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Epigenetic Studies of Breast Cancer

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Abstract: ***Cancer is a life-threatening disease with no concrete cure as of now. A type of cancer called Breast cancer is prevailing and killing many individuals. There are mainly 2 types of breast cancer in the form of BRCA1 and BRCA2. Various methods are being employed for treating this particular cancer but there are not many treatments available which use epigenetics. Epigenetically changing the gene expression can act as a biomarker in treating breast cancer without harming the DNA. Various epigenetic methods such as DNA methylation, Micro-RNA are used which modify the histone protein and act as a novel cure for breast cancer genes. In this article, we have discussed some ongoing methods as well as some experiments by other scientists and also some futuristic epigenetic ideas to treat breast cancer.***

Keywords: Breast cancer, Epigenetics, DNA methylation, Micro-RNA.

1. Introduction

Epigenetics

Our body consists of DNA and this consists of genes. These genes are responsible for regulating cells and also proper functioning of our body. Any adverse changes such as mutation in these genes can lead to tumors which in turn gives rise to cancer.

Epigenetics is the field which reads our genes without changing the DNA sequence. Epigenetic factors give the marching orders to the genes to function or not. It controls the activation and inactivation of genes which is important to our body.

It is directly related to cancer because if certain cancer genes are inactivated by epigenetic factors, then our body won't produce cancerous genes and if the same cancer genes are activated by epigenetic factors, then our cells become cancerous.Many types of epigenetic processes have been found like methylation, acetylation, phosphorylation, biotinylation, and sumolyation.

One important part which epigenetic process does is with chromatin present in each cell. The chromatin is highly coiled and consists of positively charged histones with DNA wrapped in it which contains the genetic information of our body. Epigenetic studies regulate the coiling of the chromatin fibres (Bob Weinhold, 2006). In general, tightly coiled chromatin tends to silence gene while non coiled or open chromatin tend to express various genes. These silencing and expression of genes are regulated by epigenetic factors such as DNA methylation etc.

Breast cancer

One of the deadliest cancers present in humans which can affect both men and women although the latter one gets it more often. It is estimated that around 1.9 mill people will get breast cancer in 2022 in U.S alone (Cancer Facts and Figures, 2022).

It is characterized by genes BRCA1 (Breast cancer gene 1) and BRCA2 (Breast cancer gene 2) genes located in cells near the breast. These cancers can metastasize to other parts of the body as well.

Every person has a pair of these genes, one from maternal and other from paternal side. These are actually tumor suppressor genes but if disrupted or mutated by carcinogens can lead to breast cancer but these genes can cause other cancers too like ovarian, fallopian tube cancer etc (National Cancer Institute, 2020).

BRCA 1:

This gene is composed of 22 exons, including a nuclear protein of around 1863 amino acids and is comprised of a zinc binding RING domain at the amino terminus region, and an acidic carboxyl terminus (Inês Godet and Daniele M.Gilkes, 2017). Women with BRCA1 mutations have an increased chance of developing ovarian cancer, while men have a higher risk of developing prostate cancer (Inês Godet and Daniele M. Gilkes, 2017).

BRCA 2:

The BRCA2 gene is larger than BRCA1, and it has a 10.3 kb open reading frame with a 384 kDa nuclear protein (Inês Godet and Daniele M. Gilkes, 2017). Carriers of BRCA2 mutations have a higher risk of gall bladder, bile duct, stomach cancer and melanoma apart from breast cancer (Inês Godet and Daniele M. Gilkes, 2017).

Histones:

These are proteins which play a major role in epigenetic studies of cancer. Four types are found i.e., H2A, H2B, H3 and H4. Combination of octamers of 2 types form nucleosomes. Either two tetramers of H3 and H4 form octamer or dimers of two H2A/H2B histones (Shahid Z et al, 2021). Modifications such as methylation, acetylation etc disrupt the histones to activate or suppress cancer.

Epigenetic remedy for Breast Cancer:

Many epigenetic factors like DNA Methylation, Acetylation, Micro RNA are known to have effects on cancer genes or rather on interaction histones with DNA which have been a vital help in treating breast cancer.

1) DNA Methylation:

It is nothing but the methylation (addition of CH3 molecule) on a base pair of DNA, more prominently on cytosine.

Hypermethylation of CpG islands are quite common in cancer cells. It is known to have a major role in regulation of genes that promote cancer.DNA methylation is initiated by the action of enzymes called DNA methyltransferases (DNMTs) (Maryam B. Lustberg and Bhuvaneswari Ramaswamy, 2011). There are three types of DNA methyltransferases: DNMT1, DNMT3a, and DNMT3b.

Methylation of arginine occurs on H2AR3 me2 and H3R17 me1 genes of histone which make the cancer genes active while methylation of lysine amino acid occurred on H1K186 me1 gene causes gene suppression. This can help serve as a biomarker for breast cancer.

2) Acetylation

It is the addition of acetyl group to the histone protein. Acetyl being a negatively charged group interacts with the positively charged lysine of histone and this makes the overall charge neutral. This results in uncoiling of histones and DNA and makes the genes activated.

Acetylation is usually done by HATs (Histone acetyl transferases) and HDACs (Histone deacetyltransferases) (Palak Gujral et al, 2020). Example: Lysine acetylation of H1K25ac gene results in gene activation which causes cancer.

