors and intracellular signaling molecules
- Does NOT include ligands.

- ❖ KEY Q: Is signal transduction the **WHOLE** process from receptor-ligand binding to triggering a response. OR is each step a signal transduction? (this affects whether the intracellular cascades are is_a or part_of signal transduction).

INITIATION OF SIGNAL TRANSDUCTION

DEFINITION: INITIATION OF SIGNAL TRANSDUCTION

❖ **initiation of signal transduction ; GO:0023036**

- *The process whereby a signal causes activation of a receptor, for example, via a conformation change.*
- *Comment: Note that this term is intended for the annotation of both ligands and receptors.*

Q: Where does the process start? (ligand-receptor binding?)

Q: Where does the process end? (with an activated receptor?)

Q: Is it right that both receptors AND ligands can be annotated to the term, or should its use be restricted to ligands (the signal initiator) only?

Q: Could the term be phrased better?

Q: Is the term needed, with process-function links for ‘receptor agonist activity’?

TERMINATION OF SIGNAL TRANSDUCTION

DEFINITION: TERMINATION OF SIGNAL TRANSDUCTION

❖ **termination of signal transduction ; GO:0023021**

- *The signaling process whereby signal transduction is brought to an end rather than being reversibly modulated.*
- *Comment: Note that this term encompasses both the control point when the instruction is given for the process to cease and the actual cessation of the process. A process can persist for some time after that signal that induced the process is withdrawn.*

Q: Where does the process start?

Q: Where does the process end? (with the signal no longer being passed on)

Q: What kind of gene products would be annotated to this term?

- E.g. phosphatases, proteases, ubiquitin-tagging proteins?

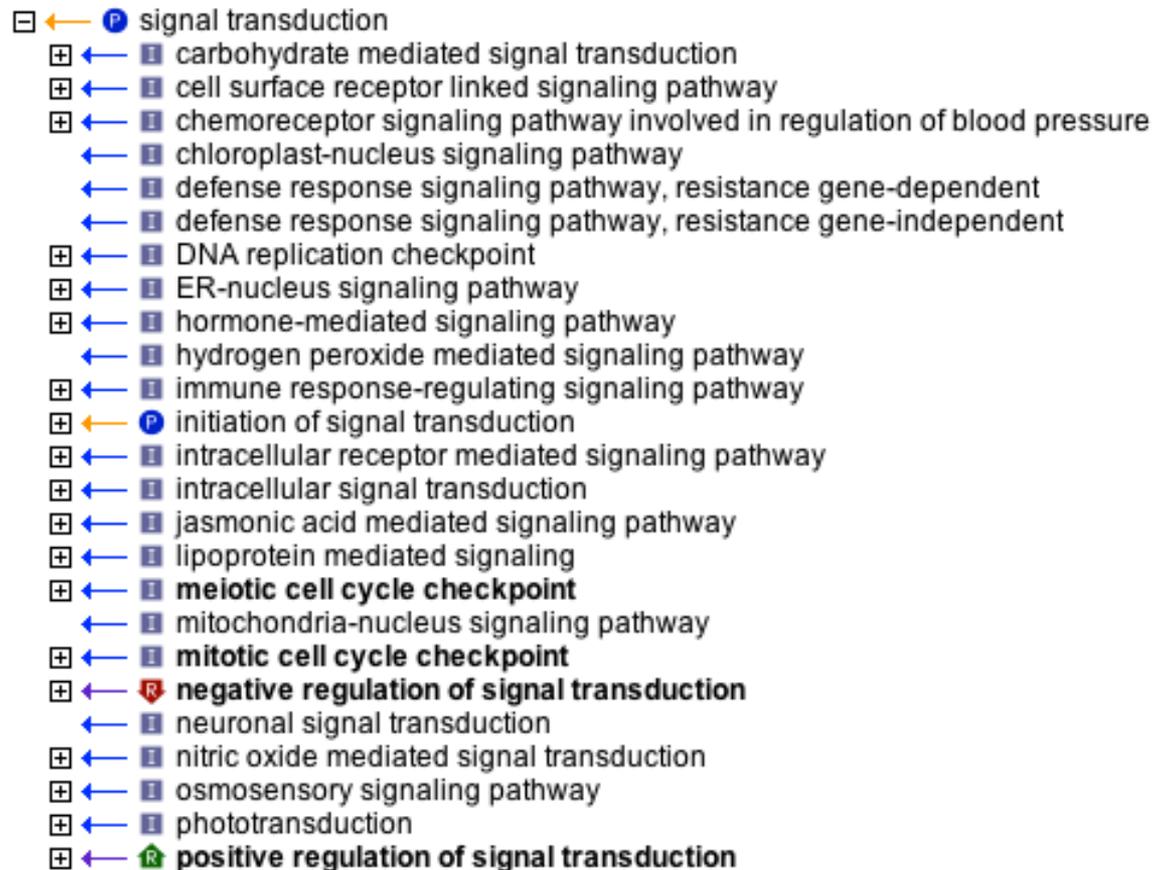
Q: Could a 'receptor agonist' be annotated to this term?

Q: Should it be part of 'signal transduction' or 'negative regulation of signal transduction'.

PATHWAYS

PATHWAY

- ❖ After removal of the process/pathway split, all pathway terms were put back under 'signal transduction', so there is no generic signaling pathway term.



PATHWAY DEFINITION

In GO:

- ❖ A signaling pathway is limited to events within the RECEIVING CELL
- ❖ The pathway begins with receptor-ligand binding.
- ❖ The pathway ends with regulation of a downstream cellular process.
- ❖ A ligand is part of the pathway (so can be annotated to signal transduction)

Q: Are the GO start and end points correct?

Q: Is it correct to name them all 'pathways' (rather than signal transduction or signal transduction pathways)?

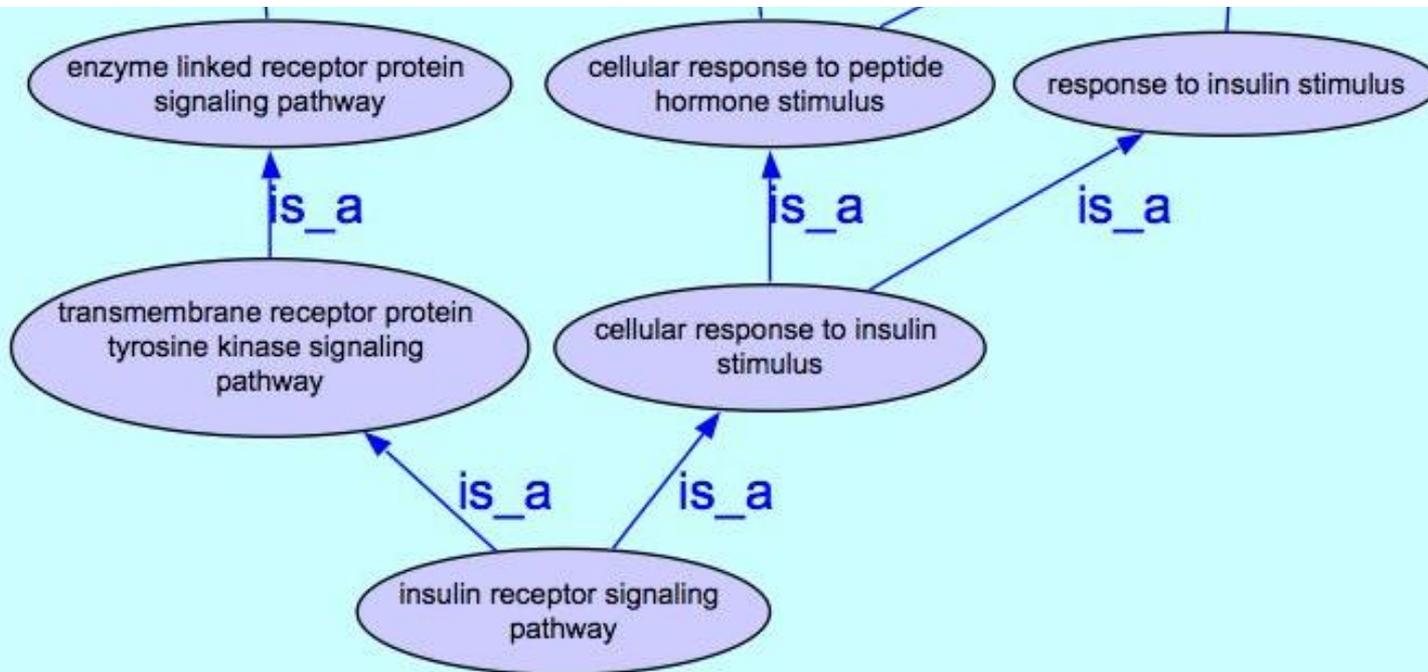
E.g.

