**The exploitation and use of epigenetic factors in cancer therapy.**

Author: Jacob Ivy

Major: Biology pre-med
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

**Epigenetics play key roles in regulating gene expression and the formation of cancer. This has led to the formation of several epigenetic drugs that have target specificity. These drugs are constantly being tested and modified to increase their efficiency and delivery. New advancements such as the detection of recently discovered biomarkers and use of nanoparticles bring newfound advantages and insights in drug efficacy. Over the course of this work we’ll dive into epigenetics and how it can be used both diagnostically and therapeutically in the ongoing war against cancer.**

**Key Words:**

Epigenetics, Biomarkers, Nanoparticles, Methylation,

**Introduction**

Epigenetics play a crucial role in the regulation and expression of the genome. This is due to the covalent modifications that affect the accessibility of DNA to proteins that initiate transcription. Therefore, epigenetics can regulate transcription of a gene without the alteration of the nucleotide sequence of the DNA. This can be done through primarily three mechanisms DNA methylation, noncoding RNAs (ncRNAs), and histone modifications.

DNA methylation is an important regulatory element throughout life and has been associated with key procedures such as chromosome stability, genomic imprinting, tissue specific gene expression, and cancer development (Roberti et al., 2019). This is done by the addition of methyl (CH3) groups to CPG islands (Cytosine and Guanine rich) in the promoter region, which is known to cause gene silencing in regards to transcription.

Another important epigenetic regulatory mechanism is ncRNAs. ncRNAs are non-translational RNAs that do not become a protein, but still retain function in regulating gene expression on both transcriptional and post-transcriptual level (Roberti et al. 2019). These ncRNAs are divided into two groups based on the length of the nucleotides. The short non coding group is usually around 20 base pairs and contains microRNA (miRNa) and small interference RNA (siRNA) that regulate many processes throughout the central dogma. On the other hand, the long non coding group contains approximately 200 nucleotides. This group is also responsible for the regulation of many cellular processes such as DNA damage response and repair, MRNA stability, splicing, and a variety of responses.

Additionally, histone post translational modification has shown that epigenetic modifications can influence histone structure and function which affects the chromosomal function. This is done by the addition or removal of a functional group from the histone. Histones can have up to over 200 modifications such as methylation, acetylation, ribosylation, phosphorylation, and a plethora of others (Roberti et al. 2019). These modifications affect the accessibility of chromatin which leads to a change in the expression of the genome. For example, methylation in the H3K4me3 position leads to an activation of the chromatin (euchromatin) or repression of the chromatin (heterochromatin) when methylated in the H3K9me3 position (Villanueva et al. 2020).

These elaborate epigenetic mechanisms mentioned above have a complex relationship with the initiation of cancer. For instance, throughout tumorigenesis the epigenome undergoes many alterations, which include selective hypermethylation of specific CpG islands in tumor suppressor genes, overall loss of DNA methylation in the genome, dysregulation of ncRNA networks, and alterations in histone modifications (Roberti et al. 2019). Because of this phenomenon, oncologists have heavily researched the use and exploitation of epigenetic factors in fighting the progression of cancer along with diagnosing it.

**Recent Progress**

Because of the advancements in understanding of the human epigenome, oncologists have been searching for a way to incorporate this information into new cancer pharmaceuticals. This is of the utmost importance because of the heterogeneity of tumors, which can influence the tumors receptiveness towards the cancer treatments. Variance in tumors can help explain the lack of efficacy in some forms of cancer treatment that have been previously successful in other patients with the same form of cancer. Because of this, oncologists are in the process of developing site specific acting cancer drugs that can target epigenetics factors in the tumor. Site specific acting cancer pharmaceuticals are localized to a specific site in the epigenome instead of impacting the whole body like what is observed in chemotherapy and radiation treatment. For example, radiation and chemotherapy are known to attack the cancer cells, but also targets healthy cells which impels non-target tissue toxicity (Roberti et al. 2019). These epigenetic targeting precision medicines have massive potential as future treatments for cancer, but none have been approved for medical use. The reason that the pharmaceuticals have not been in use is because variations in the epigenome can have issues in direction of causality. For instance, not all changes to the epigenome are completely functional, they may be caused by external factors (Roberti et al. 2019).

