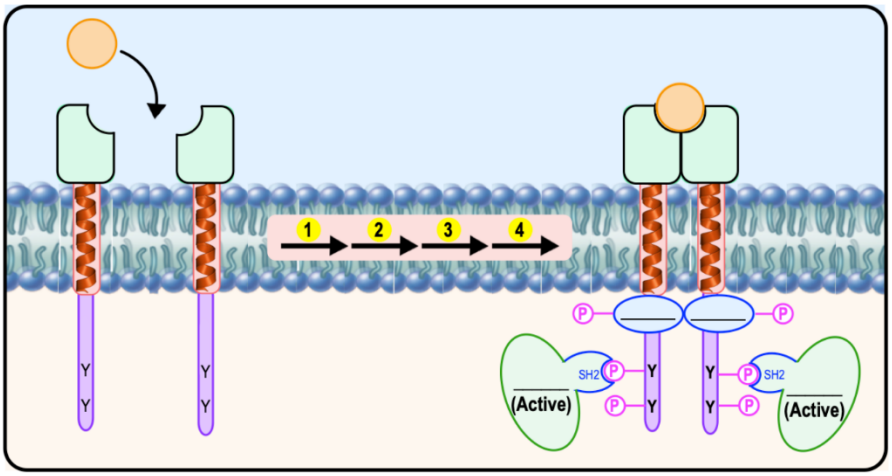
CONCEPT: JAK-STAT SIGNALING

●*JAK-STAT Signaling Pathway*: a variation of RTKs that _____ covalently-bound *Tyrosine Kinase domains*.

□ HOWEVER, they can still _____-*covalently* recruit a soluble, cytosolic *Tyrosine Kinase* (JAK2).

□ ***Ja**nus **K**inase **2*** (_____): a *tyrosine kinase* that phosphorylates & activates *STAT*.

□ ***S**ignal **T**ransducers & **A**ctivators of **T**ranscription* (_____): a specific transcription factor.



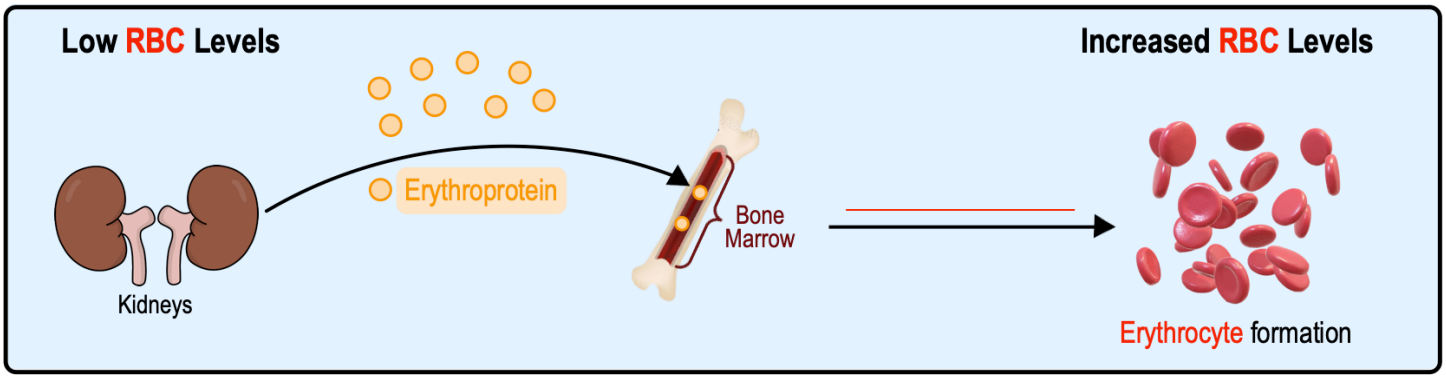
Erythropoietin Signals via JAK-STAT Pathway

●**Erythropo**ietin (_____): a 165-amino-acid protein *cytokine* released by *kidneys* to induce *hemopoiesis* in bone marrow.