glutamate signaling pathway

Notch signaling pathway

cytokine-mediated signaling pathway

hydrogen peroxide mediated signaling pathway



❖ A potential problem ??.....

- If the ligand is part of the pathway, 'insulin' would receive the annotation: 'response to insulin stimulus'.

Pathways and downstream processes

- ❖ One thing GO wanted to do was to connect up the pathways to their downstream processes. There are 2 'stages' of downstream processes:
 - **CELLULAR** (E.g. transcription, protein synthesis, apoptosis)
 - **MULTI-CELLULAR** (E.g. heart development, wound healing, pattern formation)
- ❖ Each pathway **REGULATES** a **CELLULAR PROCESS**.
- ❖ And these cellular processes are involved in multi-cellular processes (E.g. heart development, pattern formation, lung induction).
- ❖ So the GO term:
 - **Wnt receptor signaling pathway involved in kidney development ; GO:0061289**
means Wnt receptor signaling pathway involved in regulating x cellular process (probably transcription) that contributes to kidney development.

As a general rule: If a protein is part of a downstream cellular process (E.g. a transcription factor involved in transcription, glycogen synthase involved in glycogen synthesis), it's not part of the pathway itself.

How Pathways are currently split in GO

- [-] ← [I] signal transduction
 - [-] ← [I] carbohydrate mediated signaling
 - [-] ← [I] cell surface receptor linked signaling pathway
 - [-] ← [I] chemoreceptor signaling pathway involved in regulation of blood pressure
 - [-] ← [I] chloroplast-nucleus signaling pathway
 - [-] ← [I] defense response signaling pathway, resistance gene-dependent
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 - [-] ← [I] DNA replication checkpoint
 - [-] ← [I] ER-nucleus signaling pathway
 - [-] ← [I] hormone-mediated signaling pathway
 - [-] ← [I] hydrogen peroxide mediated signaling pathway
 - [-] ← [I] immune response-regulating signaling pathway
 - [-] ← [P] initiation of signal transduction
 - [-] ← [I] intracellular receptor mediated signaling pathway
 - [-] ← [I] intracellular signal transduction
 - [-] ← [I] jasmonic acid mediated signaling pathway
 - [-] ← [I] lipoprotein mediated signaling
 - [-] ← [I] mitochondria-nucleus signaling pathway
 - [-] ← [R] negative regulation of signal transduction
 - [-] ← [I] neuronal signal transduction
 - [-] ← [I] nitric oxide mediated signal transduction
 - [-] ← [I] osmosensory signaling pathway
 - [-] ← [I] phototransduction
 - [-] ← [R] positive regulation of signal transduction
 - [-] ← [I] red or far-red light signaling pathway
 - [-] ← [I] regulation of conjugation with cellular fusion by signal transduction
 - [-] ← [I] regulation of floral organ abscission by signal transduction
 - [-] ← [R] regulation of signal transduction
 - [-] ← [I] salicylic acid mediated signaling pathway
 - [-] ← [P] signal transducer activity
 - [-] ← [I] signal transduction involved in conjugation with mutual genetic exchange
 - [-] ← [I] signal transduction involved in filamentous growth
 - [-] ← [I] signal transduction involved in regulation of gene expression
 - [-] ← [I] signal transduction via conformational transition
 - [-] ← [I] signal transduction via phosphorylation event
 - [-] ← [I] SMAD protein signal transduction
 - [-] ← [I] sphingolipid signaling pathway

What the pathway regulates

X-mediated signaling

Houses the intracellular cascades
MAPK, PI3K, TOR.....

Ways in which a signal is passed on

How Pathways are split in GO

cell surface receptor linked signaling pathway ; GO:0007166

- *Any series of molecular signals initiated by the binding of an extracellular ligand to a receptor on the surface of the target cell.*

intracellular receptor mediated signaling pathway ; GO:0030522

- *Any series of molecular signals initiated by a ligand binding to an receptor located within a cell.*

X-mediated signaling pathway.

- E.g. carbohydrate mediated signaling ; GO:0009756
- E.g. jasmonic acid mediated signaling pathway ; GO:0009867
- E.g. hydrogen peroxide mediated signaling pathway ; GO:0071588
- E.g. nitric oxide mediated signal transduction ; GO:0007263
- E.g. sphingolipid signaling pathway ; GO:0003376

Q: is x a ligand or a downstream signaling molecule?

Q: What's the logical way to split the pathways in GO?

NAMING: PATHWAY

- ❖ Cell surface receptor pathways are generally named after the RECEPTOR, rather than the ligand:
 - Notch signaling pathway ; GO:0007219
 - Wnt receptor signaling pathway ; GO:0016055
 - Epidermal growth factor receptor signaling pathway ; GO:0007173

- ⊕ ← ⓘ transmembrane receptor protein serine/threonine kinase signaling pathway
- ⊖ ← ⓘ transmembrane receptor protein tyrosine kinase signaling pathway
 - ← ⓘ Ⓟ activation of transmembrane receptor protein tyrosine kinase activity
- ⊕ ← ⓘ brain-derived neurotrophic factor receptor signaling pathway
- ← ⓘ ephrin receptor signaling pathway
- ⊕ ← ⓘ epidermal growth factor receptor signaling pathway
- ⊕ ← ⓘ fibroblast growth factor receptor signaling pathway
- ⊕ ← ⓘ growth hormone receptor signaling pathway
- ⊕ ← ⓘ hepatocyte growth factor receptor signaling pathway
- ⊕ ← ⓘ insulin receptor signaling pathway
- ⊕ ← ⓘ insulin-like growth factor receptor signaling pathway
- ⊕ ← ⓘ nerve growth factor receptor signaling pathway
- ⊕ ← ⓘ platelet-derived growth factor receptor signaling pathway
- ⊕ ← ⓘ sevenless signaling pathway
- ⊕ ← ⓘ Ⓟ signal complex assembly
- ← ⓘ Tie receptor signaling pathway
- ← ⓘ torso signaling pathway

Standardizing language: X-mediated signaling pathways

- ❖ **TASK:** Go through each pathway and decide if x is a ligand or a downstream signaling molecule.
- ❖ Where X is a ligand, I'd propose renaming to:
 - X-activated signaling pathway ; GO:xxxxxxOr
 - X-initiating signaling pathway ; GO:xxxxxx
- ❖ Where X is a downstream component, we can stick with:
 - X-mediated signaling pathway ; GO:xxxxxxOr
 - signaling via x ; GO:xxxxxx

Hormone signaling pathways

- ❖ https://sourceforge.net/tracker/?func=detail&aid=2974691&group_id=36855&atid=440764

Q: How should the following pathways be connected?

