How does dysregulated histone acetylation contribute to cancer, and how can this be leveraged for cancer treatment?

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Abstract

Histone Deacetylases or HDACs play a significant part in the advancement of cancer. HDACs control the epigenome through acetylation. The epigenome is responsible for changes in gene expression outside of the nucleotide sequence of DNA. HDACs play a considerable part in the epigenome because they are specific proteins with the ability to deacetylate histones. The reason why HDACs are so important is because when specific HDACs are overexpressed they have the ability to suppress particular cancer suppressing genes. As a result, HDAC overexpression can promote cancer formation. However in recent years there has been research into HDAC inhibitors which impact the function of HDACs and restore the normal function of cancer preventing genes. Some HDAC inhibitors are specifically used towards certain HDACs while others have an impact on a wide range of HDACs. HDAC inhibitors could prove to be helpful to the advancement of cancer treatment due to their potential in more targeted treatment and their potential in combination treatments as well.

Introduction

As of 2024, breast cancer is the second leading cause of death in all women and the leading cause of death for women in less developed countries (Rifai 2018). Therefore, there has been an urgent need to find appropriate treatments for those inflicted by this disease.

Cancer is the result of uncontrolled cell division, usually due to mutations in the DNA coding for regulatory genes regarding cell division and cell death. Additionally, when cells silence or mutate genes that code for anchorage dependent proliferation, this allows for metastasis, meaning that the tumors can now travel to other parts of the body.

There are four different subtypes of breast cancer, including Luminal A, Luminal B, HER2, and TNBC (Triple Negative Breast Cancer)[Shown in Figure 1]. However among these subtypes the most aggressive is TNBC. These subtypes are characterized by what receptors they lack. For example in Luminal A, the HER2 (Human Epidermal Growth Receptor 2) receptor is normally missing while in some cases Luminal B will be lacking progesterone receptors. In the case of TNBC, and the reason it is the most aggressive, is because it lacks estrogen receptors, progesterone receptors, and additionally does not contain enough HER2 hence the name “triple negative”. Since these cells lack their normal growth factor receptors, they are able to grow out of control and cannot respond to normal cues to tell them to stop proliferating.