□ _____: small, soluble proteins regulating development/differentiation/proliferation of cells (mainly blood).

Hemopoiesis: formation of _____ (*red blood cells*).

□ EPO (& other cytokines) commonly signal via a JAK-STAT pathway.



PRACTICE: Erythropoietin is a cytokine produced in the _____ and released into the _____ to promote cell growth.

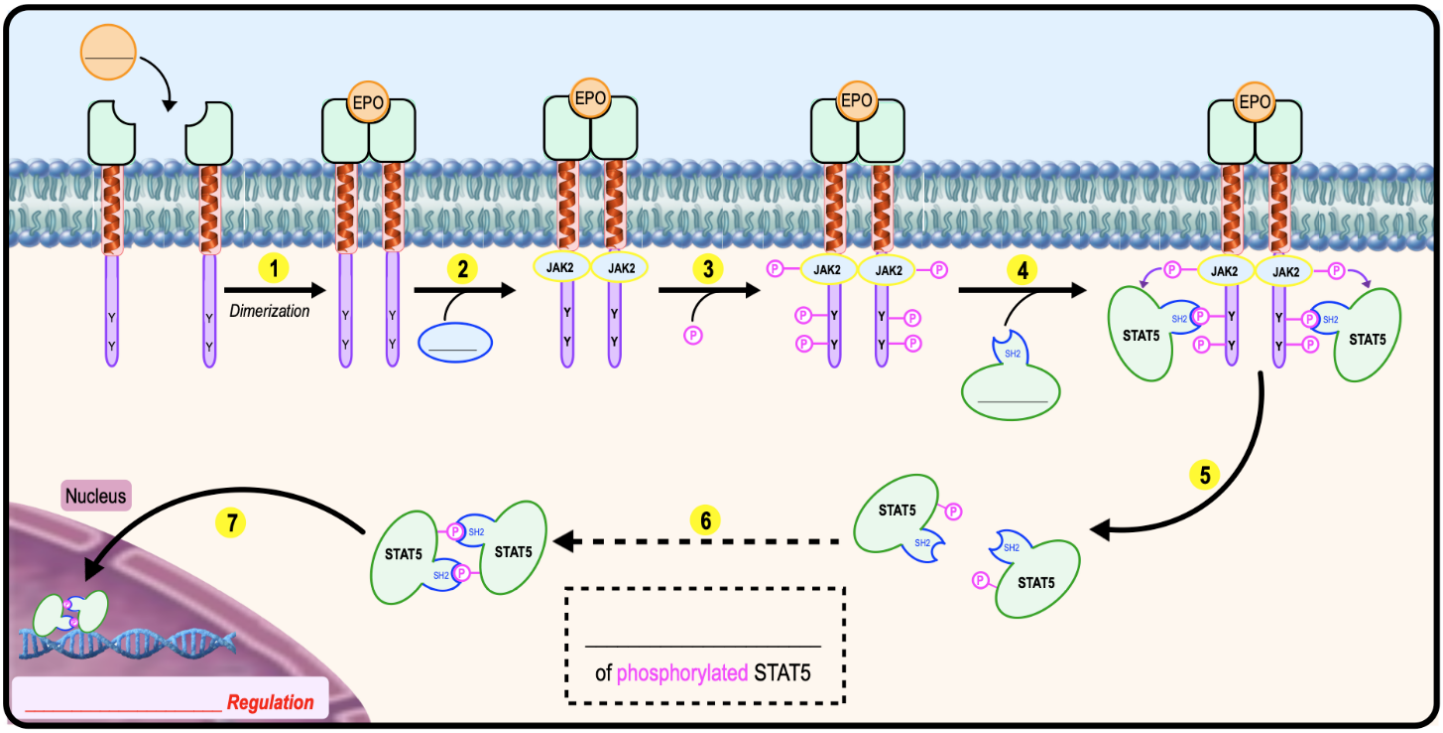
a) Liver ; Kidneys.
b) Kidneys ; Bone marrow.
c) Kidneys ; Liver.
d) Liver ; Bone marrow.

