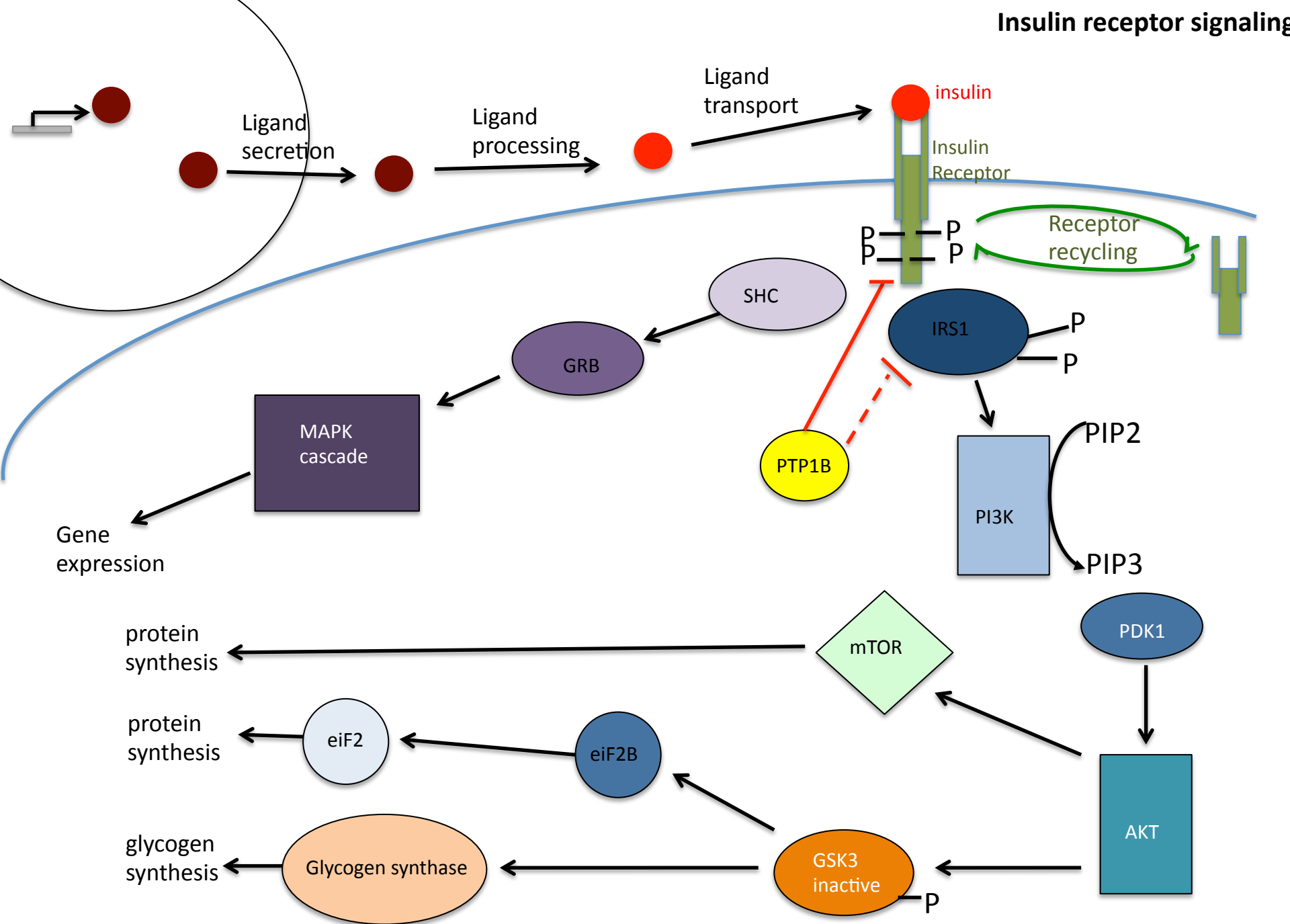


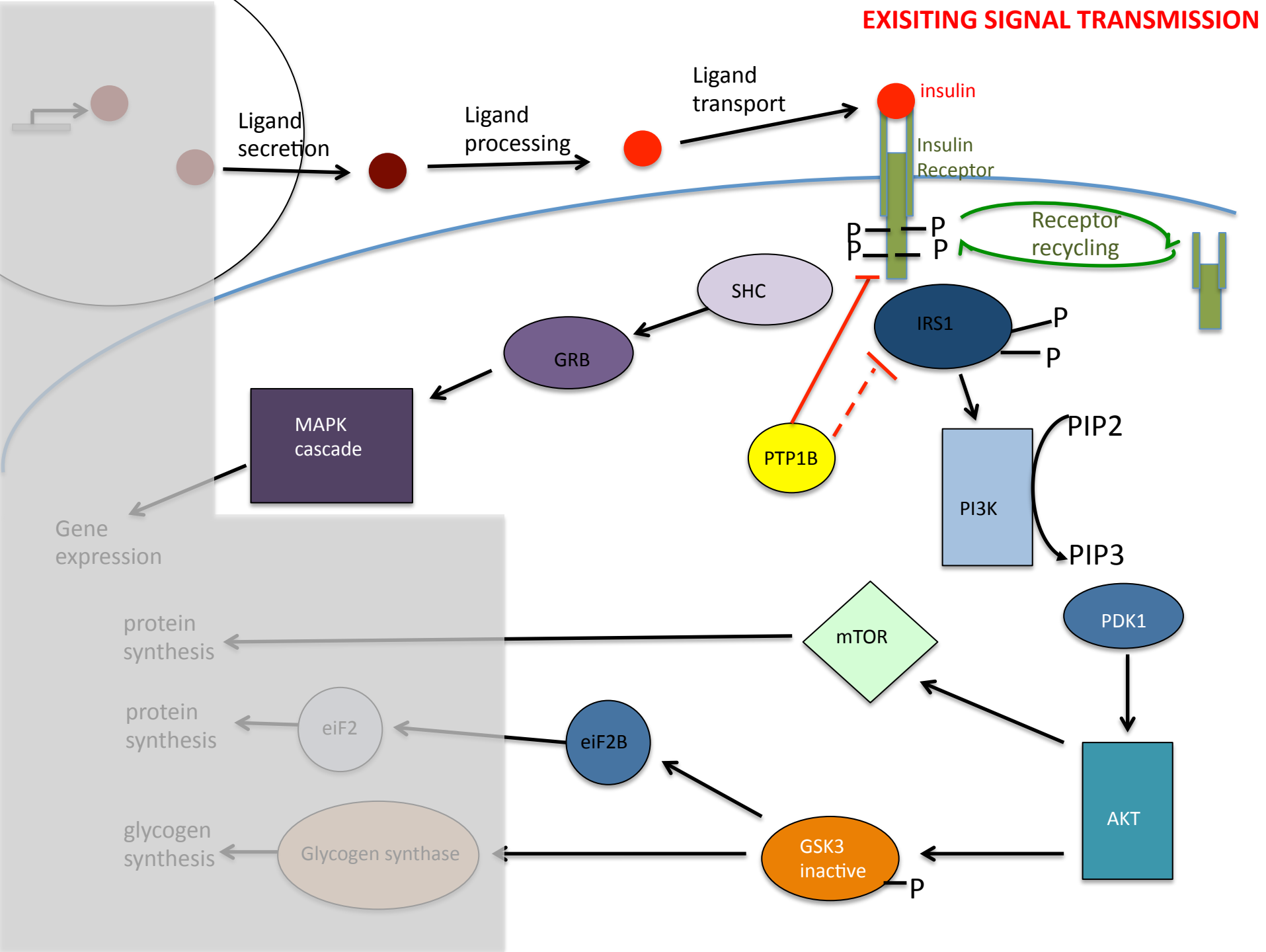
