Epigenetic Regulation: A Literature Review

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Abstract

Epigenetic regulation describes the manner in which gene expression is modified without changes to the DNA sequence. It is a complex process that involves the interaction of many biological molecules. The three most well-characterized mechanisms of epigenetic regulation are DNA methylation, histone modifications, and non-coding RNA activity. It is well established that environmental factors can regulate the activity of these mechanisms. This review specifically focuses on the manner by which physical activity and nutrition can alter gene expression through epigenetic regulation, proposing an explanation of why certain eating and exercise behaviors produce particular outcomes. The results of my research indicate that engaging in physical activity positively regulates the activity of signaling pathways that lead to tissue remodeling and an increase in aerobic capacity. Many studies have demonstrated the importance of early-life nutrition and how poor periconceptional nutrition negatively affects offspring. Type II diabetes, is a metabolic condition largely characterized by insulin resistance and the pathways that regulate insulin-mediated glucose uptake are susceptible to epigenetic regulation.

Introduction

Every hair on our head, freckle on our skin, and bone in our body is there because our DNA told it to be. With only slight variations in our genetic code, our appearance and behavior
still differs considerably from person to person. Every cell in our body contains the same DNA, yet a brain cell behaves completely differently than a stomach cell. As humans, we sometimes forget how incredibly complex our bodies are, and how specialized each organ, and each cell in each organ is to carry out functions that are essential to our survival. With only 4 nucleotides to vary, the human body has developed other methods, such as epigenetics, to aid in the differentiation and specialization of our cells. Epigenetic regulation describes the process by which gene expression can be modified without changing the actual DNA sequence (Barros and Offenbacher 2009). We can think about DNA as a coloring book and epigenetics as the individual coloring. Epigenetics doesn’t change which pictures are already in the book; those have already been predetermined. However, it can modify which pictures are colored in, what colors these pictures are, and which ones are left alone and ignored. The actual process of epigenetic regulation is much more complicated than the coloring book metaphor, as it involves complex interactions between DNA, histones, and a variety of enzymes. However, the coloring book example still illustrates the basic idea that epigenetics doesn’t change our actual DNA code, but rather regulates which genes are actively transcribed and which ones are repressed.

The central dogma of molecular biology describes the process by which our DNA is transcribed into RNA, which is then translated into a protein. While one’s DNA sequence contains the blueprint for gene expression, there are other regulatory mechanisms that determine which components of an individual’s genotype, their genetic makeup, is expressed in his or her phenotype, their observable characteristics. Epigenetics has proven to have important implications in a variety of pathologies including cardiovascular disease, cancer, autoimmune disorders, and schizophrenia. These interactions between epigenetics and disease states are
mediated by a variety of environmental factors, including diet, exercise, pollutants and smoking. (Stauffer and Desouza).

The way in which epigenetics affects the transcription of RNA and resulting expression of genes is still not completely understood, but there are three methods that have been extensively studied. The first is DNA methylation, which, in most cases, acts to silence the expression of genes (Barros and Offenbacher 2009). Histone acetylation is another regulatory mechanism, where the interaction between DNA and the histone core can result in either the expression or repression of certain genes (Howlett and McGee 2016). The third is through non-coding RNA molecules, which is responsible for the negative post-transcriptional silencing of genes (Ntanasis-Stathopoulos 2013). These modifications are dynamic in nature and the interactions between these different regulatory mechanisms and their subsequent effect on gene expression are still being characterized.

Epigenetic regulation can have a profound effect on the health of an individual, and is therefore becoming a very important factor in the prevention, diagnosis, and treatment of a variety of disorders. Some pathologies in which epigenetics play a large role are cancer, cardiovascular disease and type 2 diabetes. In cancerous states, the silencing of tumor suppressor genes as well as the uncontrolled expression of oncogenes can occur through epigenetic dysfunction (Barros and Offenbacher 2009). Heart failure, cardiac hypertrophy, arrhythmias and diabetic heart disease have been shown be mediated through a variety of epigenetic changes (Khalil 2014). A variety of enzymes involved in the onset and progression of type 2 diabetes are subject to epigenetic regulation (Ling and Groop 2009). These exact mechanisms will be discussed in more depth throughout this literature review.
This review will provide an overview of the different mechanisms of epigenetic regulation and how different factors, particularly diet and physical activity can influence epigenetics and subsequently gene expression. I will cover both past and current studies that have found important relationships between environmental factors and certain disease states. This paper aims to demonstrate the cellular basis behind the well-known ideas that a sedentary lifestyle and poor diet will promote negative health consequences, while an active lifestyle and nutritious diet can have positive systemic effects.

**Epigenetic Mechanisms:**

In order to fully understand epigenetic mechanisms, it is important to have a good grasp of the DNA molecule and its components. By using a combination of just four nitrogenous bases, deoxyribonucleic acid (DNA) is able to encode all of our genetic material. The four bases, adenine, thymine, cytosine, and guanine, are attached to a sugar molecule, ribose, and a phosphate group. This phosphate group carries a negative charge, and as a result DNA is a negatively charged molecule. The DNA molecules are wound around eight histone proteins, resulting in a compact structure known as a nucleosome (Annunziato 2008). This structure can be thought of as a yo-yo, where the string is the long DNA molecule, and the plastic center is the histone protein. While it seems counterintuitive to add a protein to make DNA more compact, the yo-yo analogy helps us to see that without the plastic center, the string would have nothing to coil up against, and would take up much more space in its unwound state. In order to facilitate the tight binding between DNA and the histone, there are strong electrostatic interactions, as a result of the positively charged histone associating with the negatively charged DNA molecule.
The association between DNA and the histones is dynamic. This refers to the fact that at different times throughout an individual’s life, some segments of DNA are wrapped more tightly around the histone than others, and are known as heterochromatin. The more closely associated the DNA segment is with the histone, the harder it is for transcriptional proteins to access it, and it is therefore not readily transcribed. On the other hand, DNA segments that are loosely associated with the histone proteins are known as euchromatin, and can be easily accessed and transcribed (Mowshowitz 2011). The state of the chromatin (heterochromatin vs. euchromatin) is a result of a variety of factors including the type of cell, the physiological state of the individual, and the time period. In addition to the intrinsic regulation of chromatin state, epigenetics plays an important role in the transcription and repression of certain genes.

