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Sophie Kopyar  
*Duquesne University*

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# Epigenetics and Cancer: Mechanisms, Diagnostics, and Treatment

By Sophie Kopyar

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## Abstract

Epigenetics connects the divide between genotype and phenotype without completely altering the genome. Modifications to certain genes can affect cell functions and produce diseased phenotypes, such as cancer. In some forms of cancer, epigenetic changes cause the cell to irregularly reproduce, avoid immunological responses, and operate under unsuitable conditions. This review explores the epigenetic changes that can occur to produce an oxygen deficient, hypoxically functioning environment that increases cancer vitality. More specifically, this review will focus on epigenetic alterations to *HIF* and *p53* genes and briefly cover other genes that can be affected in cancerous cells. This review found there are multiple reoccurring epigenetic changes that contribute to the development of cancer, and these changes can be countered by further epigenetic manipulation. Overall, this review will explain how understanding the epigenetic changes within cells is extremely beneficial for early diagnosis and, more importantly, specific treatment of genetic diseases.

**Keywords:** epigenetics, cancer, *HIF*, cancer associated fibroblasts, epigenetic therapy

## Introduction

Epigenetics is an emerging field that specifically revolves around regulation of gene expression. These modifications enable a change in phenotype, how genes physically manifest themselves, by controlling what genes are expressed. Therefore, the DNA sequence is not permanently altered. Epigenetic control on the genome can be inherited or environmentally influenced. Additionally, they can have direct or downstream effects. Downstream effects occur when there is an alteration to the genome that is not immediately recognized, and products of a pathway may become abnormal. While there are many forms of epigenetic modifications, DNA methylation and histone modification are the two most notable epigenetic changes that occur.<sup>1</sup> In DNA methylation, a methyl group may attach to certain cytosine groups in the genome. Cytosine is one of four main nucleotides of which DNA is composed. When cytosine is present on the genome in repeating groups, they are referred to as CpG islands.<sup>1</sup> The binding of a methyl group to CpG islands is typically associated with silencing the genes.<sup>2</sup> Alternatively, histone modifications alter the genome by having certain groups bind to histones, the proteins in which DNA wrap themselves, which affects the rate of transcription.<sup>1</sup> These epigenetic changes can be harmless, such as playing a role in eye color expression, or they can be devastating and cause diseases, such as cancer.

Cancer is a genetic disease specifically caused by deleterious changes to a cell's DNA. Tumors with modifications to HIF and p53 genes occur in high frequency. Typically, the *HIF* (Table 1) gene is silenced, otherwise methylated, until it is needed. However, this

gene is over-expressed in many cancer cells, meaning it has a high rate of transcription and, therefore, a more prominent phenotype. This causes the cell to exploit the glycolytic cycle, effectively trapping the cell and making it essentially immortal as it continues to endlessly divide.<sup>3</sup> Another gene affected in a majority of cancer types is *p53*.<sup>4</sup> Epigenetic modifications to the *p53* (Table 1) gene have been found to be highly correlated to many forms of cancer because these cells are not self-destructing after becoming cancerous.<sup>4</sup> There are several other genes with different functions, including *PDGF*, *ND3*, *TGF- $\beta$ 1*, *PRMT5*, as defined in Table 1, that can influence the cancer environment. These examples show how cancer is caused through several genetic and epigenetic modifications.

Modifications within the cell's DNA can cause a cancerous cell to bypass the self-checking systems that regulate growth and reproduction and cause metastasis by feeding off normal cells and escaping immune responses. Metastasis is the most devastating form cancer can take because the cells have begun to invade nearby tissues by entering the bloodstream or partaking in angiogenesis, the formation of their own blood vessels. Being able to correlate the epigenetic markers of a changing cell can aid in the future diagnosis, treatment, and prevention of cancer. This review explores multiple ways epigenetic changes to the mentioned genes contribute to metastasis via exploitation of natural cellular mechanisms, such as glycolysis and apoptosis. However, a problem within the field of epigenetics in relation to disease is the high randomization of the processes that can cause cancer. This randomization makes it difficult to predict

when and what changes will occur, leading to increased interest in epigenetic mapping to diagnosis genetic diseases earlier. This review will explore some of the epigenetic changes to the cancer genome and emphasize the importance of epigenetic understanding for cancer treatment.