# Insulin receptor signaling



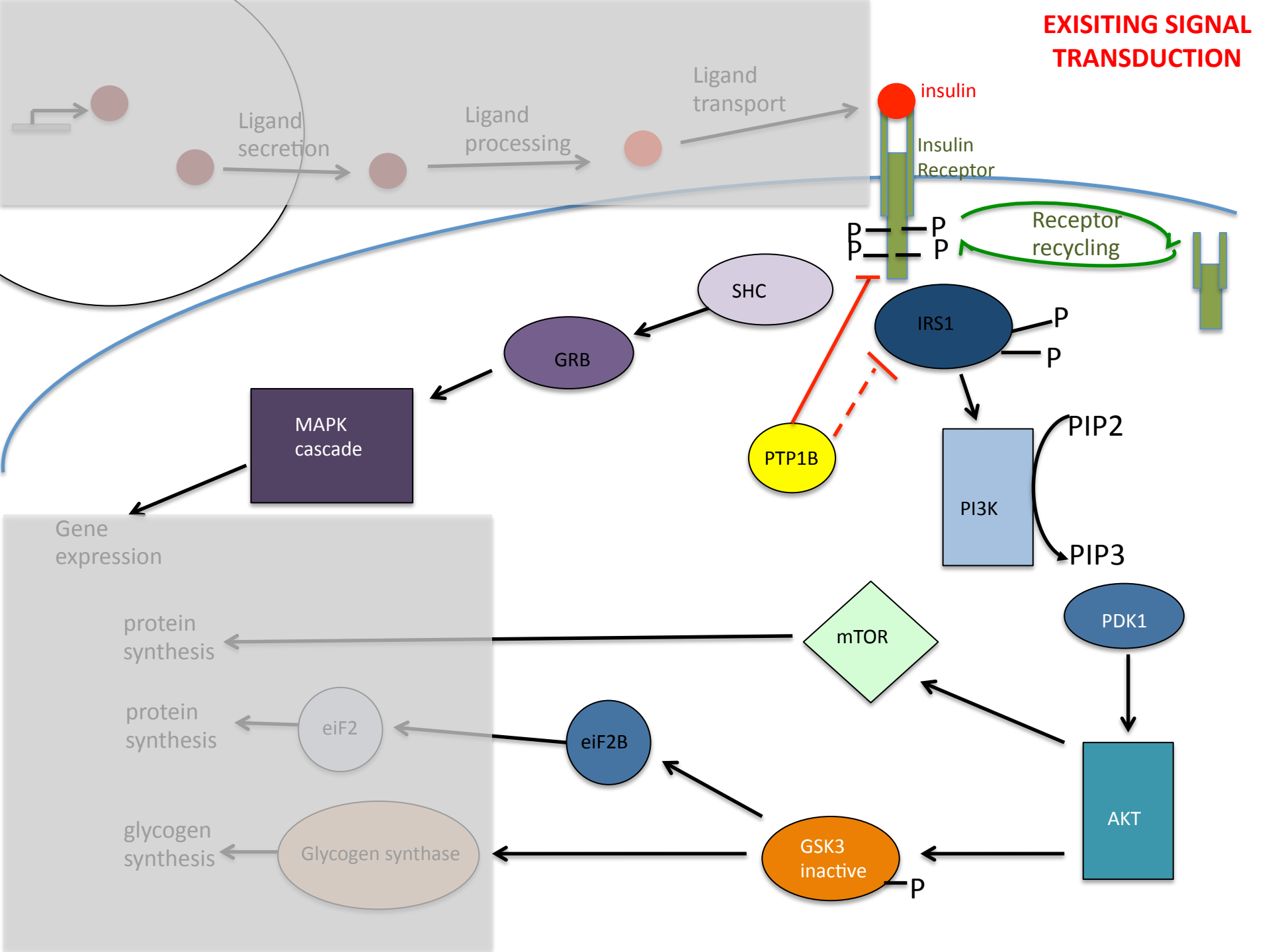
## Signal transduction initiated by insulin.