**DNA Methylation**

DNA methylation is a key player in epigenetic regulation and is regulated by a family of enzymes, known as the DNA methyltransferases (DNMT). The DNMT enzymes are primarily responsible for the addition of methyl (-CH3) groups to the cytosine nucleotide at the C5 position, particularly when a cytosine is linked to a guanine via a phosphate bond, known as a CpG dinucleotide (Howlett and McGee 2016). These CpG dinucleotides are scattered throughout the genome, but tend to be largely concentrated near transcription start sites (Phillips 2008). There are three different DNMT enzymes that are specialized for different DNA sequences. DNMT1 is responsible for preserving methylation patterns, allowing them to be maintained when cells divide. DNMT3A and DNMT3B produce de novo methylation patterns in DNA, and appear to be regulated by the surrounding DNA sequences (Howelett and Mcgee 2016). It is
important to understand that these epigenetic modifications are dynamic, and these methylation patterns can be changed and altered throughout time. There are two processes responsible for the disappearance of established methylation patterns: passive and active demethylation. Passive methylation occurs during cell division, when DNMT1 doesn’t perform adequately, and the patterns become diluted over time. Active demethylation is mediated by the activity of three enzymes, but has only been observed experimentally. This occurs when TET1-3 hydroxylates (adds an -OH) the methyl-cytosine. This is followed by AID/APOBEC deaminating (removing - NH3) the hydroxymethyl-cytosine to uracil. Subsequently, BER enzymes utilize base excision repair to replace the uracil with a cytosine.

Generally, DNA methylation is associated with repression of transcriptional activity. The exact mechanism for this phenomenon is unknown, but it is believed that the modification of the cytosine nucleotide interferes with the ability of the transcription factor to bind to the promoter area (Phillips 2008). In diseased states, such as cancer, methylation of cytosine residues is commonly found on tumor suppressor genes, which normally function to regulate cell growth. When these tumor suppressor genes become methylated and, in turn, silenced, cells experience uncontrolled growth (Phillips 2008).

**Histone Modifications**

As mentioned previously, DNA is tightly wound around proteins called histones to keep it organized and compact. There are four histones: H2A, H2B, H3, and H4 and any modifications to these histone proteins can affect how readily DNA is transcribed. One of the most common and well characterized modifications is histone acetylation, which is catalyzed by histone
acetyltransferase enzymes (HATs) and is associated with activation of genes. Histone acetylation generally takes place on the N-terminus of lysine residues, which carry a positive charge. By adding an acetyl group (CH3CO), this positive charge is essentially removed, and the negatively charged DNA is no longer as strongly attracted to the positive charged lysine. This loose conformation between the DNA and histone allows for promoters to bind to the genes, and thereby increase transcription. In the same way that the HATs can acetylate a histone, there are also histone deacetylase enzymes (HDACs). The job of the HDACs is to remove acetyl groups from histone, which will increase the affinity that the histone has towards DNA and lead to a more tightly bound conformation and therefore, a decrease in transcriptional activity.

Another type of modification is histone methylation. This modification is a little more complicated and less predictable than histone acetylation, because it can lead to either transcriptional activation or repression depending on the amino acids and the number of methyl groups added. Generally, methylation occurs at lysine (K), which can be methylated twice or arginine (R), which can be methylated three times. There are a few recurring methylation patterns that tend to produce the same outcome each time they are preset. For example, Histone 3 lysine 4 methylation (H3K4me) and histone 3 lysine 9 mono-methylation (H3K9me) both lead to activation. However, when H3K9 is methylated twice or three times, it will cause transcriptional repression. Like most epigenetic modifications, histone methylation is reversible and is facilitated through histone methyltransferases (HMTs). Histones can also be modified through processes including phosphorylation, ubiquitination, sumoylation, or ribosylation, but their effects on gene expression are not well characterized.
Noncoding RNA Activity

Noncoding RNA activity is another major contributor to epigenetic regulation and is mediated by a certain type of RNA called microRNA (miRNA). MicroRNA is transcribed by RNA Polymerase II and processed from its immature form (~70 nucleotides) to its mature form (~20-24 nucleotides). It is responsible for the negative post transcriptional regulation of gene expression, meaning it is involved in protein silencing (Ntanasis-Stathopoulos 2013). It does this by either degrading mRNA or binding to the untranslated 3’ end to inhibit translation. There are over 900 different miRNAs which have shown to be well conserved throughout species. The levels of miRNA that is expressed varies in the body, especially in certain cases of pathologies, particularly type 2 diabetes. The exact mechanism for this differential expression is yet to be fully understood, but it is well known that a relationship exists between miRNA and epigenetic regulation (Chuang & Jones 2007). A summary of the epigenetic modifications and their effects on gene expression are illustrated in Figure 1.
Figure 1. Model of epigenetic modifications. Adapted from “The effect of exercise on skeletal muscle glucose uptake in type 2 diabetes: An epigenetic perspective” by Dos Santos et al., 2015, *Metabolism: Clinical and Experimental*, 64, 1619-1628. © 2015 Elsevier Inc. Adapted with permission.

**Exercise Induced Epigenetic Modifications**

It is well known that there is a relationship between physical activity and overall wellbeing, with higher levels of physical activity associated with greater health. Individuals who exercise regularly are less likely to develop Type 2 diabetes, cardiovascular disease, or cancer (Ling & Ronn 2014). On a basic level, this relationship can be explained by the fact that regular exercise can lead to a lower percentage of body fat. This decrease in body fat contributes to a lower risk of suffering from conditions associated with being overweight or obese. On the genetic level, the relationship between exercise and wellbeing becomes much more complicated,
but is largely mediated by epigenetic changes. Systemically, exercise has widespread effects on the human body, bringing about changes in the musculoskeletal system, cardiovascular system, and nervous system.

The reason exercise is so challenging is because it puts stress on the body. However, unlike the stress of eating poorly or not sleeping, exercise is a positive stress, causing the human body to adapt in beneficial ways. These adaptations are directly influenced by epigenetic changes. As discussed previously, there are three main mechanisms by which epigenetic modifications occur to alter gene expression: DNA methylation, histone modification, and noncoding RNA activity. Generally, acute bouts of exercise result in hypomethylation in the promoter region of certain metabolic genes and is directly related to the intensity of the exercise. This means that an intense period of physical activity will result in higher levels of demethylation than low or moderate intensity exercise. Exercise can also impact gene expression in an indirect way, through the use of cytosolic messengers such as $\text{Ca}^{2+}$ and AMP, both of which are involved in gene transcription. More specifically, it has been suggested that $\text{Ca}^{2+}$ and AMP result in histone modifications through their interactions with Calcium/Calmodulin-dependent protein kinase II (CAMKII) and AMP-dependent protein kinase (AMPK), respectively.