Q: Is there a need for both hormone, AND hormone_receptor pathways?

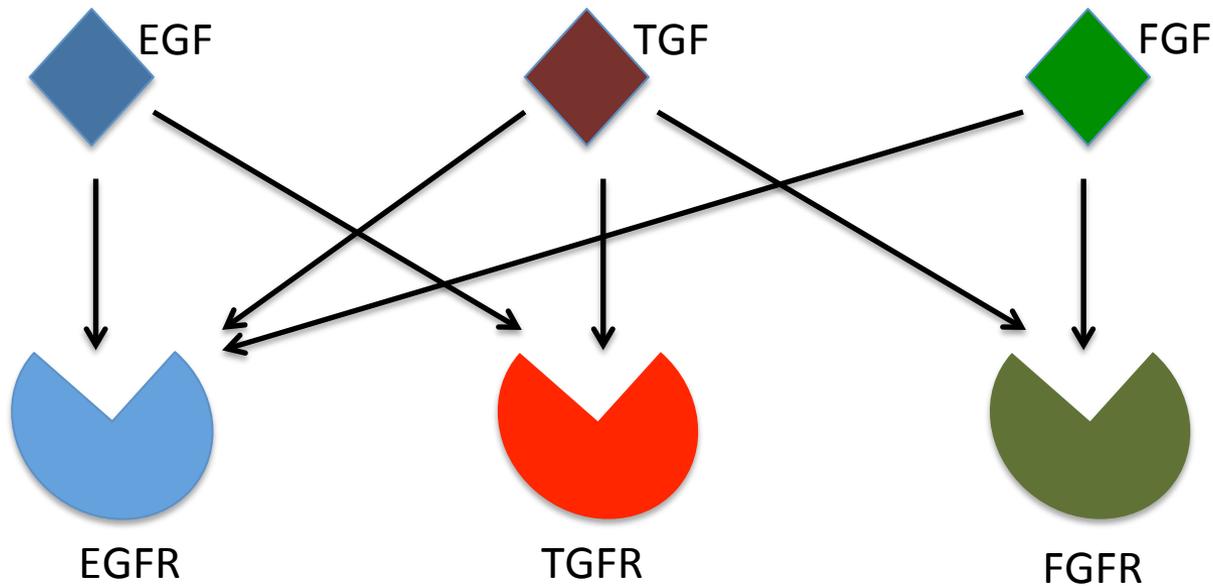
- ❖ steroid hormone mediated signaling pathway ; GO:0043401
- ❖ steroid hormone receptor signaling pathway ; GO:0030518
- ❖ glucocorticoid mediated signaling pathway ; GO:0043402
- ❖ glucocorticoid receptor signaling pathway ; GO:0042921

DEALING WITH NON 1:1 RECEPTOR-LIGAND COMBINATIONS

E.g. norrin signaling:

https://sourceforge.net/tracker/?func=detail&aid=3041964&group_id=36855&atid=440764

How do we deal with pathways where receptor-ligand binding is not 1:1?



- ❖ epidermal growth factor receptor activity ; GO:0005006
 - Combining with an epidermal growth factor to initiate a change in cell activity.
- ❖ transforming growth factor beta receptor activity ; GO:0005024
 - Combining with transforming growth factor beta to initiate a change in cell activity.

Non 1:1 receptor:ligand binding

- ❖ The problem (one of them) is that most receptors are named after the first ligand that was found to bind to them:
 - EGFR, PDGFR, TGFR, InsR, glutamate receptor etc..
- ❖ For function, we have to annotate the activity and not the gene product. To have the function of an EGFR, it has to bind EGF (and transduce the signal by a phosphorylation step). If it transmits the signal that is PDGF, it has the activity of a PDGFR (regardless of what the biologist calls it).
- ❖ For receptors named independently of the ligand, it's easier:
 - Wnt-activated frizzled signaling pathway
 - Norrin-activated frizzled signaling pathway
 - Wnt-activated signaling pathway

Non 1:1 receptor:ligand binding

Q: How do we best display cross-talk between pathways in the ontology?

RECEPTORS

(Molecular Function)

The Problems With Receptors

- ❖ They are a CLASS of protein, rather than an activity.
- ❖ They have multiple parts to their function, which are (often) carried out by different domains and create true path violations (TPVs):
 - bind a signal (function)
 - bind a downstream effector (function)
 - pass the signal on (process)
- ❖ Not all receptors are involved in signaling (e.g. transport receptors in receptor-mediated endocytosis).

The Problem With Receptors

- ❖ We could replace them with two terms
 - EGF binding involved in EGFR signaling pathway (Related synonym: EGFR).
 - Primary signal transduction involved in EGFR signaling pathway (Related synonym: EGFR).

OR

- ❖ We could accept that they're 'complex functions' and leave them in the ontology.
 - GO is moving to the idea that functions are mini-processes

if we keep receptors in function

RECEPTORS and HAS_PART PROPOSAL

https://sourceforge.net/tracker/?func=detail&aid=3103037&group_id=36855&atid=440764

Insert snapshot overview of what it would look like for EGFR.

Defining Receptors

- ❖ receptor activity ; GO:0004872
 - Current Def: *Combining with an extracellular or intracellular messenger to initiate a change in cell activity.*

- ❖ epidermal growth factor receptor activity ; GO:0005006
 - Current Def: *Combining with an epidermal growth factor to initiate a change in cell activity.*

Q: How can the definition of a receptor be improved?

Defining Receptors

Q: Should we split 'receptor activity ; GO:0004872' ? into:

- receptor activity involved in signaling ; GO:NEW
- receptor activity involved in receptor-mediated endocytosis ; GO:NEW

https://sourceforge.net/tracker/?func=detail&atid=440764&aid=2894756&group_id=36855

❖ Receptors involved in receptor-mediated endocytosis:

- lipoprotein receptor activity ; GO:0030228
- vitellogenin receptor activity ; GO:0008196

Q: Any others?

Ligand-dependent (nuclear) hormone receptors

ligand-dependent nuclear receptor activity

- Def: *A ligand-dependent receptor found in the nucleus of the cell.*
- ❖ PROBLEM: these are receptors that move to the nucleus to regulate transcription, so they need both 'transcription regulator' and 'receptor' parentage.
- ❖ Is CUP2 a receptor?
<http://www.wikigenes.org/e/gene/e/852710.html>
 - Activates transcription in response to copper

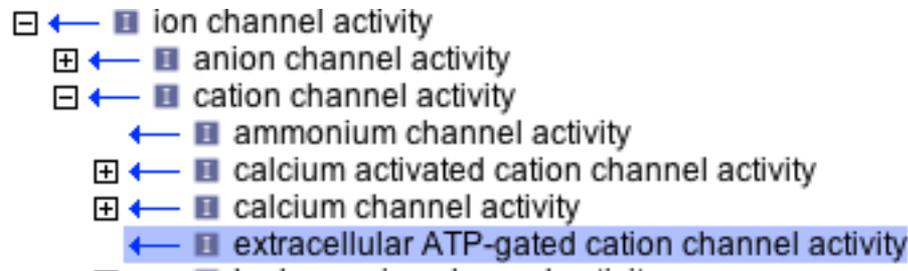
Q: do all nuclear receptors regulate transcription?

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P2X

Q: Do ligand-gated ion channels count as ‘receptor activity’?