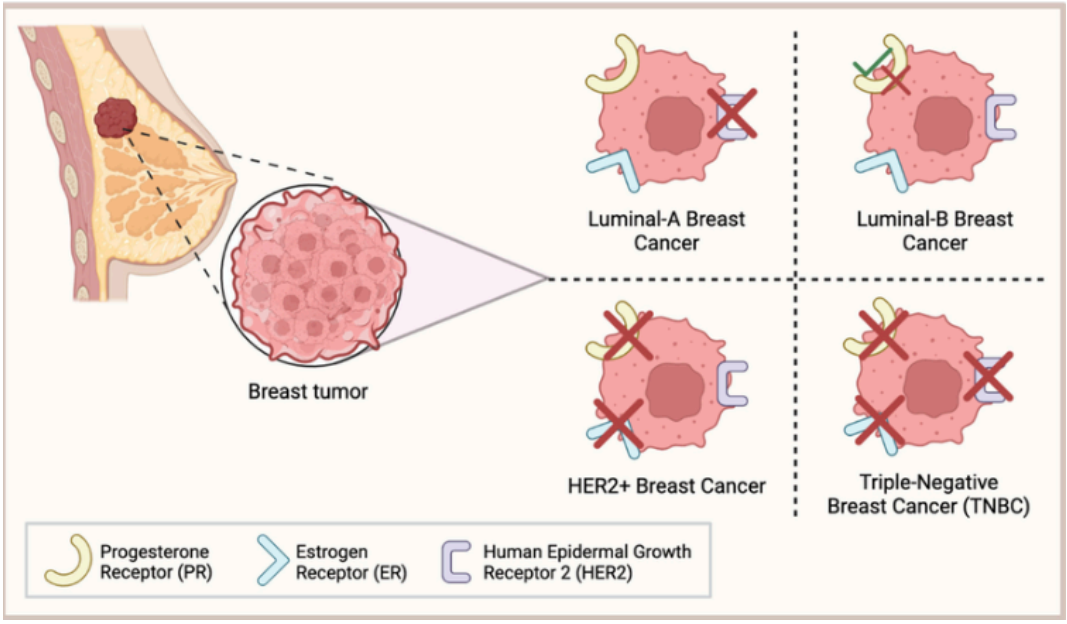

Figure 1: Overview of different breast cancer cell types
Adapted from: {The Potential of Hormonal Therapies for Treatment of Triple-Negative Breast Cancer} - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Classification-of-common-breast-cancers-Luminal-A-breast-cancer-lacks-expression-of_fig1_374161665 [accessed 7 Aug 2024]

DNA is a double stranded double helix composed of 2 main parts: the deoxyribose-phosphate backbone and the nucleotide base. The sequence of nucleotides code for specific proteins which allow the cell to function. DNA wraps around proteins called histones, forming nucleosomes. Many of these nucleosomes condense to form chromosomes.

Mutations are when errors are introduced in the DNA. Beyond this, there are other ways that cells can alter the function.expression of a protein, without changing the nucleotide sequence itself. One example of this is the epigenome, which regulates the amount of gene expression without changing the actual sequence of DNA. A key player in the epigenome is acetylation. Histones, the proteins that DNA wraps around in order to form a nucleosome, and have the ability to control the amount of expression of the genes encoded by the DNA wrapped around them. There are several types of histone proteins that can comprise the nucleosome, and these histones vary in that some of them have lysine-rich tails that protrude from the nucleosome. These lysines can be modified by the epigenetic machinery to add or remove different chemical moieties like acetylation or methylation. Acetylation impacts the expression of genes through the attachment and detachment of acetyl groups onto lysines found on histones. These acetylation marks are covalently linked to lysine residues contained within histone proteins like H3 and are attached and detached via groups of enzymes called HATs (histone acetyltransferases) and HDACs (histone deacetylases) respectively(Shahbazian 2007). It is thought that the absence of attachment of these acetylation marks enable the positively charged R group that lysines have an attraction to the also negatively changed DNA. The acetylation negates the attraction, making it so that when a histone is acetylated the overall structure of the DNA is more loosely wrapped around the histone (due to the loss of the attraction between the lysine and DNA). On the other hand, deacetylated histones result in DNA more tightly wrapped around the histone, due to the allowance of the attraction between lysine and DNA(Shahbazian 2007). This process relates to gene expression; when histones are acetylated there is more gene expression vice versa for deacetylated. A useful analogy is to consider trying to soak a ball of yarn. If there were theoretically 2 balls of yarn, one of which is less tightly wound and the

other more tightly wound, and both were dipped into a bucket of water, then the ball of yarn that is less tightly wound will be more soaked in comparison to the more tightly wound one. This is due to the fact that when the ball of yarn is less tightly wound, there is more surface area of the yarn in contact with the water. This can also be put into terms of gene expression; if the DNA is less tightly wound around the histone(acetylated), there is more surface area for the RNA polymerases to transcribe and therefore more gene expression, vice versa for deacetylated, as shown in Figure 2.

The epigenome has a significant effect on the expression of all genes, and in the case of cancer this control can prove fatal.

