No Analytical crib available  
April 26, 2014  
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1. 10 points. Why a mutation in Ras protein often renders it constitutively active?

*Mutation in Ras protein renders the on/off switch mechanism ineffective. Thus, Ras protein preferentially binds GTP compared to GDP. GTP concentration is 10 times higher than GDP in cells. As a result, Ras remains constitutively active.*

2. 20 points. A ligand binds two different receptors with a $K_d$ value of $10^{-7}$ for receptor 1 and $10^{-9}$ for receptor 2. For which receptor does the ligand show greater affinity? Calculate the fraction of receptors that have a bound ligand ($[RL]/[R_T]$) in the case of receptor 1 and receptor 2, if the concentration of free ligand is $10^{-8}$.

   *Receptor 2 has higher affinity.*

   $% Occupancy for receptor 1 will be \sim 9\%, for receptor 2 it will be close to 91\% if the concentration of free ligand is 10^{-8}.$

   *Fractional Occupancy is calculated using the following formula.*

   $[RL]/[R_T] = [L]/[L] + K_d$

3. 20 points. Why a loss of function mutation in PTEN cancer promoting? What is its function in normal cells?

   *PTEN is a phosphatase that dephosphorylates PI 3,4,5-trisphosphate. It promotes apoptosis in normal cells by reducing the levels of PI 3,4,5-trisphosphate and thus inhibits the activation and anti-apoptotic effect of Protein Kinase B. Loss of PTEN function increases PI 3,4,5-trisphosphate levels and PKB activity, which is cancer-promoting.*

4. 10 points. Provide any two mechanisms by which growth factor signaling is terminated.

   *Endocytosis and Degradation.*

5. 20 points. Name three features common to the activation of cytokine receptors and receptor tyrosine kinases. Name one difference with respect to the enzymatic activity of these receptors.

   1. Both cytokine receptors and RTKs are activated by ligands. In the resting stage, they have very low activity.
   2. Ligand binding causes a conformational change that brings together the associated kinases (for cytokine receptors), which then phosphorylate each other, leading to their
activation. RTKs have catalytic activity, and thus can phosphorylate each other without the aid of the other kinases.

3. Phosphorylation causes docking sites for other signaling proteins containing SH2 or PTB domains.

RTKs have kinase activity, whereas cytokine receptors do not have intrinsic kinase activity. These receptors are associated with kinases.

6. (20 points) What is an orthosteric drug? Provide a potential disadvantage of using an orthosteric drug. How can you address this issue?

Orthosteric drug binds at the active site. The major problem with orthosteric drugs is that they may bind to homologous proteins sharing a similar binding site. Hence, orthosteric drugs should have very high affinity towards the target; which will allow usage of a low dosage to selectively inhibit only the target protein. Alternatively, allosteric drugs can be used, which often provide more selectivity.