There are a few different mechanisms through which CAMKII and AMPK work to mediate exercise related epigenetic changes, including increased expression of GLUT4 and mitochondrial genes. This is accomplished through the actions of myocyte-specific enhancer factor (MEF2), a transcription factor in the PCG-1α pathway. (Ntanasis-Stathopoulos et al. 2013). MEF2 plays a variety of important roles in the human body from development into adulthood. In adulthood, MEF2 is largely implicated in the response to stress and the subsequent
remodeling of both cardiac and skeletal muscle tissue (Potthoff, Olson 2007). PCG-1α is a transcriptional coactivator that is incredibly important when it comes to regulating cellular energy metabolism. Transcriptional coactivators are proteins that interact with transcription factors to increase the probability that a gene is transcribed. Some of the transcription factors that PCG-1α interacts with are the peroxisome proliferator-activated receptors (PPARs). There are 3 PPARs, PPARα, PPARγ, and PPARδ. In this case, we are most concerned with PPARα and PPARγ, which are largely implicated in epigenetic signaling cascade. The first step in this pathway involves adenosine monophosphate activated protein kinase (AMPK). AMPK is activated in cases when the cell has a low energy charge, meaning the AMP/ATP ratio is high. AMP binds to the gamma subunit of protein, partially activating it. This is followed by the phosphorylation of the Thr 172 residue on the alpha subunit, fully activating the protein. This is illustrated in Figure 2.
As indicated in the figure, fully active AMPK phosphorylates serine and threonine residues on target proteins, affecting their activity. AMPK has a variety of downstream effectors, but the net result is an increase in ATP. This occurs by increasing the glycolytic flux, increasing oxidative phosphorylation, and increasing fatty acid oxidation through both inhibitory and stimulatory downstream effects. This is illustrated in Figure 3.
PCG-1α is largely responsible for the increase in mitochondrial density that is seen as an adaptation to exercise. This increase in mitochondrial density is accompanied by changes in muscle fibers, allowing them to increase their oxidative capacity (Ntanasis-Stathopoulos et al. 2013). PCG-1α also plays an important role in the metabolism of lipids and glucose, and will be discussed in more depth later in this review in terms of its involvement in Type 2 diabetes (Liang, Ward 2006).

Additionally, there are other ways in which GLUT4 expression in skeletal muscle can be regulated. These pathways involve the class II HDACs. At rest, HDAC5 and MEF2 interact,
resulting in GLUT4 becoming deacetylated and in turn, decreasing its expression. However, after periods of acute exercise, AMPK phosphorylates HDAC5, causing it to dissociate from MEF2. MEF2 is now free to interact with the co-activators PPAR-γ, PPARGC1a, and HATs. This leads to the acetylation of GLUT4 and as a result an increased expression. The importance of MEF2 should not be understated. MEF2 plays a vital role in cell differentiation and organogenesis. It has the power to activate a variety of genes, depending on the cell type. However, the mechanism by which it acts is essentially the same in all cells. MEF2 can be thought of as the middleman between the outside environment and the genome. It takes extracellular signals and transmits this information to the genome. The genome will react to this information by altering gene expression, particularly those involved in differentiation, proliferation, and morphogenesis.

In this case, we are mainly concerned with its role in skeletal muscle and how that plays into epigenetic regulation. By itself, MEF2 is not able to produce myogenic changes. In order to achieve the skeletal muscle differentiation, MEF2 works with basic helix-loop-helix (bHLH) transcription factors. These bHLH transcription factors are a part of the myogenic regulatory factor family, which includes, MYOD, myf5, MRF4 and myogenin (Sweetman 2012). This family of proteins is incredibly important during embryonic myogenesis, leading to the differentiation of muscle cells (Sweetman 2012). These proteins create a positive feedback loop network that is responsible for myogenic transcription (Cole et. al 2004). It accomplishes this through the activity of upstream regulators. In the most basic sense, upstream signals activate the expression of MYOD and MYF5. These upstream signals are biochemical in nature, and result from mechanical loading of the muscles, which occurs during exercise (Chandran et. al 2007). This results in the activation of Myogenin in the skeletal myocytes, which leads to the expression of MEF2. MEF2 acts directly to differentiate muscle cells, but it also feeds back on the promoter.
for myogenin, which amplifies the signal (Potthoff & Olson 2007). As discussed previously, MEF2 also interacts with HDAC class II molecules, specifically HDAC4 and HDAC9, to regulate myogenic transcription on an additional level. Under normal, physiological conditions, HDAC4 and HDAC9 inhibit MEF2 activity. However, MEF2 is able to regulate HDAC activity through miRNA molecules.

Micro RNA molecules, which were previously talked about as a method of epigenetic regulation, are responsible for post-translationally silencing proteins as well pre-translationally decreasing the transcription of certain genes. In addition to miRNA molecules that circulate in the plasma, there are miRNA molecules that are found only in the muscle cells, known as myomiRNAs. MyomiRNA molecules contribute to the proliferation and differentiation of myocytes and the determination of muscle fiber types. They also play a large role in appropriate regulation of muscle hypertrophy and atrophy. A failure of the miRNA molecules to be properly regulated can result in a variety of muscle diseases and dysfunction. The circulating miRNA molecules facilitate a variety of physiological processes, including angiogenesis, inflammation, muscle contractility, and adaptations to ischemic conditions. There are a few miRNA molecules whose expression can be altered by exercise. Additionally, the different miRNA molecules will respond to different types of exercise. For example, miR-21 and miR-221 respond to exhaustive aerobic exercise, miR-20a responds to sustained aerobic exercise, miR-146a and miR-222 respond to both, and miR-133 responds only to resistance exercise. (Ntannasis-Stathopoulos et al. 2013). Additionally, miR-1 plays an important role in myogenic differentiation (Potthoff & Olson 2007). This is summarized in Table 2.
<table>
<thead>
<tr>
<th>miRNA molecule</th>
<th>Condition responded to</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-1</td>
<td>MEF2 expression</td>
</tr>
<tr>
<td>miR-20a</td>
<td>Sustained aerobic exercise</td>
</tr>
<tr>
<td>miR-21</td>
<td>Exhaustive aerobic exercise</td>
</tr>
<tr>
<td>miR-133</td>
<td>Resistance exercise</td>
</tr>
<tr>
<td>miR-146a</td>
<td>Sustained and exhaustive aerobic exercise</td>
</tr>
<tr>
<td>miR-221</td>
<td>Exhaustive aerobic exercise</td>
</tr>
<tr>
<td>miR-222</td>
<td>Sustained aerobic exercise</td>
</tr>
</tbody>
</table>

Table 2. Relevant miRNA molecules and the conditions to which they respond

Aerobic exercise is responsible for decreasing the expression of the miRNAs described above. This is understandable since miRNA molecules are involved in protein silencing and decreases in transcription. Therefore, this decrease in miRNA molecules results in an increase in the expression of the genes that they target. The main genes involved are those that regulate transcription and muscle metabolism, particularly oxidative phosphorylation, therefore leading to an increase in the expression of mitochondrial enzymes and lipid oxidation enzymes. The genes RUNX1, PAX3 and SOX9 are all affected by the miRNA molecules that respond to aerobic exercise. These three genes are hypothesized to play a role in muscular adaptations that occur as a result of endurance exercise, such as an increase in mitochondrial density and oxidative enzymes (Ntanasis-Stathopoulos et al. 2013). MEF2 increases the expression of miR-1, which inhibits the activity of HDAC4. Since HDAC4 usually inhibits MEF2 activity, suppressing this inhibition leads to an increased activity of MEF2. Interestingly, MEF2 also activates HDAC9, which leads to the inhibition of MEF2, indicating that MEF2 expression is highly regulated. More research still needs to be done to fully understand these mechanisms, but it is presumed
that their activity is dependent on the stages of muscle development and remodeling (Potthoff & Olson 2007).