- ❖ These types of ‘receptors’ don’t currently have receptor parentage in GO:
- ❖ extracellular ATP-gated cation channel activity ; GO:0004931
 - Current Def: *Catalysis of the transmembrane transfer of a cation by a channel that opens when extracellular ATP has been bound by the channel complex or one of its constituent parts.*
 - Synonym: *P2X receptor*



INTRACELLULAR SIGNAL TRANSDUCTION: CASCADES

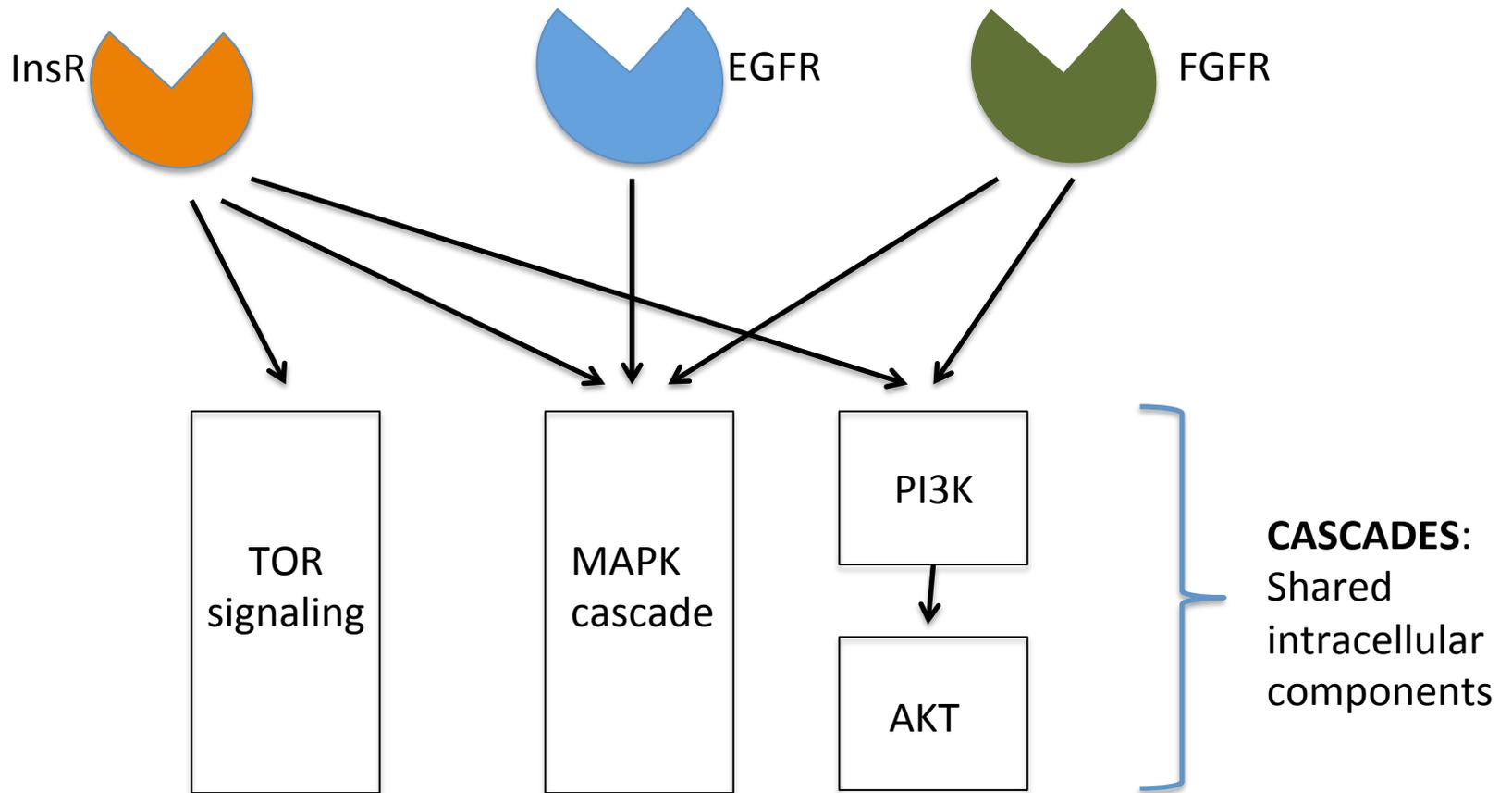
GO Cascades

- [-] ← [I] intracellular signal transduction
 - [+] ← [I] hippo signaling cascade
 - [-] ← [I] intracellular protein kinase cascade
 - [+] ← [I] I-kappaB kinase/NF-kappaB cascade
 - [+] ← [I] JAK-STAT cascade
 - [+] ← [I] MAPKKK cascade
 - [+] ← [R] negative regulation of intracellular protein kinase cascade
 - [+] ← [G] positive regulation of intracellular protein kinase cascade
 - [+] ← [I] protein kinase A signaling cascade
 - [+] ← [I] protein kinase B signaling cascade
 - [+] ← [I] protein kinase C signaling cascade
 - [+] ← [R] regulation of intracellular protein kinase cascade
 - [+] ← [I] septation initiation signaling cascade
 - [+] ← [I] stress-activated protein kinase signaling cascade
 - [+] ← [I] intracellular signal transduction involved in cell surface receptor linked signaling
 - [-] ← [I] phosphoinositide 3-kinase cascade
 - ← [R] negative regulation of phosphoinositide 3-kinase cascade
 - ← [I] phosphoinositide 3-kinase cascade involved in insulin receptor signaling
 - ← [G] positive regulation of phosphoinositide 3-kinase cascade
 - [+] ← [R] regulation of phosphoinositide 3-kinase cascade
 - [+] ← [I] second-messenger-mediated signaling
 - [+] ← [I] signal transduction by p53 class mediator
 - [+] ← [I] signal transduction in response to DNA damage
 - [+] ← [I] signal transduction involved in cell cycle checkpoint
 - [+] ← [I] small GTPase mediated signal transduction
 - [+] ← [I] TOR signaling cascade

Cascades

- ❖ GO calls any intracellular signaling module that can be linked to from multiple upstream receptors a **cascade**.
 - E.g. MAPKKK **cascade** ; GO:0000165
 - E.g. septation initiation signaling **cascade** ; GO:0031028
 - E.g. JAK-STAT **cascade** ; GO:0007259
- ❖ This distinguishes the ‘**cascades**’ (which are part of pathways) from complete pathways (which run from ligand-receptor interaction down to regulation of a downstream process).

Cascades



Cascades

Q: Is 'cascade' the correct terminology for any intracellular module/cassette?

Q: Does there have to be amplification of a response for it to be a cascade?

Protein kinase cascades

- [-] ← [I] intracellular signal transduction
 - [+] ← [I] hippo signaling cascade
 - [-] ← [I] intracellular protein kinase cascade
 - [+] ← [I] I-kappaB kinase/NF-kappaB cascade
 - [+] ← [I] JAK-STAT cascade
 - [+] ← [I] MAPKKK cascade
 - [+] ← [R] negative regulation of intracellular protein kinase cascade
 - [+] ← [G] positive regulation of intracellular protein kinase cascade
 - [+] ← [I] protein kinase A signaling cascade
 - [+] ← [I] protein kinase B signaling cascade
 - [+] ← [I] protein kinase C signaling cascade
 - [+] ← [R] regulation of intracellular protein kinase cascade
 - [+] ← [I] septation initiation signaling cascade
 - [+] ← [I] stress-activated protein kinase signaling cascade

Q: Do protein kinase cascades JUST include the phosphorylation steps, or are additional steps (E.g. translocation of a phosphorylated substrate) included?

NB: The I-kappaB/NF-kappaB, JAK-STAT and MAPKKK cascades all have the translocation step included currently.

Q: Is translocation of a downstream effector 'signal transduction'?