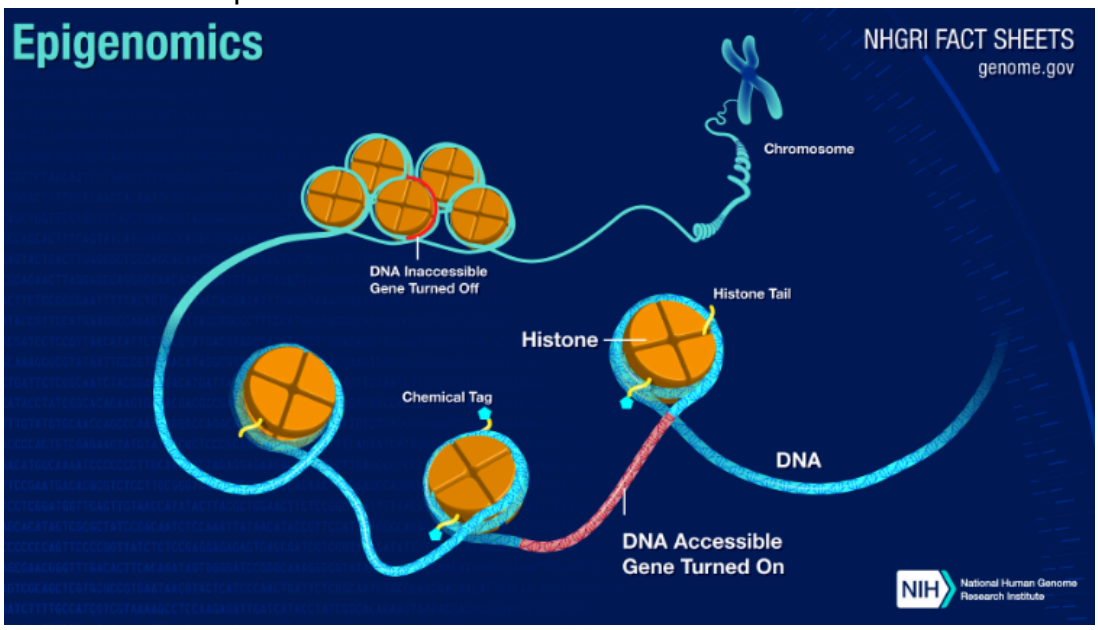

Figure 2: DNA is wound around histone to form nucleosomes
National Human Genome Research Institute, “Epigenome Fact Sheet”, accessed August 10th 2024, published August 16th, 2020

As a result,there has been a dive into enzymes like HDACs that are regulators of the epigenome. The specificity that comes with each HDAC is to be admired. Each HDAC has their own group of lysines that they regulate. For example in the case of Sirtuin 1, it primarily regulates lysines such as H3k9 and H4k16. Each HDAC is additionally assigned to their own class based on a variety of criteria such as structure and NAD+ dependence. There are 4 classes of HDACs. Class 1 includes HDACs 1, 2, 3,and 8; these HDACs have a structure similar to that found in a certain type of yeast called RPD3 (potassium dependency-3), and are expressed in most cell types(de Rujiter et al. 2003; Han 2024). Class 2 are HDACs 4, 5, 6, 7, 9, and 10, which have a structure similar to that of a certain deacetylase found in yeast called HDA1 (called histone deacetylases), and additionally are not expressed in all cell types(de Rujiter et al. 2003; Han 2024). Class 3 are the Sirtuins, which are the NAD+ dependent HDACs (while the other 3 classes are zinc dependent). The sirtuins also exhibit dual enzymic activities (ADP-ribosyltransferase and histone deacetylase). Finally, there is Class 4, which only includes HDAC 11 because it did not fit the criteria for Class 1, 2, or 3(Han 2024). The class 4 HDAC is generally localized to the nucleus and has high catalytic efficiency as a fatty acid acylase. It is generally expressed in the brain, heart, kidney, testis, and skeletal muscle (Liu et al. 2020; de Ruijter et al. 2003; Han et al. 2024). This paper will focus on 1 HDAC from each of these 4 classes, and an inhibitor for each of the 4 HDACs chosen. Specifically this paper will discuss:

HDAC1, HDAC6, SIRT1, and HDAC11. Each HDAC will have a discussed inhibitor: entinostat, BAS-6, nicotinamide, and Elevenostat respectively. Outside of the aforementioned HDAC inhibitors, this paper will also discuss pan HDACi, and chimeric compounds. Pan HDACi are essentially nonspecific inhibitors that can have an effect on basically any of the HDACs, while chimeric compounds can modulate more than 2+ targets.