Another way by which exercise can induce epigenetic changes is through the transcription of myosin heavy chain genes (MHCs) (Ntannasis-Stathopoulos et al. 2013). Myosin, the thick filament and actin, the thin filament, are the two proteins responsible for muscle contraction. Each myosin protein is composed of one or two heavy chains and several light chains. The heavy chains have three distinct regions that vary slightly depending on the myosin isoform. The first region is the head, which contains binding sites for actin and ATP and is responsible for actually generating the force. The second region is the neck region, which is associated with light chains and helps to regulate activity of the head. The third region is the tail, which carries out specific activities depending on what the isoform is (Lodish et al. 2000). Based on mouse studies, researchers found that periods of reduced muscular activity led to changes in chromatin structure. These changes include the acetylation and methylation of histone H3, which plays a role in the expression of I MHC, IIx MHC, and IIb MHC in the soleus muscle of the mouse. Additionally, HDAC5 has been implicated in increasing the amount of type I oxidative muscle fibers following bouts of exercise in mice (Ntannasis-Stathopoulos et al. 2013). Type I muscle fibers are also known as slow, oxidative fibers, and are used in periods of low intensity, long duration exercise. The soleus is an example of a muscle that is composed of mainly slow twitch fibers, which is understandable due to the fact that it is used for activities such as walking and standing, both of which are generally low in intensity but long in duration (Zierath et al. 2004). Similar results have been obtained in humans. Research has found that the percentage of type I muscle fibers as well as the VO2 max is positively correlated with the expression of acetyltransferase MYST4 (monocytic leukemia zinc finger protein-related-factor). MYST4 is a
HAT that is responsible for the regulation of a transcription factor known as Runt-domain transcription factor (RUNX2). RUNX2 plays a role in the differentiation of osteoblasts and the formation of bone (Ntannasis-Statopoulos et al. 2013).

As mentioned above, engaging in physical activity produces somewhat of a ripple effect. In addition to the changes seen in the musculoskeletal system, exercise leads to changes in the nervous and cardiovascular systems. While there is no definitive equation that determines the quantity of exercise that will lead to a particular increase in nervous function, a variety of studies have indicated a link between physical activity and improvements in cognitive function. Most of these changes are mediated through brain-derived neurotrophic factor (BDNF). BDNF is found mainly in the hippocampus and plays an important role in the development of neurons. BDNF is well known for its involvement in exercise-mediated brain plasticity, but it is also critical for neuronal excitability, learning, and memory. We will be focusing on promoter IV on the BDNF gene, since it is subject to epigenetic regulation. Under normal, resting conditions, methyl-CpG binding protein (MeCP2) is bound to a site on BDNF promoter IV, leading to the repression of BDNF transcription. However, following depolarization of the neuron, MeCP2 dissociates from the promoter. This leads to demethylation of promoter IV and as a result, an increase in transcription of the BDNF gene and subsequently the binding and activation of its tyrosine kinase receptor (TrkB). This activation at the pre- and post-synaptic sites then leads to the activation of a signaling cascade known as mitogen-activated protein kinase (MAPK) pathway. The MAPK signaling cascade is one of the most well characterized pathways and affects the body in a variety of ways, depending on the location and type of cell. In this case, the MAPK pathway responds to physical activity via a positive feedback loop that increases mRNA levels of BDNF and its corresponding receptor, TrkB. This has been successfully demonstrated in mouse
models, where exercise has increased hippocampal levels of BDNF. The hippocampus is an area in the brain that assists in both learning and memory formation. The proposed mechanism for this increase in BDNF in the hippocampus region involves two important components: the calcium/calmodulin-dependent protein kinase II (CaMKII) signaling pathway (Ntanasis-Stathopoulos et al. 2013). There are a variety of different calcium/calmodulin-dependent protein kinase pathways throughout the body, but this one in particular is associated with synaptic plasticity and spatial memory (Swulius and Waxham 2008).

In rats, a similar result was observed involving increased levels of BDNF as a result of physical activity, but the mechanisms were slightly different. It was also found that following periods of exercise, rats displayed reduced patterns of methylation in the CpG region of the BDNF promoter IV. Additionally, exercise led to an increase in acetylation of histone H3 coupled with a reduction in levels of HDAC5. Together, this resulted in an increased transcription of the BDNF gene and indicates that H3 is a key player in the epigenetic changes that occur after periods of physical activity. Another protein that is implicated in these exercise induced epigenetic changes is cAMP response element-binding protein (CREB). The plasticity of the nervous system is something that has been widely studied, and researchers believe that changes in gene expression are responsible for the long-term changes in the functionality of nerve cells. In order for this to be possible, there must be pathways that link the action potential to gene expression; this is where CREB is important. CREB, in its phosphorylated form, binds to cAMP response element (CRE), which is a sequence within the DNA, thereby affecting the transcription of downstream genes. It has been discovered that CREB is a substrate for two separate, but related pathways: Ca2+/calmodulin-dependent kinase II (CAMKII) and cAMP-dependent protein kinase (kinase A) (Dash et al. 1991). The CAMKII pathway is well
characterized by its ability to translate intracellular calcium signals to downstream targets (Swulius and Waxham 2008). In this case, the action potentials lead to an influx of calcium, which activate the CAMKII pathway and lead to the phosphorylation of CREB. As stated previously, CREB in its phosphorylated form can bind to CRE to induce changes in gene expression and regulation of synaptic plasticity (Dash et al. 1991). More importantly, exercise increases the levels of phosphorylated CREB via CAMKII. CREB, in its phosphorylated form, recruits CREB- binding protein (CBP), a transcriptional coactivator. As discussed earlier, transcriptional coactivators are responsible for activating transcription factors, in this case CREB. CBP molecules have strong histone acetyltransferase activity, leading to an increase in BDNF transcription.

