Highlights Gene Expression (continued)

1. Enhancer sequence elements allow transcription factors that a made in specific tissues to specifically activate (or in some cases inhibit) transcription of genes under their control in those specific tissues.

2. Modifications to the chromatin (by acetylation/deactylation of lysines in histones) can activate or inactivate (respectively) transcription of genes in eukaryotes. Alterations to the DNA, such as methylation of cytosine can act to inactivate transcription. Such modifications can be inherited across generations and are referred to epigenetics.

3. Nuclear hormone receptors, such as the estrogen receptor, have DNA binding domains and ligand binding domains. The binding of the estradiol (and estrogen) ligand to the estrogen receptor causes a conformational change in the protein, but does not change the binding of the protein to DNA. Binding of the estradiol DOES appear to activate the protein and thus activate transcription of the genes that the receptor binds to the promoter of.

4. The key to action of the nuclear hormone receptor that binds estradiol is that binding of estradiol favors binding of the receptor to co-activator proteins. These co-activator proteins help to turn on transcription of the relevant genes. Binding of co-activator proteins by transcriptional factors, such as the estrogen receptor is called recruitment.

5. An antagonist of the estrogen receptor is the drug tamoxifen. Antagonists bind proteins and prevent them from acting. Binding of tamoxifen by the estrogen receptor stops the receptor from activating transcription of genes that it normally activates.

6. Tamoxifen appears to act by binding the estrogen receptor (I use the terms estrogen receptor and nuclear hormone receptor here as the same thing), with a part of the molecule extending into the region of the protein that normally binds to co-activators. Thus, tamoxifen acts by stopping recruitment by the receptor of co-activators. Tamoxifen is used to treat tumors that are stimulated by the binding of estrogens to the receptor.

7. Altering chromatin structure is an essential function for transcriptional activation in eukaryotes. Co-activator proteins appear to play a role in this process by catalyzing the acetylation of lysine residues in histones. Acetylation of histone lysines neutralizes their positive charge, changing the affinity of histones for DNA and changing the nature of their interaction with DNA, thus allowing more proteins to be able to gain access to the DNA where the acetylation has occurred.

8. Proteins involved in transcriptional control often have bromodomains. These regions of protein recognize and bind to acetylated lysine residues in histones.

9. Altering chromatin structure involves a process called remodeling. Steps in this process include 1) binding of a transcription factor to a promoter sequence; 2) recruitment of co-activators; 3) acetylation of histone lysines by co-activators; 4) binding of the 'remodeling engine' at the acetylation site; 5) exposing of DNA by the remodeling engine; and 6) binding of RNA polymerase II to the exposed DNA.

10. In eukaryotic cells, the ferritin mRNA has a region of it called an iron response element that can be bound by a protein called IRP (iron response element binding protein). IRP binds the iron response element when iron is absent. If IRP is NOT bound to the iron response element (high iron conditions), ferritin is made

because the IRP does not block the ribosome from translating the mRNA. Thus, when iron concentration is high, ferritin is synthesized to hold it. When IRP is bound to the iron response element (low iron conditions), ferritin is not made. Thus when iron is not available, ferritin is not made. Gene expression of ferritin is therefore a function of translational control.

11. The transferrin receptor has multiple iron response elements at the 3' end of its mRNA. When IRP binds to it, the 3' end is protected and transferrin receptor is made. Thus, when iron is low, the IRE-BP binds the mRNA, protecting it, and the transferrin receptor is made to bring iron into the cells. When iron is high, the IRE-BP leaves the mRNA's 3' end, leaving it susceptible to degradation. Gene expression of the transferrin receptor is therefore a function of stability of the gene's mRNA.

12. Thus when iron inside the cell is high, ferritin is made to hold onto it and when iron is low inside the cell, transferrin receptor is made to bring more iron in.

13. Micro RNAs are short RNA molecules that play an important role in regulating levels of eukaryotic mRNAs. They are completementary to the mRNA the regulate and when combined with the target mRNA in a protein called Argonaute, result in cutting of the mRNA and reducing or eliminating its effectiveness.

Highlights Sensory Systems

1. Smell arises from nerve signals originating in nasal epithelia. Molecular components of this process include 7TM proteins that bind odorants, which activates a G protein called G_{olf} . G_{olf}, in turn, binds GTP, activates adenylate cyclase, stimulating cAMP synthesis. cAMP binds to a cAMP-gates ion channel in the cell membrane allowing cations to enter the cell, starting the nerve signaling process.

2. Humans have a small percentages of their odorant rcceptors active, whereas rodents a large percentage of their 1000 receptor genes active. Olfactory receptors (ORs) are similar in slightly structure to the beta-adrenergic receptor involved in epinephrine signaling. Each olfactory neuron synthesizes only a single OR. This differs from individual taste buds, which each synthesize several receptors for tastes.

3. We are able to perceive a VERY wide range of smells, due to the combinatorial mixing of signals from the many different 7TMs at the end of olfactory cells.

4. OR signaling proceeds via 7TM receptors that synthesize cAMP when an odorant binds to the 7TM (through the usual mechanisms). cAMP binds to a channel protein that opens when cAMP binds to it, allowing Ca++ and Na+ into the cell, thus starting the signal.

5. Smell neurons terminate in very different regions of the brain.