 Epigenetic factors can also help in the diagnosis of cancer by the detection of specific associated biomarkers. Biomarkers are a substance that is detected in an organism which indicates some form of disease or ailment. The primary focus around biomarkers, in regards to epigenetics, is based on methylation of the DNA because comparably histones are fairly unstable. For instance, the best-characterized epigenetic biomarker is the hypermethylation of GSTP1 (glutathione S-transferase) gene that is located in the fluids of patients with prostate cancer (Roberti et al. 2019). Because of this observable hypermethylation, oncologists can successfully distinguish between the benign tissue and the malignant primary cancer with high efficacy. Epigenetic biomarkers can also be used to prognosticate the tumors responsiveness towards certain cancer therapies. For example, hypermethylation of the BRCA1 gene is correlated with higher sensitivity to platinum-based chemotherapy in breast and ovarian cancer (Roberti et al. 2019). This is of paramount importance because it can determine the efficacy of a treatment before starting said treatment, which could save many lives by ensuring each patient’s treatment would be responsive.

Another recent advancement in regards to epigenetics is the development of nanoparticles for the interaction and transmission to the epigenome. Nanoparticles are tiny particles varying from 1-100nm in size, and are designed to transport a strong concentration of the drug to its specific target with minimal damage to surrounding healthy tissue. The way nanoparticles are able to facilitate these complex interactions is through the enhanced permeability and retention effect (EPR). EPR refers to the accumulation of nanoparticles into tumors because sustained angiogenesis allows nanoparticles to enter the interstitial space, and the loss of lymphatic drainage is the cause for retention (Roberti et al. 2019). Although, EPR is known to variate between different forms of tumors, and variations within the same tumor over time. Because of this, treatment with nanoparticles are not universal and may require a specific type or size of tumor to be effective. These nanoparticles may be the solution to the many complications involved with epigenetic pharmaceuticals. For example, the current epigenetic drugs lack locus specificity, which induces off-target effects, lack of inducing long-term response, and high drug toxicity (Roberti et al. 2019). Because of this target specificity is a very important topic and the use of nanoparticles can help with the ability to target the tumor and the bioavailability of the drug. Many of these drugs are currently in trial and showing promising results in combatting cancer through epigenetic means. For instance, combining DAC with arsenic trioxide leads to a synergistic affect when treating Myelodysplatic syndrome by packaging the drugs into alendronate-conjugated bone-targeting nanoparticles that release the drugs near the target site (Roberti et al. 2019). While most of these epigenetic treatments are still in development or clinical trials, the impact these treatments will have in 5-10 years may be revolutionary in the ongoing battle against cancer.

**Discussion**

Epigenetic cancer treatments are a very viable option to combat many different forms of cancer. These treatments may even phase out some of the current treatments if the progress continues. The primary reason for epigenetic treatments possibly replacing the current treatments is that the current treatments are not specific and cause a fair amount of collateral damage to healthy cells. Contrasting this, epigenetic treatments are very site specific and attempt to minimize exposure to healthy cells. Although, these treatments are not without flaws because they can lack locus specificity for particular genes. But when the treatments are combined with the use of biomarkers and nanoparticles they can mitigate the lack of specificity. These new measures are designed to help with the target delivery system which would allow direct attacks at the epigenome. However, the nanoparticles still have some drawbacks like lack of sustainability and bioavailability. The disadvantages of these nanoparticles are far outshined by their potential for improving epigenetic pharmaceuticals efficacy. Overall, epigenetic factors play a huge role in the development and progression of cancer if properly utilized they may be a wide spread treatment option after more research and trials.

**References**

Roberti, A., Valdes, A. F., Torrecillas, R., Fraga, M. F., & Fernandez, A. F. (2019). Epigenetics in cancer therapy and nanomedicine. Clinical epigenetics, 11(1), 1-18.

Villanueva, L., Álvarez-Errico, D., & Esteller, M. (2020). The contribution of epigenetics to cancer immunotherapy. Trends in immunology, 41(8), 676-691.