Exercise is commonly discussed in terms of its ability to promote a healthy mental state. The basis of this statement has to do with the role that BDNF levels play in development of neurological disorders and brain syndromes. For example, Alzheimer’s disease, depression, manic episodes, bipolar disorder, REM sleep deprivation, and attention deficit hyperactivity disorder (ADHD) all result from a low level of BDNF. In ADHD specifically, using exercise as a treatment method has demonstrated positive results, mediated by chromatin remodeling that makes the BDNF gene more accessible and therefore increases its expression. The type of exercise (endurance vs. resistance) does not seem to affect these results. In a study involving rats, researchers found that another positive effect of increased levels of BDNF result in neurogenesis, which may be protective against neurodegenerative disorders, such as Alzheimer’s. Aside from changes that result from BDNF, exercise also alters the HAT/HDAC ratio in a way that increases HAT activity while decreasing HDAC activity in the hippocampus. This increase in the HAT/HDAC ratio has been associated with higher levels of transcriptional activity. This is
important in mice, where a decrease in histone acetylation has been associated with neurodegeneration. Exercise is implicated in this because it induces histone acetylation, thus restoring the HAT/HDAC balance and aiding in neuroprotection and proper memory function and therefore protecting against neurodegenerative diseases.

The cardiovascular system is also subject to adaptations as a result of physical activity. However, the relationship between exercise and epigenetics is still not well established. That being said, there is compelling data and evidence that indicates that a relationship may exist, it is just a matter of conducting more research to determine the exact nature of it. The first target of this epigenetic regulation involves pro-inflammatory cytokines (Ntanasis-Stathopoulos 2013).

Cytokines are small proteins that have an effect on the way cells communicate and interact with each other. Amongst other categories, cytokines can be subdivided into pro-inflammatory and anti-inflammatory groups. As the names suggest, pro-inflammatory cytokines perpetuate states of inflammation and are usually activated by macrophages. Anti-inflammatory cytokines help to decrease inflammation by controlling the pro-inflammatory response (Zhang & An 2007).

Exercise has been shown to affect the epigenetic regulation of genes that code for pro-inflammatory cytokines, an example being the ACS gene. Physical activity leads to an increase in methylation of these genes, and as a result a decrease in transcription. Additionally, exercise induced epigenetic changes can impair the binding of NFxB to DNA. Under normal circumstances, the binding of NFxB to DNA is crucial for the expression of pro-inflammatory cytokines. This binding is mediated by the actions of HAT and HDAC molecules, where HDACs reinforce the binding between NFxB and DNA and HAT impairs it. Transcriptional coactivators such as CBP and P-300-CBP associated factor (PCAF) have the ability to function as HATs
thereby impairing the binding between NFkB and DNA and decreasing the expression of pro-inflammatory cytokines.

As mentioned previously, the anti-inflammatory cytokines play an important role in ensuring that the pro-inflammatory cytokines are not causing unregulated damage in the cells. This balance between the two classes of cytokines is regulated by epigenetic mechanisms. However, for a variety of reasons, these mechanisms can become dysregulated and as a result, the balance can be thrown off. This can lead the development of cardiovascular diseases, including stenosis and atherosclerosis. Additionally, without the proper regulation of the HAT/HDAC ratio, the matrix metalloproteinases (MMPs) will not be expressed at their normal levels (Ntanasis-Stathopoulos 2013). MMPs are responsible for degradation of the extracellular matrix proteins during periods of growth and tissue turnover. Generally, they are expressed at low levels. However, in pathological conditions that lead to tissue deterioration, the expression of MMPs are much higher (Sorsa et al. 2004). In terms of the cardiovascular system, altered expression of the MMPs can cause pathological changes to the vessel walls, proliferation in endothelium myocytes, and even lethal cardiomyopathies. By engaging in physical activity, an individual can restore the HAT/HDAC ratio to its normal level, therefore working as a protective mechanism against cardiovascular damage.

Finally, miRNA molecules are implicated in the cardiovascular epigenetic changes seen with physical activity. This is accomplished through myocardium remodeling, a process that leads to the phenomenon “athlete's heart”. This condition is commonly seen among athletes and is characterized by cardiac hypertrophy and neo-angiogenesis. The mechanism through which this occurs isn’t completely understood, however it is known that it involves the addition of new sarcomeres. This increases the length of the cardiac cells and as a result increases stroke volume.
and cardiac output, two changes that allow for an improved aerobic capacity. Previous research has shown that aerobic exercise modifies the expression of various miRNA molecules. Specifically, it decreases the expression of miRNA-1, -133a, and -133b and increases the expression of miRNA-29a, -29b, -29c, -27a, and -27b. All of these miRNA molecules affect different signaling pathways, but the overall effect is the growth and differentiation of cardiac cells, an increase in compliance of the ventricles, anti-fibrosis, and in the long term, cardiac hypertrophy. It is important to note that these changes are protective and should not be confused with pathological remodeling that induces cardiac hypertrophy, a symptom that is present in many cardiac diseases. While these are also largely mediated by changes in miRNA expression, they involve different signaling molecules and pathways.

**Nutrition Related Epigenetic Modifications**

There is a well-known saying, “You are what you eat.” While this isn’t entirely true, the foods that individuals eat can have lasting effects on their genomes. These effects are mediated by the nutrients and bioactive food components that are able to interact with components of DNA to alter the expression of genes. On a basic level, we know that certain foods are healthy while others are not. However, by breaking these foods down into their components and studying how these components interact with genetic material, we are able to better understand exactly why certain foods produce the observed outcomes.

