SP.235 / ESG.SP235 Chemistry of Sports
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EPIGENETICS
is
KEWL!

Epigenetics means….

- Literally: “Above genetics”

Epigenetics: Key Point

- Refers to the idea that chemical labels on DNA that do not alter the DNA nucleotide sequence may nonetheless alter the regulation of that DNA, affecting gene expression and thus phenotype variability. Similar to typical genetic variation, these chemical labels can be inherited, but they are more easily modifiable than the DNA sequence."

Epigenetics: The next layer of the onion

- Basically, DNA determines protein structure while epigenetic modifications can determine which proteins are expressed. So, epigenetics is the study of heritable changes in gene function that occur *independent* of changes in DNA sequence.

EXAMPLE:

- Hair or coat color in some mouse strains has been shown to be heritable, but independent of genetic sequence variation present in the parents of the offspring.
- Coat color in the offspring of these animals can be altered by the manipulation of the dietary intake of the parents.

EXAMPLE:

- In humans, a few studies have correlated such phenotypes as birth weight and cardiovascular disease in individuals with the dietary patterns of their grandparents, apparently *independent* of direct DNA sequence inheritance.
- Many identical twins (monozygotic) are discordant for the presence of various heritable diseases (i.e., one affected, one unaffected) despite similar shared environments and identical genetic profiles.

ENVIRONMENTAL FACTORS:

- Environmental factors can influence DNA, but without changing the nucleotide sequence.
- DNA can be “decorated” with chemical labels that can affect gene regulation without affecting the DNA sequence.

METHYL GROUPS:

- These labels, the most common of which are *methyl groups* attached to cytosine nucleotides (DNA methylation), can be added or removed depending upon environmental stimuli presented to the cell.
- When the methyl group labels are present in the promoter region of a gene or some other regulatory region, they can affect the ability of transcription facts to bind to the gene, thereby affecting expression.

900 CATS: YIKES!

- In the 1940s, Dr. Francis M. Pottenger conducted a 10-year study using *900 cats* to determine the effects of food on the body.
- Dr. Pottenger noticed that over the course of four generations, cats on a cooked food diet became progressively more diseased over three generations to the point that no fourth generation was ever born.
- Cats following a raw food diet continued to produce healthy vibrant kittens.

HERITABLITY OF EPIGENTIC MARKS:

- Epigenetic marks are replicated during cell division and passed on to daughter cells.
- Thus, epigenetic marks are *transient* in one sense, yet *heritable* in another.
- Epigenetic marks provide potent therapeutic targets because they can be *added* or *stripped*, but we wouldn't be talking about them if they were heritable.
- Neither mutations nor misplaced methyl marks would induce tumors if they were diluted out when cells divide.

MANIPULATION OF THE EPIGENOME:

- Scientists have manipulated the epigenomes of mice to explore methylation patterns previously linked to tumor formation.
- They tinker with methyl marks and watch the results – an approach that permits scientists to establish *cause* and *effect*.

GENE EXPRESSION:

- So, it appears that what we are talking about is *gene expression*.
- Gene expression is what keeps people that are "genetically susceptible" to a disease from actually getting the disease.
- Most diseases are not inherited – rather, a tendency for that disease is passed from parent to child.
- For example, many people that have a family history of diabetes, heart disease or cancer never develop those diseases.

DISEASE DEVELOPMENT:

- The development of disease is dependent on gene expression.
- So, *what drives gene expression?*

GENE EXPRESSION:

- Research currently being done says gene expression is related to *lifestyle* and *environmental factors*.
- And what are the environmental factors that can most easily be controlled?

CONTROLLABLE ENVIRONMENTAL FACTORS:

- Research currently being done says that the environmental factors that can most easily be controlled are:

  Diet and exercise!

TAKING CARE OF YOURSELF:

- So, even though someone may be susceptible to something due to epigenetic inheritance from their parents or epigenetic markers placed throughout their life, by taking care of themselves, they can overcome these diseases.

THE EPIGENOME: YOUR BODY'S FIREWALL:

- The epigenome serves as a kind of firewall, hiding certain genes while exposing others.
- Example: some methyl groups on the promoter of a gene can keep it concealed and silent in a particular tissue.

OTHER EPIGENETIC MARKS:

- Though methyl marks are the best understood of the epigenetic marks, there are other marks:
- Example: packaging proteins do the same thing.
- These proteins block access to genes by coiling bits of the sequence into neat spools.
- This is how a brain cell knows it's supposed to be a brain cell and a skin cell knows it's supposed to become a skin cell.

ACCESSORIZE YOUR EPIGENOME:

- Given their essential function, epigenetic marks hardly serve as DNA accessories.
- But, they *can* be changed like a pair of earrings or a necklace.
- Example: An enzyme called Dnmt3a places methyl marks on previously unmethylated DNA.
- Typically active in developing embryos this particular enzyme helps establish tissue specific DNA methylation patterns.
- So, whether we switch on or inhibit certain genes epigenetically can theoretically determine everything from how we age, how much we weigh, or whether we develop cancer.

EPIGENETICS AND DIET:

- The strongest evidence of genetic variation brought on by epigenetic factors is in the area of diet. Specifically, calorie restriction ("CR").
- For more than 70 years, CR has been known to extend lifespan.

CALORIE RESTRICTION:

- While the exact molecular basis for slowing down the aging process is not fully understood, recent studies have pinpointed a few molecular pathways that appear to regulate the aging process.

HOW DOES CALORIE RESTRICTION WORK?

- According to Koubova and Guarente, CR has been known to extend life in a remarkable range of organisms including yeast, rotifers, spiders, worms, fish, mice, rats and non-human primates.
- CR also has been shown to delay a large spectrum of diseases including kidney disease, a variation of neoplasias, autoimmune disease, diabetes and neurodegenerative disorders such as Parkinson's disease or Alzheimer's disease.

HOW DOES CR DO THIS?

- While the exact mechanism remains unclear, CR has multiple affects including metabolic, neoendocrine and apoptotic (single deletion of scattered cells due to preprogrammed cell death) changes which vary in intensity and exhibit striking differences among specific organ systems.
- Example: CR causes epigenetic changes in the SIR2 gene which regulates the lifespan in yeast. Mutations that inactivate the SIR2 gene shorten life and overexpression of the SIR2 gene extends it.
- The study also showed that genes involved in the control of the cell cycle, apoptosis, detoxification and cholesterol metabolism could be switched on or off by CR.

AGING: GENE SILENCING OR GENE ACTIVIATION?

- A study by Burzynski, SR suggests that the key process in aging involves reduced expression of a number of genes.
- Several mechanisms associated with CR including the methylation of DNA leads, histone modification and chromatin remodeling leads to the silencing of certain genes involved in the aging process.
- CR normalizes the expression of a number of genes which are associated with typical diseases of old age.

EFFECTIVE EXERCISE:

- In a study by Huffman, DH called *Effect of Exercise and Calorie Restriction on Biomarkers of Aging in Mice*, the author noted that in their study, exercise, unlike calorie restriction, fails to extend maximum lifespan.

WHAT DOES IT ALL MEAN?

- Epigenetics means that the choices we make about lifestyle can not only affect ourselves, but can also *determine* the health of our children and our grandchildren.

MORE GOOD NEWS:

- While epigenetic factors play a large role in phenotype variability and can determine whether we live a normal lifespan or get sick, epigenetic modifications appear to be *reversible* as well!
- So, while you can't go back to your childhood and make your parents treat you better or un-experience a tragic event, *if you manage your stress, diet and exercise you can correct genes that have been altered!*