Micro RNA

These are small non-coding RNAs that play a major role in cancer associated processes such as cell cycle, proliferation etc. They regulate post translational gene expressions by interacting with the 3' UTR (Untranslated regions) of primary transcript. These are converted into large precursor RNAs called pri-miRNAs by RNA Polymerase II. This pri-miRNAs are subjected to capping and polyadenylation to form pre-miRNAs by enzyme Drosha. Exportin 5 transports these miRNAs to nucleus and are processed using an RNA Polymerase III enzyme called Dicer. This form double stranded RNA's. RISC (RNA Inducing Silencing Complex) are formed with the help of AGO proteins which in turn can cleave or degrade transcripts as guided by Mi-RNA (Yong Peng and Carlo M Croce, 2016).

Micro-RNA can act as oncogenes or tumor suppressor genes. As it binds to the m-RNA, it can induce the m-RNA to either translate into protein or get destroyed. The translated protein can either overly express the cancer gene or silence it which makes it an important biomarker in breast cancer therapy as these can in turn change the phenotype of cancer.

Recent experiment on breast cancer metastasis by epigenetic method:

(Bingqiu Xiu et al, 2019) from Fudan University identified and experimented on lncRNAs (long non-coding RNAs) which are known to promote cancer progression. Highly expressed lncRNAs were identified by micro array method and invasion assay to confirm the phenotype of LINC02273. Using mammary fat model and sample tissues from breast cancer patients as study, RIP assay was used to identify the interaction between hnRNPL and LINC02273.Various other tests revealed that hnRNPL and LINC02273 regulated AGR2 protein.

They found that long non coding RNA LINC02273 were expressed highly in metastatic breast tumor. A protein called hnRNPL stabilized this non coding RNA but mechanically a complex formed by hnRNPL-LINC02273 epigenetically activated the AGR2 transcription which promoted cancer metastasis.

This concluded that a relation between lncRNAs-hnRNPL and its epigenetic effect on AGR2 can act a novel biomarker in breast cancer metastasis.

Another experiment was done by (Han-TsangWu et al, 2021) on TNBC (Triple negative breast cancer), a type of breast cancer and used a natural flavonoid called Luteolin to see the effects on cancer cells. They prepared TNBC cells in vivo and viability was checked by cytotoxicity test. Cell was proliferated and stained using Bromodeoxyuridine (BrdU). The cells were incubated with Luteolin in a chamber and kept overnight. Gene expression analysis was done by RT-qPCR.

They found that Luteolin resisted the growth and spreading of androgen receptive-positive TNBC. It also reversed the epithelial-mesenchymal transition (EMT). Luteolin decreased the levels of AKT/mTOR promoting H3K27Ac and H3K56A genes on the MMP9 promoter region.

They concluded that Luteolin can inhibit TNBC cells by epigenetic regulation of MMP9 pathway.

2. Conclusion and Discussion

Cancer is a deadly disease that is having a toll on lives. A type of cancer called Breast cancer causes cells near the breast to grow uncontrollably and become invasive in serious cases. Many treatments are being done and researched but, in my article, I talked about a less known novel cure called epigenetics which changes the gene expression without altering the DNA sequence. Various studies have been conducted and have proved that epigenetically we can change the expression of genes to either silence or activate them which have a direct role in breast cancer. Epigenetic methods like DNA methylation, Acetylation, micro-RNA are widely studied and are known to produce great results in avoiding the metastasis of breast cancer cells and also diminish them.

But other methods like Sumoylation (SUMO protein), Biotinylation (Biotin), Ribosylation (ADP ribose) are less studied and researched.

Can we somehow experiment and research on them to see if they have strong relation with gene silencing and activation and in turn have effect on breast cancer?

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References

[1] Weinhold, Bob. (2006), Epigenetics: The Science of Change, Environmental Health Perspectives Vol (114) 3, A 163.
[2] Cancer Facts and Figures. (2022). A Cancer Journal for Clinicians. Retrieved from https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html.
[3] BRCA Gene Mutations: Cancer Risk and Genetic Testing (2020), National Cancer Institute. Retrieved from, https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet.
[4] Godet, Inês., Gilkes, Daniele M. (2017), BRCA1 and BRCA2 mutations and treatment strategies for breast cancer, Integrative cancer science and therapeutics 4(1), 2 and 3.
[5] Z, Shahid et al., (2021), Histone Modifications and Cancer, Cold Spring Harbor Perspectives in Biology, 3.
[6] Lustberg, Maryam B., Ramaswamy, Bhuvaneswari. (2011), Epigenetic Therapy in Breast Cancer, Curr Breast Rep 3(1), 34.
[7] Gujral et al., (2020), Histone acetylation and the role of histone deacetylases in normal cyclic endometrium, Reprod Biol Endocrinol **(**84)18, 3.
[8] Peng, Yong., Croce, Carlo M. (2016), The role of micro-RNA in Cancer, Signal Transduct Target Ther. Retrieved from 10.1038/sigtrans.2015.4.
[9] Xiu, B., Chi, Y., Liu, L. et al., (2019) LINC02273 drives breast cancer metastasis by epigenetically increasing AGR2 transcription. Mol Cancer **(**187)18.
[10] Wu HT, Lin J, Liu YE, Chen HF, Hsu KW, Lin SH, Peng KY, Lin KJ, Hsieh CC, Chen DR. (2021) Luteolin suppresses androgen receptor-positive triple-negative breast cancer cell proliferation and metastasis by epigenetic regulation of MMP9 expression via the AKT/mTOR signalling pathway. Phytomedicine. Retrieved from 10.1016/j.phymed.2020.153437.