Of all the epigenetic modifications, changes in methylation patterns as a result of nutrition are the most well characterized. Folate, vitamin B-12, methionine, choline, and betaine have the ability to affect both DNA and histone methylation through changes in one-carbon
metabolism (Choi & Friso 2010). One-carbon metabolism is an important metabolic pathway for de novo pyrimidine and thymidylate synthesis as well as methylation reactions that involve the conversion of homocysteine to methionine (Stover 2009). Folate and vitamin B-12 are coenzymes in this metabolic pathway. The pathway begins when one carbon unit is taken from either serine or glycine and transferred to tetrahydrofolate (THF) to form methylene-THF. It is important to note that THF is derived from dietary folate. Using dihydrofolate reductase, the body can convert the folate we consume into tetrahydrofolate, a molecule that carries 1-carbon groups in many different biological reactions. At this point, methylene-THF can be used in three ways. It can be used to synthesize thymidine, the pyrimidine nucleoside, it can be oxidized to create formyl-THF, a molecule that is used to synthesize purines, or it can be reduced to form methyl-THF, which then can donate a methyl group to homocysteine to form methionine. The reaction to convert homocysteine to methionine is catalyzed by a methyltransferase which contains vitamin B-12 (Selhub 2002). Additionally, betaine and choline play an important role in the conversion of homocysteine to methionine. Choline can be obtained from the diet or synthesized de novo in the body and can be oxidized to yield betaine (Ueland 2011). Betaine can also donate a methyl group to homocysteine, using the enzyme betaine-homocysteine methyltransferase (Ueland et al. 2005). This occurs mainly in conditions of folate deficiency, by providing an alternate pathway to decrease homocysteine levels (Ueland 2011). Most of the methionine that is created is converted to S-adenosylmethionine (SAM or AdoMet). SAM is responsible for donating methyl groups to a variety of molecules including DNA, RNA, hormones, neurotransmitters, membrane lipids, and proteins (Selhub 2002). The other metabolite of one-carbon metabolism that affects the methylation of DNA and histones is S-adenosylhomocysteine (SAH or AdoHcy). As opposed to SAM which acts as a methyl donor for
methylation reactions, SAH inhibits the activity of methyltransferases. Therefore, any nutrient that can alter the levels of SAM or SAH have the ability to alter the methylation patterns in DNA and histones, and as a result contribute to epigenetic regulation of the genome.

As mentioned previously, DNA methylation adds a methyl group to a cytosine base at a CpG dinucleotide residue. DNMT enzymes are responsible for catalyzing these reactions. Folate has been the most extensively studied nutrient in terms of its effects on epigenetic regulation since it delivers the methyl group that converts homocysteine to methionine. However, research has indicated that there are other nutrients that affect DNA methylation, including methionine, choline, betaine, and vitamin B-12. Additionally, bioactive compounds in foods, including tea polyphenols and genistein from soy have been shown to alter DNA methylation status. One great example of epigenetic effects of the diet is in honeybees, who are either destined to be queens or workers depending on whether they consume royal jelly or beebread, two different types of honey. The variable consumption of jelly leads to differences in phenotypes of the bees, and this has been suggested to occur through epigenetic regulation. Most nutrition-related epigenetic studies have demonstrated the importance of how nutrition early in life, specifically during embryonic development, affects the epigenome.

An important factor of nutritional epigenetics is that it can be affected by maternal dietary intake during the gestational period. This has been indicated in numerous studies in both animal models and humans. One example is dietary protein restriction in maternal rats, which has been shown to lead to abnormalities in the phenotypes of the offspring. These abnormalities include hypertension, dyslipidemia, and impaired glucose metabolism and are a result of decreases in DNA methylation of the glucocorticoid receptor and PPARα in the liver cells of both child and adult offspring. In addition, it is well known that folate supplements are recommended during
pregnancy as a preventative measure against neural tube defects. It has been suggested that these neural tube defects arise as a result of abnormal reprogramming of DNA methylation (Choi & Friso 2010). A study by Steegers-Theunissen et al. looked at the effect of periconceptional folate intake on methylation patterns at the differentially methylated region (DMR) of the insulin-like growth factor 2 gene (IGF2). The study looked at 120 children at the age of 17 months, 86 of whom had mothers who took folate supplements during the periconceptional period and 34 of whom did not. The results of the study indicated that mothers who used folic acid supplements had a 4.5% higher methylation pattern of the IGF2 DMR (Steegers-Theunissen et al. 2009). The exact role of IGF2 puzzled scientists for years, and still much less is known about it than IGF1. Recent research has implicated IGF2 in maintaining proper endocrine and metabolic function, and is especially important during fetal development. Dysregulation of IGF2 has been observed in many diseases, including diabetes, obesity, polycystic ovary syndrome (PCOS), liver disease, and cancer (Livingstone & Borai 2014). Beckwith-Wiedemann syndrome, a disease characterized by overgrowth and possibly asymmetry during childhood has been linked to defects in proper IGF2 DMR methylation patterns. Additionally, complete loss of the IGF2 DMR has been associated with an increased risk in colorectal adenomas. Although the exact mechanisms are not completely understood, it is apparent that folic acid is crucial for maintaining proper DNA methylation, and dysregulation of these patterns can lead to harmful pathologies (Steegers-Theunissen et al. 2009).

The ability of IGF2 to be epigenetically regulated was also demonstrated in a study involving individuals who were prenatally exposed to famine during the Dutch Hunger Winter. This famine occurred in the Netherlands in 1944-1945 as a result of a food embargo that the Germans imposed. The study looked at whether periconceptional exposure to the famine had
epigenetic consequences later in life, as indicated by differences in methylation status of IGF2 DMR. The study occurred six decades after the Dutch Hunger Winter, and looked at 60 individuals, all of whom were conceived during the famine. In order to have some basis for comparison, these individuals were compared to same-sex siblings who were not conceived during the famine. Researchers looked at five CpG nucleotides in the IGF2 DMR to determine methylation status. Results indicated that periconceptional exposure to the famine resulted in four of the five CpG dinucleotides being substantially less methylated (5.2%) than those of the same-sex sibling (Heijmans et al. 2008). Researchers went even further to determine whether the timing of exposure affected the intensity of the epigenetic modifications. They found that exposure during the third trimester, when most of the fetal growth occurs, resulted in more pronounced growth-stunting effects than exposure during the second trimester (Wang et al 2012). This indicates the importance of early-life nutrition for proper DNA methylation as well as the perpetual nature of these epigenetic changes.

Another important study that demonstrates the importance of maternal diet on the fetal epigenome involves agouti mice. In these mice, their coat color is established by epigenetic regulation that occurs early in their development. The wild type agouti gene can produce two types of melanin pigments: black eumelanin or yellow phaeomelanin. The allele that determines the fur color is known as Agouti variable yellow (\(\text{Agouti}^{\text{va}}\)). This allele is known as a metastable epiallele, which means that it has variable expression as a result of epigenetic modifications that occur early in development. The metastable epiallele is a result of an intracisternal A particle (IAP), which is a transposon that inserted itself upstream of the transcription start site of the Agouti gene. The methylation status of the IAP can vary, and as a result the coat color of mice can range from yellow to brown, which is known as pseudoagouti. The degree to which the IAP
has been methylated correlates inversely with the expression of the *Agouti* gene, but ranges from a yellow coat color if unmethylated to a pseudoagouti color if completely methylated. More importantly, transcription of the *Agouti* gene is present in every cell, not just the hair follicles. This leads to the yellow (*Agouti*) mice presenting with adult-onset obesity, diabetes, and tumorigenesis, while the pseudoagouti mice do not (Dolinoy 2008). Experimentally, this result was determined through maternal dietary supplementation with genistein, the major isoflavone in soy, which has been previously shown to increase levels of DNA methylation (Day et al. 2002). In this experiment, supplementation with genistein resulted in an increase in DNA methylation at six CpG sites within the IAP of the *Agouti* gene. Based on tissue examination from three germ layers, results indicated that the DNA methylation occurs during the early stages of embryonic development, but persists into adulthood where it decreases the expression of the *Agouti* gene and protects the mice from obesity, diabetes, and tumorigenesis. Although this study was conducted in rodents, it may have important implications in human health. Researchers predict that this could explain the lower incidence of certain cancers in Asian populations, that consume more soy in their diets, compared to Westerners. Additionally, Asians who immigrate to the United States present with increased cancer incidence than those who do not immigrate. More research is needed to determine exactly how the *Agouti* mice studies relate to the human epigenome, and whether other methyl donors such as folic acid or other isoflavones have similar effects (Dolinoy 2008).
Epigenetic Regulation of Type 2 Diabetes