### **The Tumor Genome: An Anoxic Environment**

Several genetic modifications cause tumor growth and acceleration, particularly through metabolic shifts within a cell. Epigenetics is profoundly relevant in cancerous tumors because the tumor environment is so genetically distinct. A large part of the tumor environment is the fibroblasts associated with them. Tumor fibroblasts are connective tissue cells that enable the tumor to interact with other noncancerous cells. These tumor fibroblasts are genetically distinct from normally functioning fibroblasts, which allows for comparative research to be conducted in order to understand the modifications at play.<sup>5</sup>

#### **1. *Cancer Associated Fibroblasts***

A key feature of the tumor environment are the metabolites associated with it. Measuring lactate production has become intrinsically important in lab testing to recognize when a cell has become cancerous. An increase in production indicates a change within a cell's metabolism that should not be occurring under proper conditions.<sup>6</sup> When the cell does not proceed to aerobic respiration, it recycles cellular materials back into the glycolytic and pyruvate cycle to produce lactate.<sup>6</sup> Results from studies conducted on cancer associated fibroblasts (CAFs) show that CAFs have nearly double

the amount of lactate production at every timepoint.<sup>7</sup> The overproduction of lactate is caused by the overexpression of *TGFβ-1* and *PDGF* genes (Table 1) within CAFs trigger a metabolic switch. This switch revitalizes the glycolytic cycle regardless of oxygen conditions and allows tumor cells to feed off the byproducts of this cycle, creating cells that are allowed to thrive in adverse conditions. Overall, different epigenetic modifications cause the overaction of hypoxia response genes present in CAFs, which encourages the cell to continue operating anoxically and accelerates the proliferation of cancerous cells.<sup>3</sup>

## **2. Inside A Tumor**

While CAFs essentially line a tumor, there are genes *within* the tumor that are genetically modified as opposed to healthy cells. One gene directly within the tumor environment is the gene *p53* (Table 1).<sup>4</sup> Epigenetic modifications can have downstream effects to *p53* that can contribute to a hyperactive cell, especially when in combination with mutations to mitochondrial gene *ND3* (Table 1). Deletions and overexpression of *ND3* cause a rise in toxic oxygenic radicals, inhibit apoptosis, and contribute to the recycling of glycolysis.<sup>8</sup> Toxic oxygenic radicals are produced when oxygen is not reduced properly in the oxidative phosphorylation, the process in which ATP is produced. The inhibition of apoptosis means that the cell will not “self-destruct” if DNA has become irreparably damaged. This was supported by analyzing cells with overactive *ND3* genes and recognizing downstream effects: high ADP/ATP ratio, increases in glucose consumption, and increases in lactate production.<sup>8</sup> High ADP/ATP ratios and the

presence of oxygenic radicals indicate that metabolism is not proceeding past glycolysis and the pyruvate cycle. Epigenetic overexpression of *ND3* also leads to an inhibited *p53* apoptotic pathway. While certain studies conducted by Duffy et al didn't show a direct correlation to tumor formation, it indicated metabolic changes triggered by genetic changes, showcasing downstream and direct effects of epigenetic modifications.

## **Epigenetic Diagnosis and Therapies**

### **1. Genetic Markers**

Epigenetics understanding can be used to treat cancer in a multitude of ways. Several studies are utilizing the knowledge of epigenetic markers to diagnose when cells have become cancerous. Cheung et al has formatted a system which maps changes in chromatin through mass cytometry.<sup>9</sup> By mapping chromatin changes, researchers can more easily identify the specific genetic fluctuations that contribute most to cancer genesis.

### **2. HIF Therapy**

Other ways epigenetics are beneficial is through the treatment of cancer. Specific research is being conducted to study the effects of epigenetic therapies in the form of pharmaceuticals. One drug that has shown promise in epigenetic therapy towards cancer is acriflavine. This drug has been shown to directly bind to HIF genes in tumors, inhibiting the cell's capabilities of operating anoxically.<sup>10</sup> Furthermore, studies showed that treatment with acriflavine stunted tumor growth, and in some cases even shrank tumor size with minimal side effects.<sup>10</sup> Acriflavine's binding acts as an epigenetic modification

to inhibit HIF within cells and halt hypoxic operations. A different, indirect approach involves a family of fungal derived HIF1 inhibitors, Epidithiodiketopiperazines (ETPs). ETPs have shown to inhibit tumor growth via blocking *HIF1*'s activator binding complex and thus inhibiting its hypoxic response functions.<sup>11</sup> Findings support the viability of these drugs, as tumor volume was reduced to nearly half of the control group after the treatment of different ETPs. Another indirect approach to inhibiting *HIF* has been studied, as certain drugs have combated the downstream effects of *HIF* overexpression. One pharmaceutical compound that has shown potential is isoliquiritigenin, ISL, a naturally occurring dietary element. When administered in 25 mg/kg and 50 mg/kg doses, tumor volume was nearly half and a fourth of their original size compared to that of the control group.<sup>12</sup> Supplementally, the body weight of the control group and the experimental group hardly varied.<sup>12</sup> It's believed that ISL has both direct and downstream effects towards *HIF*, as *HIF* was degraded when in combination with other inhibitors but was stabilized regardless of ISL presence.<sup>12</sup> Overall, these studies show that understanding the epigenetic modifications within cancer cells is critical for developing hyperspecialized treatment. Additionally, this shows promise in inhibiting the gross effects of cancer mutations.