MAPKKK cascade

https://sourceforge.net/tracker/?func=detail&aid=3085150&group_id=36855&atid=440764

- ❖ MAKKK cascade ; GO:0000165
 - Current Def: *A cascade of at least three protein kinase activities culminating in the phosphorylation and activation of a MAP kinase. MAPKKK cascades lie downstream of numerous signaling pathways.*

Q: Where does the cascade begin?

Q: Where does the cascade end?

Q: Is the activity of MAPK included in the cascade?

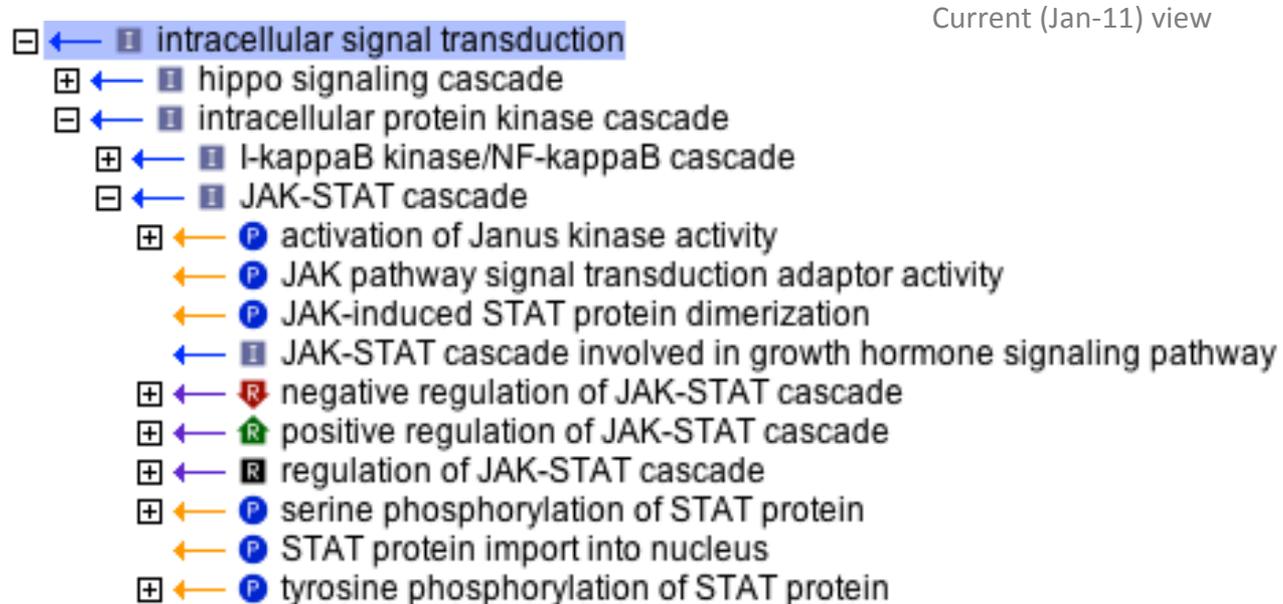
Q: Is translocation of MAPK to the nucleus part of the cascade?

- [-] ← [I] intracellular signal transduction
 - [+] ← [I] hippo signaling cascade
 - [-] ← [I] intracellular protein kinase cascade
 - [+] ← [I] I-kappaB kinase/NF-kappaB cascade
 - [+] ← [I] JAK-STAT cascade
 - [-] ← [I] MAPKKK cascade
 - [+] ← [P] activation of MAPK activity
 - [+] ← [P] activation of MAPKK activity
 - [+] ← [P] activation of MAPKKK activity
 - [+] ← [I] BMK cascade
 - [+] ← [I] ERK1 and ERK2 cascade
 - [+] ← [P] inactivation of MAPK activity
 - ← [P] inactivation of MAPKK activity
 - ← [P] inactivation of MAPKKK activity
 - [+] ← [I] JNK cascade
 - [+] ← [P] MAPK import into nucleus
 - [+] ← [I] MAPKKK cascade involved in cell wall biogenesis
 - [+] ← [I] MAPKKK cascade involved in conjugation with cellular fusion
 - ← [I] [MAPKKK cascade involved in epidermal growth factor receptor signaling](#)
 - [+] ← [I] MAPKKK cascade involved in innate immune response
 - [+] ← [I] MAPKKK cascade involved in osmosensory signaling pathway
 - [+] ← [R] negative regulation of MAPKKK cascade
 - [+] ← [G] positive regulation of MAPKKK cascade
 - [+] ← [R] regulation of MAPKKK cascade
 - [+] ← [I] stress-activated MAPK cascade

JAK-STAT cascade

JAS-STAT cascade ; GO:0007259

Current Def: Any process in which STAT proteins (Signal Transducers and Activators of Transcription) are activated by members of the JAK (janus activated kinase) family of tyrosine kinases, following the binding of cytokines to their cognate receptor. Once activated, STATs dimerize and translocate to the nucleus and modulate the expression of target genes.



Q: Where does the cascade begin?

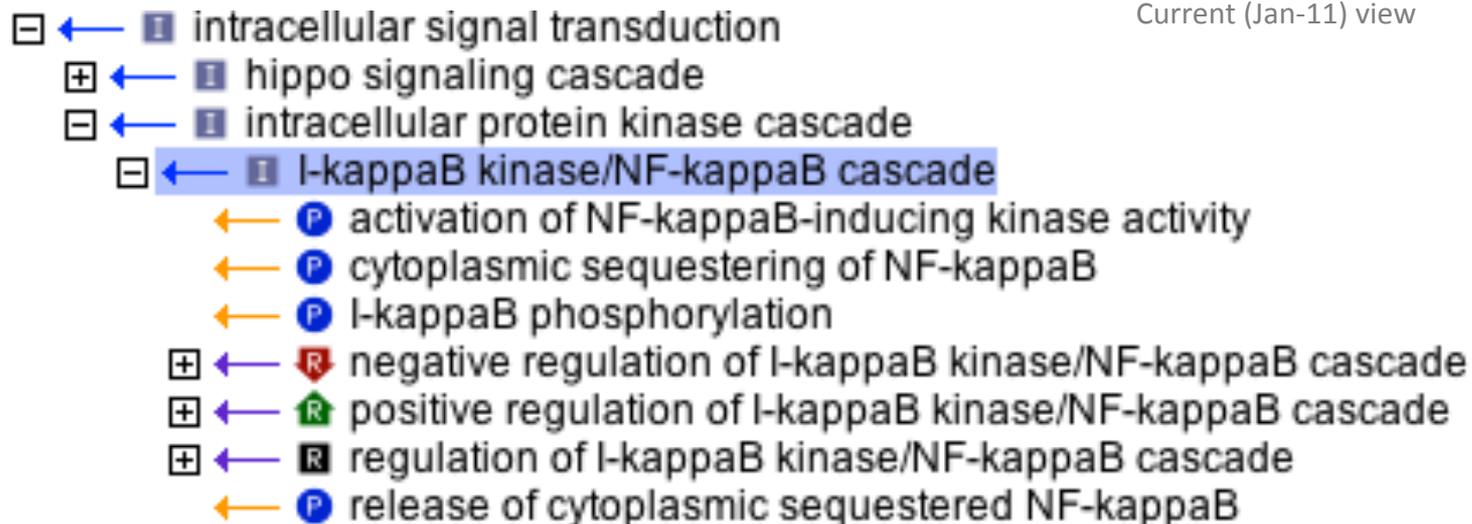
Q: Where does the cascade end?

Q: Does the cascade include nuclear translocation of STAT?