Type 2 diabetes (T2D) is a pathology that results, in most cases, from poor eating habits and a sedentary lifestyle. This disease is well characterized by insulin resistance and as a result, high levels of blood glucose. It is known that GLUT4, an insulin dependent glucose transporter, does not perform adequately in cases of type 2 diabetes. In addition, PGC1, which is largely important for proper mitochondrial function, is unable to keep up with the demands of the body. It is now becoming more evident that epigenetics is responsible for mediating some of these changes in the intracellular signaling pathways. Research suggests that individuals who suffer from type 2 diabetes have different epigenetic patterns on the promoter regions of GLUT4 and PGC1 than those who do not. It is known that exercise is helpful in increasing glucose uptake in type 2 individuals, but research is looking into whether these changes may have an epigenetic basis. More research still needs to be conducted to understand the precise mechanisms behind the mitochondrial dysfunction and insulin resistance in T2D, but there is compelling evidence that suggests epigenetics plays a large role.

Under normal physiological conditions, insulin is largely responsible for the uptake of glucose from the bloodstream into the tissues. In this case, we will focus specifically on the uptake into skeletal muscle, where insulin is responsible for ~80% of the glucose that enters. It is not insulin directly that brings the glucose into the skeletal muscle cell; instead it works through a signaling cascade which finally culminates in the translocation of the GLUT4 transporter to the plasma membrane. The major players involved are the insulin receptor (IR), to which insulin binds to, and the insulin substrate receptor (IRS), which is activated by the IR. Phosphorylation of IRS results in the activation of downstream effectors including phosphatidylinositol-3-kinase
(PI3K), protein kinase B (AKT), and atypical protein kinase C (aPKC). AS160 is the substrate of AKT and when it is phosphorylated, it releases GLUT4 vesicles towards the muscle membrane. When everything is functioning correctly, the release of insulin and the subsequent signaling cascade allows for glucose homeostasis to be maintained. However, in pathologies such as type 2 diabetes, there is a disruption in this cascade that results in insulin resistance and a resulting disruption in glucose homeostasis. The main problems arise from defects in the responses of IRS, PI3K, and aPKC. In addition to glucose intolerance, diabetic individuals will experience decreased rates of lipid oxidation due to mitochondrial dysfunction. This leads to increased intramuscular triglycerides, lipid metabolites, and oxidative stress. This will be further discussed in the following paragraphs.

As discussed earlier, one of the major contributing factors in developing T2D is a lack of physical activity. It is well known that even once a diagnosis for T2D has been made, an individual can still increase his sensitivity to insulin through exercise and muscle contraction. An added benefit of exercise is that it can increase glucose uptake into skeletal muscles through GLUT4 translocation, but through a pathway that is somewhat independent of the IR. The exact mechanism by which this phenomenon occurs remains unknown, but there are two main postulates. The first suggests that there is an increase in the AMP/ATP ratio as a result of exercise, which then activates AMPK. The second postulate proposes that depolarization of the sarcolemma leads to a signaling cascade in which Ca2+ activates Ca2+/ calmodulin-dependent protein kinase (CAMK). Both of these would result in the activation of AS160 and aPKC, leading to the translocation of GLUT4. This phenomenon is illustrated in Figure 4. As discussed previously, exercise results in epigenetic modifications associated with the expression of AMPK and CAMK, two proteins that play an integral role in GLUT4 mediated glucose uptake.
The mitochondria is the organelle that is responsible for providing the cell with energy in a usable form. One way it does this is through fatty acid oxidation. However, in cases of type 2 diabetes, the metabolites of fatty acid oxidation accumulate, contributing to insulin resistance. Peroxisome-proliferator-activated receptor alpha (PPARα) was discussed earlier in terms of its role in lipid metabolism and its ability to increase mitochondrial density in response to exercise. Additionally, PGC-1α, which is encoded by the PPARGC1A gene, plays a role in a variety of pathways that modulate mitochondrial metabolism. Research has shown that changes on the epigenetic level have been implicated in the insulin resistance and mitochondrial dysfunction seen in type II diabetes and other diseased states (Dos Santos et al. 2015). A study done by Barres et al. found that the skeletal muscle of type II diabetic patients showed hypermethylation on the PPARGC1A gene, leading to a decrease in the expression of PGC-1α mRNA as well as mitochondrial DNA (mtDNA). Without proper expression of PGC-1α, fatty acid oxidation is
impaired. Decreased PGC-1α expression coupled with a lower mitochondrial density can explain the mitochondrial dysfunction that is seen in type II diabetic patients. Furthermore, the promoter region for PGC-1α was also hypermethylated in patients who suffered from impaired glucose tolerance (IGT), but were not classified as type II diabetic. This could mean that these epigenetic modifications occur early in the development of disease (Barres et al. 2009).

Nutritional factors are also implicated in the onset of type II diabetes. In particular, hyperlipidemia has been shown to contribute to insulin resistance. A study by Dobbins et. al used rat models to determine how intramyocellular lipid (IMCL) concentration affects insulin-mediated glucose disposal. Researchers fed normal rats either a low-fat or high-fat diet for four, consecutive weeks. Additionally, they fed two other groups of rats a diet that contained R-etomoxir, which is a of carnitine palmitoyltransferase-1 inhibitor. Inhibiting carnitine-palmitoyltransferase-1 prevented the rats from transporting fatty acids into the mitochondria to be oxidized for energy, simulating physiological conditions by which fatty-acid oxidation is impaired. The study showed that the high fat diet and the R-etomoxir treatment impaired insulin sensitivity and resulting insulin-mediated glucose disposal (IMGD) in the rats. Researchers established an inverse relationship between IMGD and IMCL, meaning that low levels of IMGD correlated with high levels of IMCL. These high levels of IMCL can be achieved through inhibition of fatty-acid oxidation or through a diet that is rich in saturated fats. Using this information, they were able to conclude that elevations in skeletal lipid muscle stores, which are commonly increased in patients with type II diabetes, impairs IMGD and therefore largely contributes to the well-characterized insulin resistance (Dobbins et al. 2001). On an epigenetic level, this is explained by the interaction between fatty acids and PCG-1α promoter. This lipid overload results in an increased level of free fatty acids (FFA). Upon exposure to these FFAs, the
PCG-1α promoter becomes hypermethylated and therefore the expression of PCG-1α RNA is decreased.