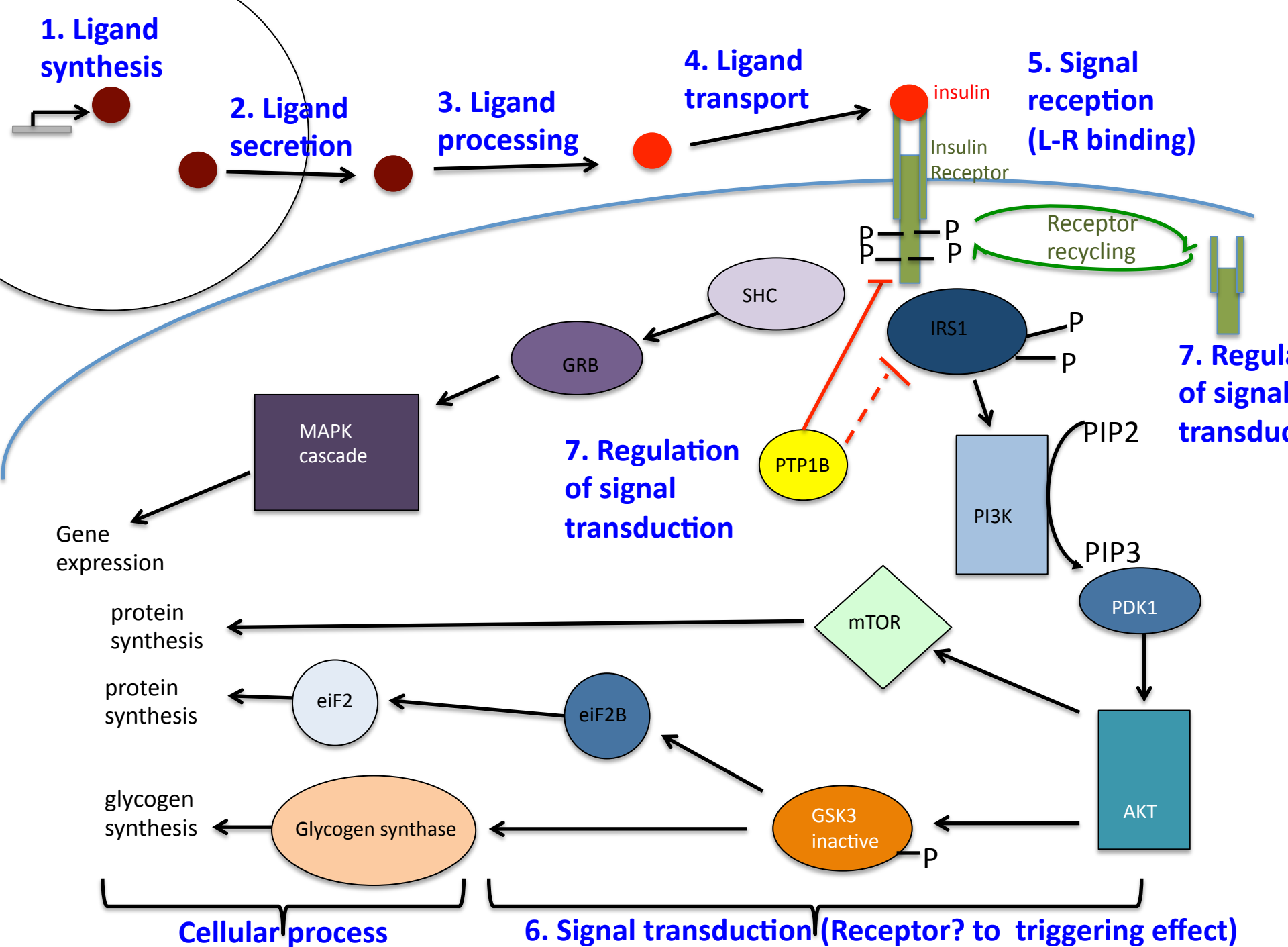
- Insulin binding to the insulin receptor tyrosine kinase (IR) promotes its dimerization and autophosphorylation.
- The phosphotyrosine motifs recruit various adapters, including the insulin receptor substrates IRS-1 and IRS-2.
- Phosphorylation of the IRS proteins in turn recruits and activates PI3K.
- (Dephosphorylation of a subset of phosphotyrosines on IR, and perhaps IRS proteins, by PTP1B attenuates PI3K activation by insulin)
- PI3K generates several phosphoinositides that activate downstream kinases, such as the phosphoinositide-dependent protein kinases (PDKs).
- (The inositol 3-phosphatase activity of PTEN prevents activation of these downstream kinases)
- The downstream signals from PDK to AKT eventually result in the phosphorylation and inhibition of glycogen synthase kinase 3 (GSK-3). The proposed insulin-stimulated phosphorylation of  $G_M$  and concomitant activation of PP1 are currently under debate. The net dephosphorylation of glycogen synthase (GS) increases glycogen deposition.