I-kappaB kinase/NF-kappaB cascade

❖ I-kappaB kinase/NF-kappaB cascade ; GO:0007249

Current Def: A series of reactions initiated by the activation of the transcription factor NF-kappaB. NF-kappaB is sequestered by the inhibitor I-kappaB, and is released when I-kappaB is phosphorylated by activated I-kappaB kinase.



Q: Where does the cascade begin?

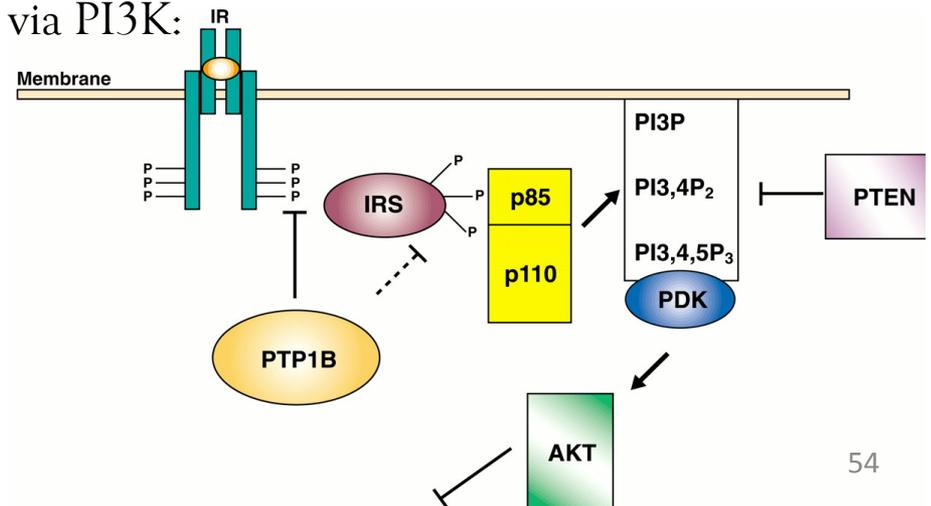
Q: Where does the cascade end?

Q: Does the cascade include nuclear translocation of NF-kappaB?

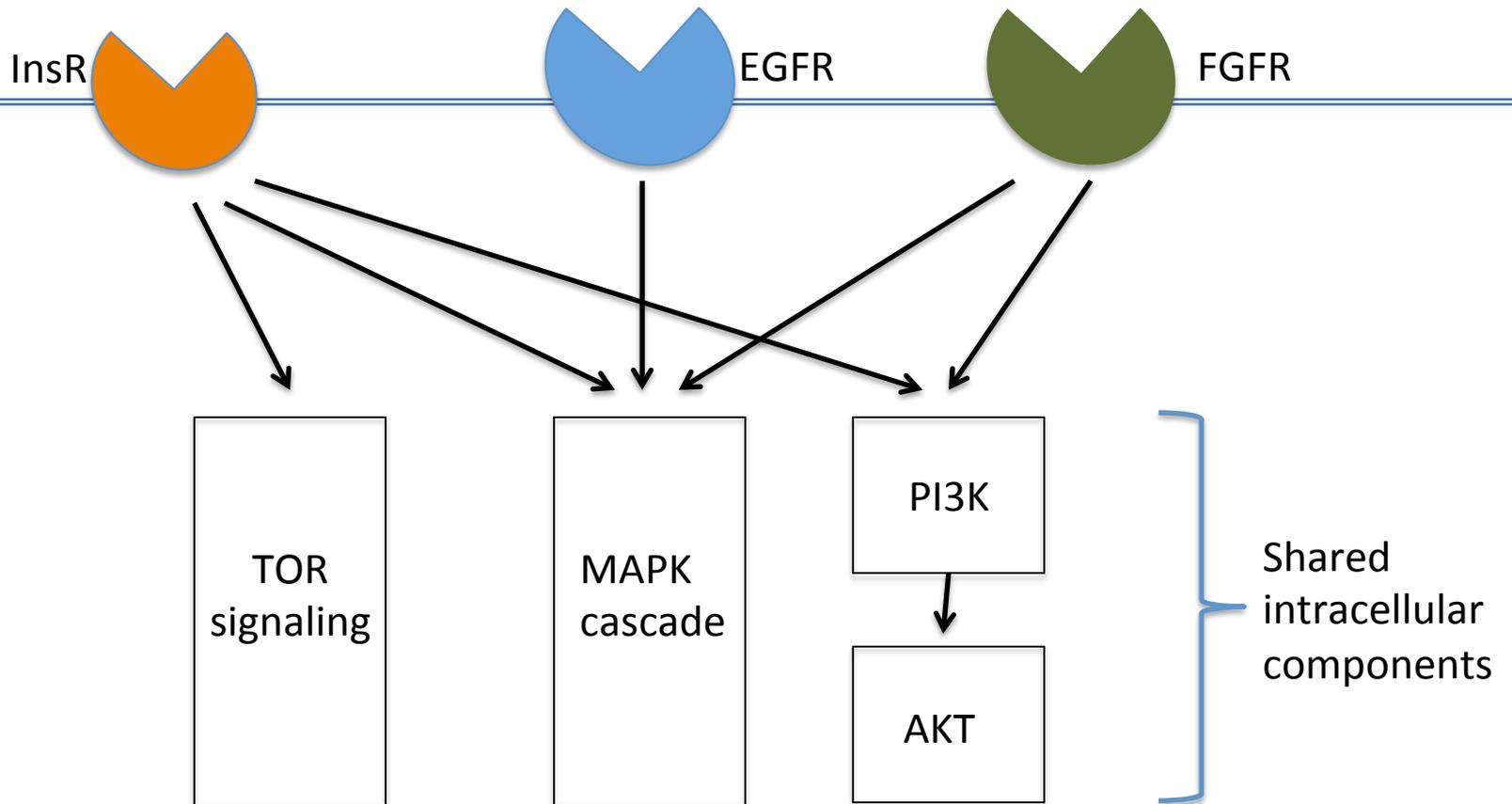
PI3K and AKT cascades

- ❖ phosphoinositide 3-kinase cascade ; GO:0014065
 - *Current Def:* A series of reactions, mediated by the intracellular phosphoinositide 3-kinase (PI3K). PI3K cascades lie downstream of many cell surface receptor linked signaling pathways and regulate numerous cellular functions.
- ❖ protein kinase B signaling cascade ; GO:0043491
 - *Current Def:* A series of reactions, mediated by the intracellular serine/threonine kinase protein kinase B, which occurs as a result of a single trigger reaction or compound.
- ❖ Most but not all AKT activation occurs via PI3K:

PMID: 21129803. High dose human insulin and insulin glargine promote T24 bladder cancer cell proliferation via PI3K-independent activation of Akt.



CONNECTING CELL SURFACE
RECEPTORS WITH THE
INTRACELLULAR MODULES THEY
SIGNAL THROUGH



Q: How can we connect up the cell-surface receptors and the intracellular cascades in the ontology?

❖ Wnt signaling via hippo cascade:

https://sourceforge.net/tracker/?func=detail&aid=3032564&group_id=36855&atid=440764

❖ Wnt signaling via JNK cascade:

https://sourceforge.net/tracker/?func=detail&aid=3023417&group_id=36855&atid=440764

❖ PI3K/AKT signaling:

https://sourceforge.net/tracker/?func=detail&aid=3008502&group_id=36855&atid=440764

OPTIONS- OVERVIEW

- ❖ 1/ insulin receptor signaling pathway VIA TOR signaling cascade
- ❖ 2/ TOR signaling cascade INVOLVED IN insulin receptor signaling pathway
- ❖ 3/ REGULATION OF TOR signaling cascade by insulin receptor signaling pathway

❖ 1/ insulin receptor signaling pathway VIA TOR signaling cascade

Insulin receptor signaling pathway

[is_a] insulin receptor signaling pathway via TOR signaling cascade

[HAS_PART] TOR signaling pathway

❖ 2/ TOR signaling cascade INVOLVED IN insulin receptor signaling pathway

Insulin receptor signaling pathway

[part_of] TOR signaling cascade involved in insulin receptor signaling pathway

TOR signaling cascade

[is_a] TOR signaling cascade involved in insulin receptor signaling pathway

❖ 3/ REGULATION OF TOR signaling cascade by insulin receptor signaling pathway

Insulin receptor signaling pathway

[is_a] regulation of TOR signaling cascade by insulin receptor signaling pathway

TOR signaling cascade

[regulates] regulation of TOR signaling cascade by insulin receptor signaling pathway

(may have to reconsider where a pathway ends)

OPTIONS

Q: What gene products are we going to be annotating with these terms?

