

7.013 Recitation 12 - 2013

Summary of Lectures 19 & 20:

Cell signaling: A cell responds to signals from its surrounding environment. In general, the signal molecule binds to a receptor, conveys the message to the inside of the cell and then the cell changes its activity in response to the signal. These signals can be autocrine (chemicals act on cells that produce them), paracrine (diffuse to and out of a nearby cell) or endocrine (hormones that travel through blood to reach the target cells).

Signal receptors can either be membrane bound or cytosolic. G protein-linked receptors are examples of membrane-bound receptors. On binding to their ligand, these receptors are activated and in the active form, they interact with a GTP binding protein (G protein) to activate it. Once in the active GTP bound state, the G protein activates additional components of the signaling pathway. Once the G protein hydrolyzes the GTP into GDP, the signal is stopped.

The same signaling molecule can elicit different responses in different cell types. These responses may either be direct i.e. it is the function of the receptor itself and occurs at the plasma membrane or indirect which are more common and involve second messenger like cAMP etc. In either case, cascade of signals gets initiated, each step adding towards amplification of the signal. The result is a change in the activities of the cell.

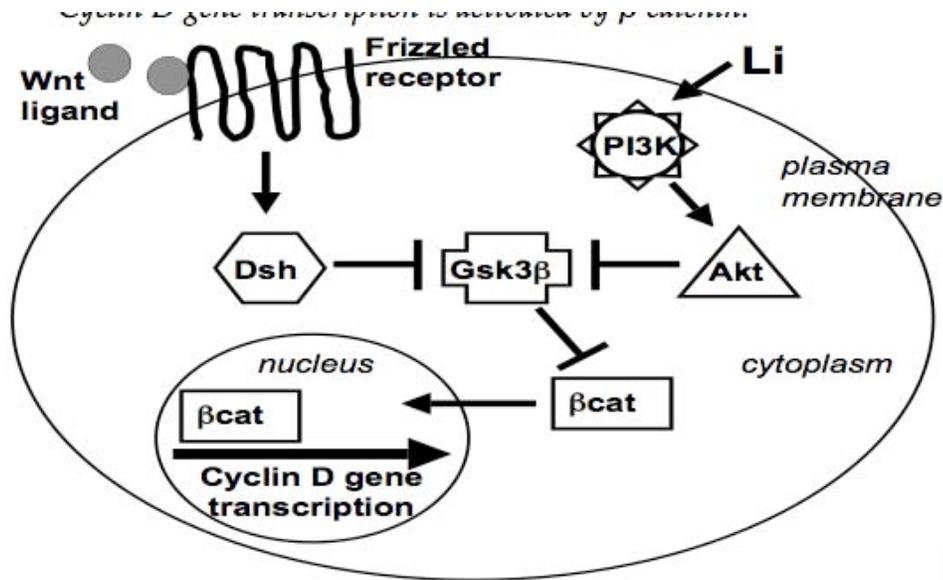
Cyclins, CDKs and Cell cycle: The cell cycle is the process by which one cell becomes two identical cells. The cell cycle is the chain of events that occur in only those cells that are actively growing and dividing. Cells preparing to undergo cell division must first copy each of their double-stranded DNA molecules (or chromosomes) in a process called DNA replication. The cell cycle consists of four stages – G1, S (DNA synthesis), G2, and M (mitosis). G1 phase is when the cells are preparing to replicate their DNA, which occurs in S phase. G2 is when the cells are preparing to divide, which occurs in M phase. Of these the S and M phases have fixed lengths but the G1 phase shows variable length in different cell types. The transition from one phase to other is regulated by a set of cell cycle checkpoints. The cell-cycle control system is based on two families of proteins: the cyclin-dependent protein kinases (Cdk) and the cyclins. Cyclins bind and activate specific Cdks, which phosphorylate selected proteins to promote cell division. Expression of cyclins is transient; they undergo a cycle of synthesis and degradation with each division cycle. The cyclic assembly, activation, and disassembly of cyclin-Cdk complexes are the pivotal events that drive the cell cycle.

Apoptosis: There are 3 different mechanisms by which a cell commits suicide by apoptosis; one generated by signals arising within the cell; two by death activators binding to receptors at the cell surface:(TNF- α , Fas ligand) and third triggered by reactive oxygen species that activate mitochondrial cytochrome C. Apoptosis involves the activation of proteins called caspases that promote cytoskeletal breakdown, nuclear condensation, DNA cleavage resulting hence cell death.

Question:

1. The *wnt* signaling pathway is one of the most important in biology. It is required for cell proliferation and its inhibition leads to programmed cell death. As diagrammed below

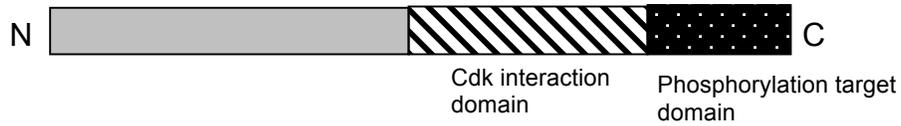
- *Wnt* ligands bind to frizzled receptors.
- These receptors bind to disheveled (*Dsh*) and activate its function.
- The *Dsh* inhibits *GSK3β*, a kinase.
- *GSK3β* phosphorylates the transcription factor β -catenin (β cat). The phosphorylated β -catenin is unstable and gets degraded.
- Thus *wnt* signaling inhibits *GSK3β*, promotes β -catenin stability and translocation to the nucleus.
- *GSK3β* can also be inhibited by addition of Lithium, acting through PI3 kinase/ Akt pathway.
- Cyclin D gene transcription is activated by β -catenin.
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Compare the expression of cyclin D protein levels in the pairs of cells described below and explain your reasoning. In each case **both cells of the pair are treated with wnt ligand**. For your answers you should consider only those components that are shown in the schematic above or listed as bullet points in the explanation and explain only in the space provided. You may ignore the effect of Lithium while answering the questions. State the changes that will be elicited by the following mutations.

- Mutant cells having a Frizzled receptor that lacks its ligand binding domain.
- Mutant cells that express a constitutively active *Dsh* protein.
- Mutant cells in which β -catenin lacks its *GSK3β* phosphorylation site.
- Wild type cells treated with Chiron 92060, a *GSK3β* inhibitor.

2. The cyclin D protein has the following structure.



- i. What effect would the deletion of the Cdk-binding domain of Cyclin D have on cell proliferation? Explain.
 - ii. Using a temperature sensitive variant of Cyclin D, you find that the cells fail to divide at the non-permissive temperature. The arrested cells have a diploid DNA content ($2n$) in a single nucleus. At what cell cycle checkpoint (or stage of cell cycle) is cyclin D likely to act? Explain.
 - iii. How would the Cdk protein levels vary during the normal cell cycle?
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