# EXISTING SIGNAL TRANSMISSION



# EXISTING SIGNAL TRANSDUCTION





- [-] ← [I] signaling
  - [+] ← [I] behavioral 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] **signaling pathway**
  - [+] ← [P] signaling process
- [-] ← [I] signaling process
  - [+] ← [I] consequence of signal transmission
  - [+] ← [I] generation of a signal involved in cell-cell signaling
  - [+] ← [I] initiation of signal transduction
  - [+] ← [I] receptor recycling
  - [+] ← [R] regulation of signaling process
  - [+] ← [I] signal release
  - [-] ← [I] signal transmission
    - [+] ← [P] signal release
    - [-] ← [P] **signal transduction**
      - [+] ← [I] DNA replication checkpoint
      - [+] ← [P] initiation of signal transduction
      - [+] ← [I] intracellular signal transduction
      - [+] ← [I] **meiotic cell cycle checkpoint**
      - [+] ← [I] **mitotic cell cycle checkpoint**
      - [+] ← [R] **negative regulation of signal transduction**
        - ← [I] neuronal signal transduction
      - [+] ← [I] phototransduction
      - [+] ← [R] **positive regulation of signal transduction**
      - [+] ← [I] **regulation of conjugation with cellular fusion by signal transduction**
      - [+] ← [I] regulation of floral organ abscission by signal transduction
      - [+] ← [R] **regulation of signal transduction**
      - [+] ← [P] signal transducer activity
        - ← [I] **signal transduction involved in conjugation with mutual genetic exchange**
        - ← [I] **signal transduction involved in filamentous growth**
        - ← [I] SMAD protein signal transduction
      - ← [I] signal transmission via air
      - ← [I] signal transmission via conformational transition
    - [+] ← [I] signal transmission via diffusible molecule
    - [+] ← [I] signal transmission via phosphorylation event
      - ← [I] signal transmission via transcytosis
    - [+] ← [I] signal transmission via vascular system
    - [+] ← [I] transmission of nerve impulse
    - [+] ← [I] two-component signal transduction system (phosphorelay)
  - [+] ← [I] termination of signal transduction

- [-] ← [I] signaling
  - [+] ← [I] behavioral signaling
  - [+] ← [I] cell-cell signaling
  - [+] ← [I] extracellular matrix-cell signaling
  - [+] ← [I] mitogenic signaling initiating cell movement in cerebral cortex
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  - ~~[-] ← [I] signaling pathway~~
  - [+] ← [P] signaling process
- ~~[-] ← [I] signaling process~~
  - ~~[-] ← [I] consequence of signal transmission~~
  - [+] ← [I] generation of a signal involved in cell-cell signaling
  - [+] ← [I] initiation of signal transduction
  - [+] ← [I] receptor recycling
  - [+] ← [R] regulation of signaling process
  - [+] ← [I] signal release
  - [+] ← [I] signal transmission
    - [+] ← [P] signal release
    - ~~[-] ← [P] signal transduction~~
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        - ← [I] neuronal signal transduction
      - [+] ← [I] phototransduction
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      - [+] ← [R] **regulation of signal transduction**
      - [+] ← [P] signal transducer activity
        - ← [I] **signal transduction involved in conjugation with mutual genetic exchange**
        - ← [I] **signal transduction involved in filamentous growth**
        - ← [I] SMAD protein signal transduction
    - ~~← [I] signal transmission via air~~
    - ~~← [I] signal transmission via conformational transition~~
    - ~~[-] ← [I] signal transmission via diffusible molecule~~
    - ~~[-] ← [I] signal transmission via phosphorylation event~~
    - ~~← [I] signal transmission via transeytosis~~
    - ~~[-] ← [I] signal transmission via vascular system~~
    - [+] ← [I] **transmission of nerve impulse**
    - [+] ← [I] two-component signal transduction system (phosphorelay)
    - [+] ← [I] termination of signal transduction

Transmission of nerve impulse? Does it belong here?

signaling

Generation of a signal

Signal secretion

Signal transport

Signal transmission

Signal processing

Receptor processing

Receptor transport to membrane

Receptor recycling

Signal transduction

Signal reception (initiation of signal transduction)

Intracellular signal transduction

Termination of signal transduction

Ligand-named signal transduction

receptor-named signal transduction

InsR signaling

MAPKKK cascade

PI3K/AKT

TOR signaling

NB: signal transmission would no longer include signal transduction: it is merely placing the signal in the right place.