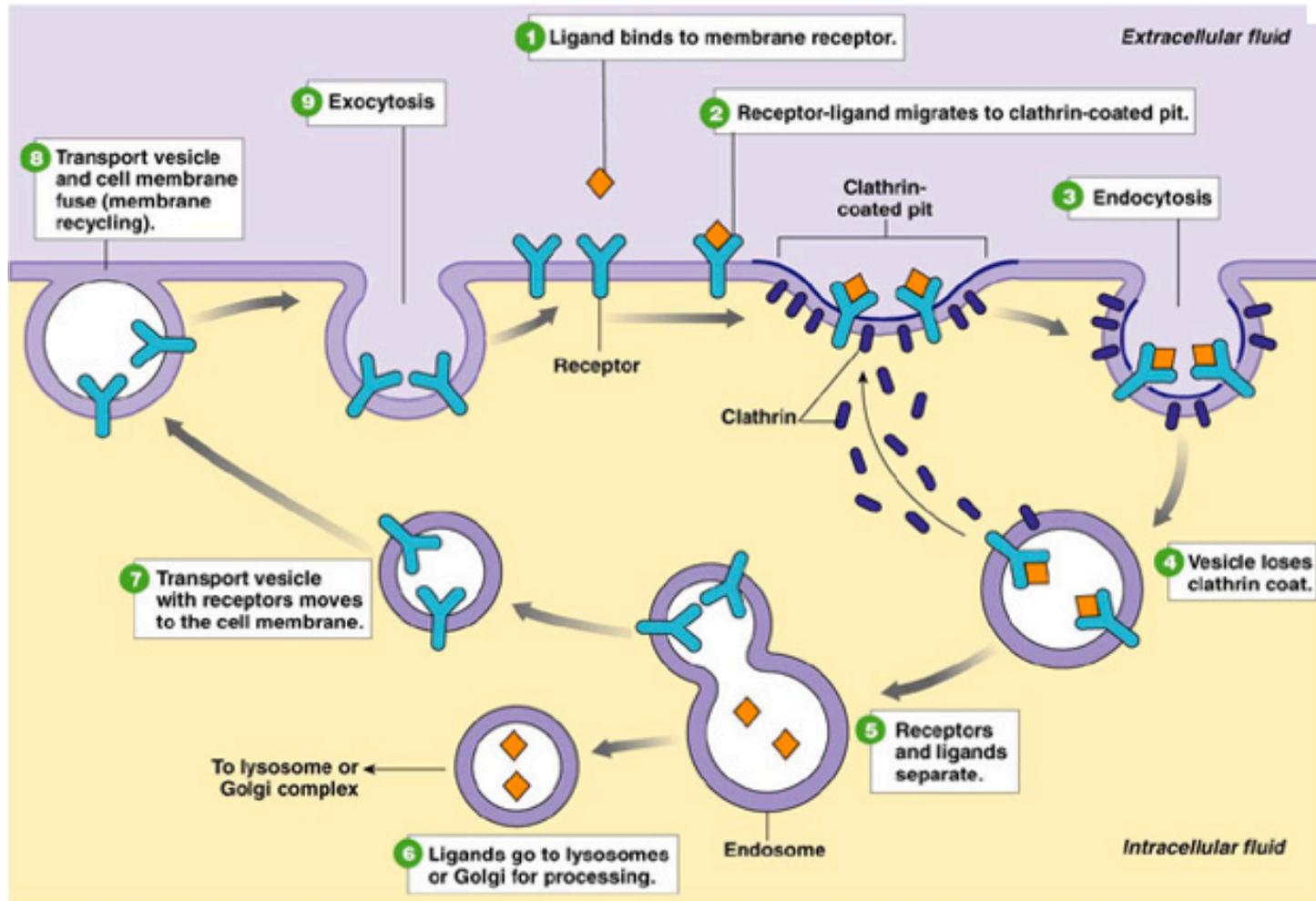
- A gene product will act at one step in a pathway. Do we want to say what it's acting downstream and upstream of?

Q: Can they be scaled-up to include multiple intracellular cassettes?

Note: We don't want to reproduce Reactome. We're not looking to fill in all the steps of any given pathway.

RECEPTOR-MEDIATED ENDOCYTOSIS

RECEPTOR-MEDIATED ENDOCYTOSIS: AN OVERVIEW



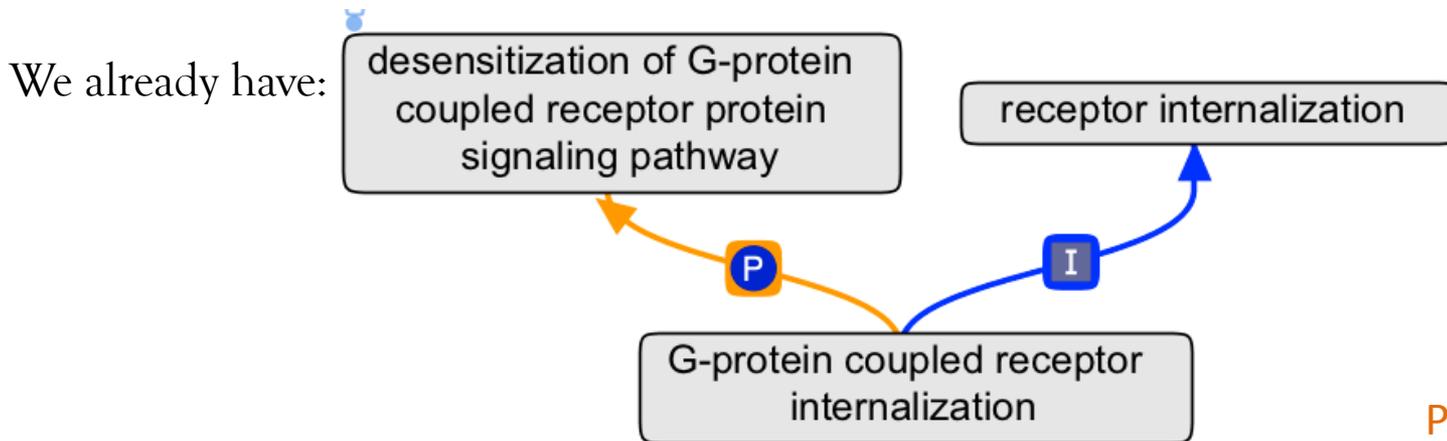
Receptor-mediated endocytosis

Q: How does RME fit into signaling?

Q: Is signal transduction involved in any of the steps of receptor-mediated endocytosis?

- Does binding of the substrate to the receptor count as signaling?
- The receptor has to be activated to endocytose... is this signaling?

Q: Is it enough to create involved_in terms or part_of links?