### **3. Restoration of p53**

Not all epigenetic therapies involve the inhibition of a gene. Instead, some drugs attempt to reverse epigenetic modifications to restore the genome to a more stable state. One such way this is being done is through the study of berberine, a naturally



occurring plant compound.<sup>13</sup> Berberine's ability to influence methylation and histone deacetylation in addition to having minimal cytotoxic effects is an incredible feat in finding a compound viable for pharmaceutical use.<sup>13</sup> Polymerase Chain Reaction (PCR), a process involving the amplification of a specific gene, enabled a visualization of berberine's restoration of *p53*: the berberine treated group had a significantly darker mark of *p53* as opposed to the control group.<sup>13</sup> Restoring *p53* enables cells to better self-regulate and destroy themselves should they become cancerous. This study furthermore supports a need for an understanding of epigenetic modifications, as their potential for legitimate cancer treatment becomes increasingly evident.

#### ***4. Other Therapies***

While studies on *HIF* and *p53* are prominent due to their high frequency of mutations within cancer cells, there are several other ways epigenetic therapies have helped to evolve cancer treatments. Firstly, researchers are attempting to treat cancer epigenetically by promoting anti-*PD-1* responses in cancer cells.<sup>14</sup> Healthy cells have ligands on their plasma membrane that are recognizable to immune cells and prevent an inflammatory response. *PD-1* is a protein on immune cells that helps them *not* attack healthy cells by binding to healthy cell ligands. Cancer cells utilize this mechanism by having *PD-1* binding-ligands and avoiding immunological attacks. Drugs that have targeted this mechanism by silencing *PD-1* hope to expose cancer cells and promote a better immune response.<sup>15</sup> A different approach suggests coupling chemotherapy with epigenetic modifications in order to preserve the overall health of patients. The

promotion of *PRMT5* and related genes enabled the repair of breaks within the DNA strand.<sup>16</sup> Chemotherapy compromises the strength of the DNA and coupling it with drugs that preserve this strength show much promise.

## **Conclusion**

Due to the nature of cancer, the study of epigenetics is of extreme value and holds much promise when trying to understand and treat the disease. There are several ways that epigenetics can cause cells to become oncogenic. Evidence that verifies the effects of these modifications are shown through a rise in hypoxic and acidic environments, due to the cells recycling of glycolysis and producing lactic acid. Coupled changes allow for tumors to become increasingly potent through evasion of the immune system through PD-1 binding. Understanding epigenetics is key in treatment of cancer. Observance of epigenetic markers allow for earlier and more effective treatment. Much research must still be done to determine what causes these changes and how they can be prevented. The randomization of epigenetics makes this a difficult task, but a deeper understanding of how such changes occur could allow for revolutionized treatment of genetic diseases.

**Table 1. Gene and Drug Abbreviations and their Relation to Cancer**

Abbreviation	Name	Definition	Relation to Cancer
<i>HIF</i> <sup>3</sup>	Hypoxia Induction Factor	Gene that encodes for the cell's response to hypoxic conditions by triggering glycolysis	Gene is overexpressed; hypomethylated
<i>p53</i> <sup>8</sup>	N/A	Gene that encodes multiple pathways for compromised cell destruction/apoptosis	Gene is silenced; hypermethylated
<i>PDGF</i> <sup>7</sup>	Platelet Derived Growth Factor	Aides in cellular growth	Aid in transitioning normal fibroblasts to cancerous ones
<i>ND5</i> <sup>8</sup>	NADH Ubiquinone Oxidoreductase Subunit 5	Mitochondrial gene that encodes a protein that is part of complex 1 of oxidative phosphorylation	Gene is overexpressed; creates excessive oxygen radicals and contributes to the recycling of glycolysis
<i>TGFβ-1</i> <sup>7</sup>	Transcription Growth Factor beta-1	Aides in cellular growth	Aids in transitioning normal

			fibroblasts to cancerous ones
PRMT <sub>5</sub> <sup>16</sup>	Protein Arginine Methyltransferase 5	Aides in regulating cellular processes via methylation of target genes required for cell division, differentiation, and growth.	Overexpressed in many cancers
PD-1 <sup>15</sup>	Programmed Cell Death Inhibitor	Aides in the immunological response by ensuring that t-cells don't attack healthy cells	Helps cancer cells avoid immunological response by binding to special receptors on tumor cells <sup>15</sup>
ETP <sup>11</sup>	Epidithiodiketopiperazine	Fungal compounds such as chetomin, chaetocin, and gliotoxin	Inhibit HIFs by blocking their ability to bind with activators
ISL <sup>12</sup>	Isoliquiritigenin	A naturally occurring compound with various preventative properties	Can bind directly to cancer-inducing genes or block cancerous pathways.

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