Biochemistry 673 Lecture 1

This course is "regulation of metabolism." In the past, its content has changed markedly depending on who has taught the class. At one time, it was focused on enzymology and regulation of metabolic pathways. Recently, Dr. Beckett has focused more on allostery. As biochemistry has advanced, we can now understand molecular mechanisms for more of the decision making that goes on in the cell as well as regulation of individual pathways or enzymes, and that is the focus of the current

I am going to cover several examples of regulatory networks, trying to cover some systems to show how understanding develops and also trying to give examples of the ways in which signal transduction works in general. We will have a few lectures on each topic, then discuss papers in class, and then have student presentations. Each student will present once during the semester. You will lead the discussion much as I do, except that you will also provide the class with a 2-page discussion of the paper, focusing on how their experiments support (or don't support) their claims. You can present on any area that we have covered or are covering, after clearing your proposed paper with me first to make sure we don't get too much concentration in any one area.

The 2-page report is an analysis, not a summary or the abstract. Read the syllabus and the web page on plagiarism.

Grading will be based on class participation in paper discussions, the student presentation, one in-class exam, and the final.

Basics of signal transduction:

Chapters 10 and 20 of Lodish are a good source, as well as the texts.

An internal or external change induces a cell to alter its metabolic or gene expression program. Stimuli include changes in nutrient levels, hormones/chemokines/growth factors, chemoattractants or repellents, neurotransmitters, light.

Often the stimuli are external to the cell but the response usually occurs inside. Somehow information has to pass through the plasma membrane. This can be done via ion channels, so that a physical entity passes through, or conformational change, especially via dimerization/multimerization.

The stimuli are detected by receptors, for example 7TM (7-transmembrane receptors that often interact with G-proteins), or intracellular hormone receptors.

Receptors then activate or inactivate target molecules. These can be

- enzymes that synthesize "second messengers," as in the stimulation of adenylate cyclase by epinephrine to give increased concentrations of cAMP. Or they may be
- kinases, as in the activation of receptor tyrosine kinases in stimulation by EGF or insulin. These kinases can set off "kinase cascades," as in the MAP kinases that are involved in stress responses and differentiation. Or they may be

- receptors can be transcription factors, like the estrogen receptor, so affect chromatin remodeling machinery. Or
- ion channels, as in synaptic transmission

Either the initial effector proteins or the second messengers then change the properties of downstream proteins. Typical mechanisms include:

- phosphorylation on Ser/Thr or Tyr, or His or Asp for bacterial two-component signalling systems
- other covalent modifications such as methylation, acetylation, SUMOylation, ubiquitination (as for the "histone code"), uridylation, glycosylation
- proteolysis, as in the blood clotting cascade or ubiquitin-mediated proteolysis via the proteasome, or the apoptotic caspases
- ligand binding, as in activation of transcription by CAP or CREB upon binding cAMP, or simple feedback inhibition by binding of Trp to Trp repressor, or a regulatory subunit that controls an enzyme. Binding of calmodulin+Ca++ to target proteins.
- subcellular localization, as for the glucocorticoid receptor or NFKB, in which ligand binding or a receptor-initiated cascade ending in proteolysis respectively lead to revealing nuclear localization signals. Or the release of cytochrome c from mitochondria as a commitment to apoptosis.

Eventually the activities of metabolic enzymes or motor proteins or channels or other enzymes must be affected, or else the cellular program of gene expression is changed.

It is quite common for several detailed molecular mechanisms of activation/repression to be observed within a single pathway.

It is equally important to be able to turn off the signal by:

- Reversing covalent modifications (protein phosphatases)
- Having built-in decay of activity (G proteins are active as long as they bind GTP, but are themselves GTPases), Bacterial response regulators spontaneously dephosphorylate.
- Endocytosis (and subsequent recycling) of receptors
- Negative feedback loops via gene expression.

and to respond differently to changes in the level of a stimulus. When the lights go out, we see it is dark immediately, but it takes a while to ratchet up the sensitivity of our eyes. Methylation of chemotactic receptors gives them a memory of how much of a chemoattractant was present a few seconds ago.

Pathways can intersect to integrate signals from different sources or for redundancy or for tenability. For example the web of insulin signals is phenomenally complicated. A lot of current interest in the genomics/proteomics/transcriptomics field is concerned with identifying all of the targets of signal transduction pathways. There is a great deal of theoretical interest in how cells maintain robust signalling while avoiding too much noise.

[Cartoon on the board showing communication from outside to inside.]