# REVISED DEFINITIONS

## signal transduction

The process whereby an activated receptor conveys information down the signaling pathway, resulting in a change in the function or state of a cell.

To:

The series of steps that convert a stimulus from one form to another to trigger a change in the function or state of a cell. (For example, in signal transduction from a cell surface-receptor, a chemical stimulus is converted to a change in cell activity through a series of interactions and phosphorylation events).

Comment: A receptor ligand is part of signal transduction.

## signal transducer activity

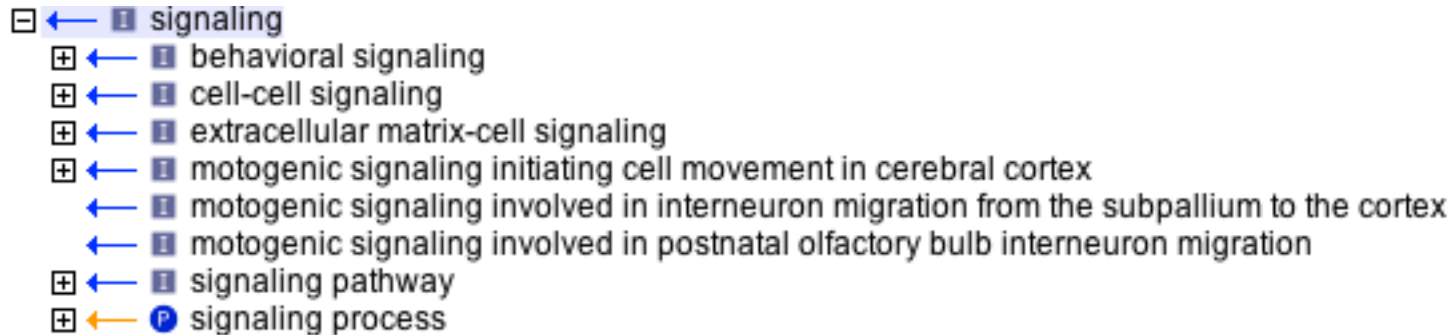
Mediates the transfer of a signal from the outside to the inside of a cell by means other than the introduction of the signal molecule itself into the cell.

To:

Converts a stimulus from one form (chemical, light or mechanical) to another.

(Comment: A receptor ligand is not a signal transducer)

# Signaling at different levels



- I think we need to split the signaling node more clearly into:
  - signaling at organismal level (behavioral signaling)
  - signaling at tissue/system (eg nervous system) level?
  - signaling at cell level (between cells AND within a cell)