Each of the HDACs have key roles in regulating many important cell processes such as cell death(apoptosis), cell differentiation, and more. Hence their importance towards the path to cure cancer.

Class 1 HDAC

There have been many studies investigating the function of HDAC 1, and in general overexpression of HDAC 1 has resulted in increased cell proliferation. This makes sense especially considering what genes it regulates. One of these genes is called *ER-α* (estrogen receptor alpha). This gene is a growth regulatory gene, and expression of this gene when HDAC1 is overexpressed is minimal. HDAC1 suppresses this growth regulatory gene through AF-2 (activation function domain 2) and DBD (DNA binding domain) of ER-*α* (Kawai et. al, 2003 and Garcia-Martinez et. al, 2021). Additionally HDAC1 regulates this gene via the inhibition of estrogen mediated transcription. The ligand of ER-*α* is 17 beta estradiol, and the ligand itself stimulates the growth of ER (estrogen receptor) positive tumors via functional ERs. However an endocrine therapy, such as anti-estrogens or ovarian ablation, has already been found to mitigate its effects.

There has been research into how to directly combat this ER-*α* suppression through the use of a certain HDAC inhibitor called trichostatin A (TSA) which has been proven to allow normal levels of ER-a mRNA to return. This has not been tested in human subjects yet, but has been tested in cell lines (Kawai 2003).

Beyond just TSA there are many HDAC inhibitors that are specific to class 1 HDACs, such as entinostat, which has been shown to convert ER negative tumors to ER positive tumors. This works well with another treatment called the letrozole treatment because it requires ER positive tumors in order to lower the levels of oestrogen in the body. Beyond this, entinostat has been shown to upregulate genes involving development of vasculogenic mimicry, which is a tumor blood supply system independent of angiogenesis. There have also been some associations in certain cell lines such as MDA-MB- 231 with compromised tumor initiation and impaired lung metastasis.

There has also been some research into deriving compounds from HDACis in order to create more effective treatment while allowing the inhibitors to actually survive in the body. Based on Entinostat and Tucidinostat, there are 2 different synthesized scaffolds(pyrimidine or purine core based), and these synthesized HDACi also have a inhibitor CAP group. There has been some research into substituting position 4 of the aniline in these synthesized HDACi, which gave potent antiproliferative effects(Maccallini 2022). It has also been proven that the presence of the amino group of position 2 at the purine core is important when observing the selectivity of action against HDAC1. This has proven effective in a triple negative breast cancer human cell line known as MDA-MB-231. Essentially how this works is that they work to combine several different combinations of CAP constructs, linkers, and zinc binding motifs [Shown in Figure 3]in order to find the most effective combination(Bocheng 2023). Class 1 HDACs are expressed in most cell types, and if these HDACs do not function properly then there are many serious consequences as shown in this paper. Hence, the need for HDAC inhibitors for this class, such as entinostat and TSA.

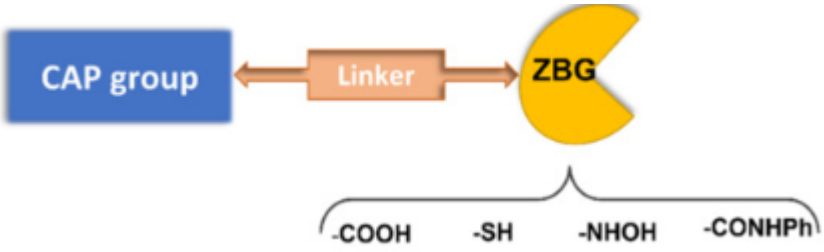

Figure 3. Cristina Maccallini, Alessandra Ammazzalorso, Barbara De Filippis, Maria Luigia Fantacuzzi, Letizia Giampietro, Rosa Amoroso "HDAC Inhibitors for the Therapy of Triple Negative Breast Cancer", 2022,