Hyperglycemia provides another mechanism that links nutritional intake to epigenetic regulation. Frequently, the development of type II diabetes results from the consumption of foods with a high-glycemic index, leading to spikes of hyperglycemia. Research has shown that even transient hyperglycemia can lead to lasting changes, which are mediated by epigenetic mechanisms. These changes were seen in the promoter region of nuclear factor kB (NF-kB) p65 subunit in aortic endothelial cells, resulting in increases in p65 gene expression, monocyte chemoattractant protein 1 and vascular cell adhesion molecule 1 expression. Furthermore, these changes continued to persist for up to six days after the hyperglycemic episode, despite having normal blood glucose levels (El-Osta et al. 2008). The NF-kB pathway has been well studied in its role in promoting the expression of proinflammatory genes, including cytokines, chemokines, and adhesion molecules (Lawrence 2009). The results of the study indicate that short-duration bouts of hyperglycemia can have lasting effects on vascular cells and may contribute to many of the diabetic complications (El-Osta et al. 2008).

Community Involvement

As a way to involve the community in the results of my research, I created a nutrition program to teach to 4th grade students at Blenman Elementary School. In order to tailor this program to the age group I am teaching it to, I focused more on the basic nutrition concepts. Nutrition is not generally taught at the elementary school level, however I believe that implementing it into the curriculum could be incredibly beneficial in combating the growing
obesity epidemic and reducing the incidence of chronic diseases in pediatric populations. My hope is that my nutrition program will empower children to make healthier food choices. I am aware that in lower-income areas, accessibility to healthier food can be limited. However, I still believe that equipping the students with the knowledge to make better food-related choices is better than teaching them nothing at all.

This nutrition education program began with introducing students to MyPlate, which has replaced the food pyramid, which was previously used as the nutritional hierarchy. MyPlate shows the proportion of fruits, vegetables, protein, grains, and dairy that should be consumed in a meal. I recreated the figure on the whiteboard and had the students give examples of healthy options for each of these categories of foods. Using the information from the MyPlate website, I found the amounts required for fruits, vegetables, protein, grains, and dairy and gave them examples of what that would equate to in terms of actual foods. For example, boys and girls 9-13 years old need 1.5 cups of fruit per day, which is equal to about a medium-sized apple. Next, I explained to the students, in a basic sense, the roles of each of the macronutrients. I described to them that carbohydrates are our main source of energy, protein is important for a healthy immune system as well as proper growth and development, and that fats are important for storing energy as well as cushioning our organs. I talked about the certain vitamins and minerals that were relevant to each of the macronutrient categories and briefly explained their physiological role. Finally, I explained the importance of physical activity and engaged the students by asking them to share what they do for exercise. I made the nutrition education program as interactive as possible in order to engage the students. They were all very excited to share their favorite healthy foods and seemed very interested in the information I shared with them about vitamins, minerals, and physiological functions.
**Conclusion**

Epigenetic regulation is a growing field that is implicated in a variety of important physiological pathways. The three main mechanisms in which epigenetic modifications occur include DNA methylation, histone modification, and non-coding RNA activity. These mechanisms have been extensively studied and their effects have been demonstrated in many studies using both humans and animal models. There is an old and well-known debate, known as nature vs. nurture, which attempts to determine whether an individual’s development is predisposed by his or her DNA, or whether life experiences largely impact how he or she grows and changes. The research in this field provides compelling evidence for the ways in which nature asserts its influence over one’s predisposed genetic code, and therefore provides a link between an individual’s DNA and environmental conditions. While this has implications in many fields, I think it is especially important in the context of health.

In an era where chronic diseases, such as type II diabetes, metabolic syndrome, and hypertension are being seen at unprecedented levels, the role of proper nutrition and physical activity have become increasingly important. While it is possible that many individuals’ conditions are a result of apathy, I believe that there are others who are subject to a lack of education. In most cases, we are taught that exercising and healthy eating are beneficial, but there is a disconnect between how these activities produce positive outcomes. Perhaps, if individuals could make the direct association between health and their genome, they would be more conscientious of their decisions.

The results of my research indicate that while there is still a great deal of information to be discovered, a definitive relationship exists between physical activity, nutrition, and epigenetic
regulation. In terms of exercise, many studies have demonstrated how certain transcriptional coactivators and transcription factors, such as PGC-1α and the PPARs, respectively, have the ability to be regulated on an epigenetic level, and in turn affect a variety of signaling pathways. At the moment, most of the research on nutritional epigenetics focuses on early-life and periconceptional diet, and how this affects offspring and future generations. Results have indicated a strong relationship between the metabolites in one-carbon metabolism, particularly folate, and DNA methylation patterns. Furthermore, these genomic influences have the ability to be passed from one generation to another, as indicated by the Dutch Famine Winter studies.

Type II diabetes is a pathology that results from a sedentary lifestyle and poor eating habits, and the defining symptom, insulin resistance, has been shown to be a result of epigenetic regulation. Researchers will continue to look into the field of epigenetics to gain further understanding into some of the more precise mechanisms of the biochemical pathways.

Additionally, some of these molecules that participate in epigenetic regulation will become targets for disease treatment and prevention, and could yield promising results once successfully targeted. This will require a great deal of specificity and understanding. For example targeting all DNMT enzymes would disrupt DNA methylation patterns in every cell, and would therefore alter the expression of genes everywhere. While there is still much more that needs to be studied, there is currently an abundance of well-established epigenetic research, which can provide us with the tools to make important and informed decisions about our health.

I believe that educating the youth about the importance of proper nutrition and exercise is incredibly important in raising a more health-conscious generation. If the children learn this information early in life, they are more likely to make it a habit. My main constraint in my nutritional education program was lack of time. I believe that a short program taught once a
A week that covered basic, yet important nutritional topics would be the most beneficial. In the future, I hope to expand my program to other schools and make it even more interactive. The children seemed to learn a lot and the teacher even claimed that she learned some new information, confirming my beliefs that there is not a large enough emphasis put on nutrition education. However, I do believe that as a nation we are transforming into a society that is more health-oriented and this type of education will become more prevalent in the future.
References