cellular process

**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.**

multi-organism process

**Any process by which an organism has an effect on another organism of the same or different species.**

- [-] ← [i] signaling
  - [+] ← [i] behavioral signaling
  - [-] ← [i] cell-cell signaling 
    - ← [i] autocrine signaling
    - ← [i] cell-cell signaling involved in amphid sensory organ development
    - [+] ← [i] cell-cell signaling involved in cell fate commitment
    - [+] ← [i] cell-cell signaling involved in kidney development
    - [+] ← [i] cell-cell signaling involved in lung development
    - ← [i] cell-cell signaling involved in mammary gland development
    - ← [i] cell-cell signaling involved in placenta development
    - ← [i] cell-cell signaling involved in quorum sensing
    - [+] ← [i] cerebellar Purkinje cell-granule cell precursor cell signaling involved in regulation of granule cell precursor cell proliferation
    - ← [i] determination of muscle attachment site
    - ← [i] ectoderm and mesoderm interaction
    - [+] ← [i] endodermal-mesodermal cell signaling
    - ← [i] epiblast cell-extraembryonic ectoderm cell signaling involved in anterior/posterior axis specification
    - [+] ← [i] epithelial-mesenchymal cell signaling
    - [+] ← [i] generation of a signal involved in cell-cell signaling
    - [+] ← [i] mesenchymal-epithelial cell signaling
    - [+] ← [i] mesodermal-endodermal cell signaling
      - ← [i] regulation of branching involved in mammary cord morphogenesis by fat precursor cell-epithelial cell signaling
      - ← [i] regulation of mammary gland cord elongation by mammary fat precursor cell-epithelial cell signaling
      - ← [i] regulation of pre-tubular aggregate formation by cell-cell signaling
      - ← [i] stromal-epithelial cell signaling involved in prostate gland development
    - [+] ← [i] synaptic transmission
      - ← [i] visceral mesoderm-endoderm interaction involved in midgut development
    - [+] ← [i] extracellular matrix-cell signaling
    - [+] ← [i] motogenic signaling initiating cell movement in cerebral cortex
      - ← [i] motogenic signaling involved in interneuron migration from the subpallium to the cortex
      - ← [i] motogenic signaling involved in postnatal olfactory bulb interneuron migration
  - [-] ← [i] signaling pathway

Lots of the signaling pathways (esp the cell-surface receptor ones, eg Notch, EGFR etc signal between cells).

Lots of 'signaling processes' are involved in signaling between cells.

# Suggestion:

signaling

--[i]multi-organismal signaling ; GO:NEW

----[i]behavioral signaling ; GO:NEW

--[i]cellular signaling ; GO:NEW

----[i]cell-cell signaling ; GO:0007267

-----[p]signal release

----[p]signal processing

----[p]signal transduction

----[p]receptor recycling

cell-cell signaling ; GO:0007267

Any process that mediates the transfer of information from one cell to another.

This would limit signal transduction to events at a cellular level.

**Q: are there any instances where signal transduction would NOT be within/between cells??**

**Q:Would it work for single-celled organisms? Val?**

# 'PATHWAY'

- Do we want to keep 'pathway' on the end of the terms?

Notch signaling pathway ; GO:0007219

Notch signal transduction?

Notch signaling?

Notch signaling network?

cell surface receptor linked signaling pathway ; GO:0007166

has the exact synonym: cell surface receptor linked signal **transduction**

red or far-red light signaling pathway ; GO:0010017

--<red, far-red light phototransduction ; GO:0009585

red or far-red light signaling pathway ; GO:0010017

**The series of molecular signals initiated upon sensing by photoreceptor molecules of red light or far red light. Red light is electromagnetic radiation of wavelength of 580-700nm. Far red light is electromagnetic radiation of wavelength 700-800nm. An example of this response is seen at the beginning of many plant species developmental stages. These include germination, and the point when cotyledon expansion is triggered. In certain species these processes take place in response to absorption of red light by the pigment molecule phytochrome, but the signal can be reversed by exposure to far red light. During the initial phase the phytochrome molecule is only present in the red light absorbing form, but on absorption of red light it changes to a far red light absorbing form, triggering progress through development. An immediate short period of exposure to far red light entirely returns the pigment to its initial state and prevents triggering of the developmental process. A thirty minute break between red and subsequent far red light exposure renders the red light effect irreversible, and development then occurs regardless of whether far red light exposure subsequently occurs.**

red, far-red light phototransduction ; GO:0009585

**The sequence of reactions within a cell required to convert absorbed photons from red or far-red light into a molecular signal; the red, far-red light range is defined as having a wavelength within the range 660-730 nm.**

# transmission of nerve impulse

signal transmission ;

--[i]transmission of nerve impulse ; GO:0000160

----[p]synaptic transmission ; GO:0007268

cell communication

--[p]transmission of nerve impulse ; GO:0000160

--[i]cell-cell signaling

----[i]synaptic transmission ; GO:0007268

transmission of nerve impulse ; GO:0000160

The neurological system process by which a signal is transmitted through the nervous system by synaptic transmission and the sequential electrochemical polarization and depolarization that travels across the membrane of a nerve cell (neuron) in response to stimulation.

synaptic transmission ; GO:0007268

The process of communication from a neuron to a target (neuron, muscle, or secretory cell) across a synapse.