CONCEPT: JAK-STAT SIGNALING

JAK-STAT Pathway

●JAK-STAT pathway occurs in _____ steps:

1. EPO ligand binds *Cytokine Receptor*, causing it to _____.
2. *Dimerized Cytokine Receptor* recruits & activates _____.
3. *Activated JAK2* _____ Cytokine Receptor (a process which *resembles* autophosphorylation).
4. SH2 domain of STAT5 _____ *phosphorylated Cytokine Receptor* (bringing STAT5 closer to JAK).
5. JAK2 _____ STAT5,
6. Phosphorylated STAT5 _____ with another phosphorylated STAT5.
7. STAT5 dimerization exposes a signal, transporting it to the _____ to function as a *transcription factor*.



PRACTICE: When the JAK-STAT signaling cascade is activated, which of the following occurs?

a) Adenylate cyclase produces cAMP.
b) Ras GTPase activity is activated.
c) Activated STAT5 is translocated to the nucleus.
d) Grb2 binds Sos.

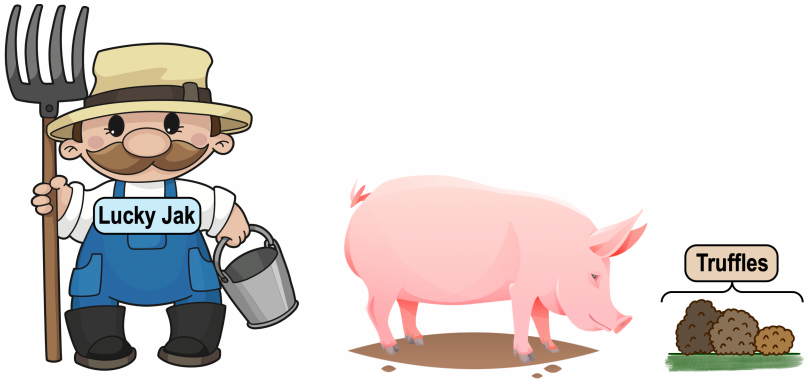
PRACTICE: How could a cell inhibit the JAK-STAT signal transduction pathway?

a) Dephosphorylating cytokine receptor tails using phosphatases.
b) Dephosphorylating STAT dimers using phosphatases.
c) Using proteins that bind STAT dimers to inhibit their DNA binding.
d) All of the above are ways to inhibit the JAK-STAT signaling pathway.

CONCEPT: JAK-STAT SIGNALING

How to Remember JAK-STAT Signaling?

1. **____ucky** (**L**igand binds, and receptor dimerizes)
2. **____ack's** (**J**AK activation)
3. **____ig** (**P**hosphorylation of JAK)
4. **____potted** (**S**TAT5 recruitment)
5. **____olka** (**P**hosphorylation of STAT5)
6. **____otted** (**D**imerization of STAT5)
7. **____ruffles** (**T**ranscription Regulation)



EXAMPLE: List the following steps of the JAK-STAT pathway in order of their occurrence (from 1-7):

a) SH2 domain of STAT5 binds to the phosphorylated receptor _____.
b) Recruitment and activation of JAK2 by the receptor _____.
c) Regulation of transcription by dimerized STAT5 _____.
d) JAK2 phosphorylation of the receptor _____.
e) EPO binds stimulating receptor dimerization _____.
f) Dimerization of two phosphorylated STAT5 proteins _____.
g) JAK2 phosphorylation and activation of STAT5 _____.

PRACTICE: Which of the following statements is not true of the JAK-STAT signal transduction pathway?

a) JAK2 is both a protein kinase and a target of phosphorylation.
b) The ligand initiates a kinase cascade by phosphorylation of the JAK2 protein.
c) Receptor dimerization is required for recruitment & phosphorylation by JAK2.
d) Phosphorylated STAT5 protein enters the nucleus and functions as a transcription factor.
e) The receptor must be phosphorylated in order to bind cytoplasmic STAT5 protein.