PMID:
14718562

RME regulates signaling pathways

- ❖ Receptor-mediated endocytosis can regulate signaling pathways:
- ❖ Receptor internalization
 - Can downregulate signaling (decreases receptors availability at cell surface)
 - Can upregulate signaling (quicker transport of signaling complex to nucleus)

Q: Is receptor-mediated endocytosis ever part of the pathway (i.e. necessary for the pathway, rather than just regulating it)?

REVIEWS:

Regulation of Wnt signalling by receptor-mediated endocytosis.
PMID: 17317692

Receptor-mediated endocytosis in renal proximal tubule.
PMID: 19499243

Different Routes of Bone Morphogenic Protein (BMP) Receptor Endocytosis Influence BMP Signaling
PMID: 16923969
<http://mcb.asm.org/cgi/content/short/26/20/7791>

OUTSTANDING QUESTIONS

Ligand Transport

- ❖ Do we want to describe HOW the ligand gets from the signaling cell to the receiving cell?
 - Via vascular system
 - Diffusion (what would you annotate to this?)

- Q: What would we annotate to these terms if so?
- The protein that is transporting the ligand?

Calcium-mediated signaling

https://sourceforge.net/tracker/?func=detail&aid=3077377&group_id=36855&atid=440764

Q: Where does calcium-mediated signaling begin?

Is calcium transport part of calcium signaling?

OR

Does calcium transport REGULATE calcium signaling?

Receptor signaling protein

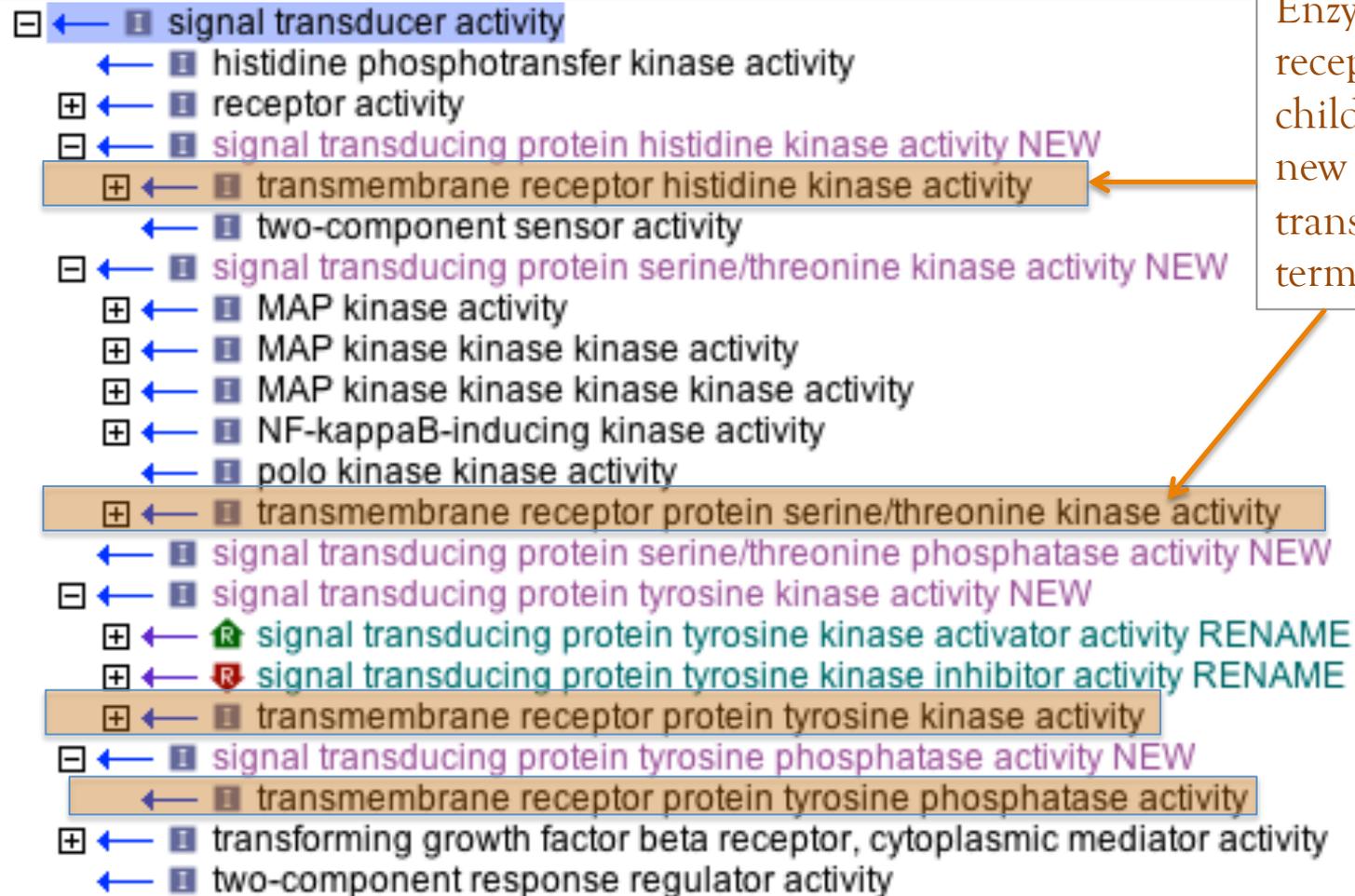
- ☐ ← ⓘ molecular transducer activity
 - ⊕ ← ⓘ energy transducer activity
 - ☐ ← ⓘ signal transducer activity
 - ← ⓘ histidine phosphotransfer kinase activity
 - ⊕ ← ⓘ receptor activity
 - ☐ ← ⓘ receptor signaling protein activity
 - ☐ ← ⓘ receptor signaling protein serine/threonine kinase activity
 - ⊕ ← ⓘ MAP kinase activity
 - ⊕ ← ⓘ MAP kinase kinase kinase activity
 - ⊕ ← ⓘ MAP kinase kinase kinase kinase activity
 - ⊕ ← ⓘ NF-kappaB-inducing kinase activity
 - ← ⓘ polo kinase kinase activity
 - ← ⓘ receptor signaling protein serine/threonine phosphatase activity
 - ☐ ← ⓘ receptor signaling protein tyrosine kinase activity
 - ← ⓘ receptor signaling protein tyrosine kinase activator activity
 - ← ⓘ receptor signaling protein tyrosine kinase inhibitor activity
 - ← ⓘ receptor signaling protein tyrosine phosphatase activity
 - ☐ ← ⓘ transforming growth factor beta receptor, cytoplasmic mediator activity
 - ← ⓘ transforming growth factor beta receptor, common-partner cytoplasmic mediator activity
 - ← ⓘ transforming growth factor beta receptor, inhibitory cytoplasmic mediator activity
 - ← ⓘ transforming growth factor beta receptor, pathway-specific cytoplasmic mediator activity
 - ← ⓘ two-component response regulator activity
 - ← ⓘ two-component sensor activity

receptor signaling protein activity ; GO:0005057

- ❖ Currently defined to mean anything that acts DOWNSTREAM of a receptor (directly or indirectly).
 - Current def: Conveys a signal from an upstream receptor or intracellular signal transducer, converting the signal into a form where it can ultimately trigger a change in the state or activity of a cell.
 - NB: annotations are not necessarily correct (we have some annotations to receptors).
- ❖ Proposal to rename the ‘receptor signaling protein x kinase activity terms’ to:
 - signal transducing x kinase activity ; GO:NEW

Q: In GO:FUNCTION, Do we want to distinguish WHERE in a pathway a product acts, or should it be captured using ‘intracellular signal transduction’?

One option... move the receptors under the enzyme signal transducers:



Enzymatic receptors are children of the new signal transducing terms

- NB: The proposal would remove the distinction between receptors and the molecules that signal downstream of them.