ZBG: zinc binding group

Linker; Linker

Cap group:Surface recognition motif

Class 2 HDAC

The next HDAC that will be discussed is HDAC6. This HDAC has been shown to limit HSF1(heat shock factor 1) activation in vitro. This is important because HSF1 acts as an activator for *CYLD*(cylindromatosis tumor suppressor gene) and *Hsp*(which are heat shock protein encoding genes). However this has not been proven to happen in vivo(Aldana-Masangkay 2011). Additionally, HDAC6 expression has proven essential for tumor growth and the maintenance of oncogenic phenotypes. It allows for metastasis by allowing anchorage independent proliferation, meaning that the cancer cells do not need to be attached to another cell in order to proliferate(Aldana-Masangkay 2011). Outside of epigenetics, HDAC6 can also detach ubiquitin from a damaged protein (meaning that the damaged protein will not be disabled, and run free in the cell). Ubiquitin has a way of recycling damaged protein by acting as a tag which essentially labels that protein as waste. The remains of the protein are then recycled to make new proteins. In the testis of a mouse model, it was shown the HDAC6 has a vaselin containing protein/protein 97 and phospholipase A2 activating protein/ubiquitin fusion protein 3(Aldana-Masangkay 2011). Together these proteins have the ability to de-ubiquitinylate a protein. Apoptotic resistant cells have also been linked to overexpression of HDAC6, and the inhibition of HDAC6 has led to apoptosis(Aldana-Masangkay 2011). Therefore, if there is too much HDAC6 it may be able to de-ubiquitinylate proteins that normally would be targeted for destruction. This can then disrupt normal cell behavior and promote cancer growth because the cell is not able to regulate the amount of "trash" it is producing properly. This is important because it can mean more targeted killing of cancerous cells through possibly tissue specific administration, which differs from the commonly used chemotherapy that targets all fast growing cells in the body.

HDAC6 also has an impact on a specific protein called Hsp90 which impacts the maturation of glucocorticoid, which is an anti-inflammatory and immunosuppressive, and therefore has the capability to somewhat disable the human immune and inflammatory response (Aldana-Masangkay 2011). On top of all of this HDAC6 can also form a complex with SGs (cytoplasmic stress granule) and G3BP1(SH3 domain-binding protein 1) in order to induce reversible translation. Essentially how this works is that G3BP1 allows SG and MT(motor protein) movement. The presence of SGs allows MTs and HDAC6 to directly bind due to the ubiquitin positive nature of SGs. However the disruptions of MTs were found to also disrupt SGs as well. The HDAC6 stress mediated response that ensues shows that HDAC6 has an impact

on RNA translation and metabolism. This is important because it helps transformed cells to survive environmental stress (Aldana-Masangkay 2011).

There have been several HDAC inhibitors that have shown specific potency against class 2 HDACs, one of which is BAS-6 which has the ability to kill apoptotic resistant cells by inducing their glycolytic metabolism alteration. Additionally, in general, flavonoids(which is the larger denomination of BAS-6) have been shown to generally have antiproliferative effects and antineoplastic, inhibits tumor growth, effects as well. BAS-6 itself has shown no cytotoxicity in the human body as well, so may serve as an important player in research in the future(Maués 2019).

We see that class 2 HDACs such as HDAC6 play an important role in what makes some cancer cells apoptotic resistant, which emphasizes the need for HDAC inhibitors such as BAS-6 to counteract this problem.

Class 3 HDAC

SIRT1 is a class 3 HDAC which has been shown to generally regulate histones 3 and 4. The sirtuins have many functions outside of histone acetylation, however in this paper only its role in histone acetylation will be covered. However, it is important in regulating the promoters of 5 genes called *AR, BRCA1, ERS2, EZH2,* and *EP300*(Rifai 2018). Research has shown that silencing of these 6 gene promoters have contributed to the advancement of breast cancer(Rifai 2018). Therefore when SIRT1 is overexpressed it allows for over deacetylation of the mentioned gene promoters and therefore more advanced breast cancer.

There have been specific HDAC inhibitors for SIRT1, and the one that will be discussed in this paper is a pan-sirtuin inhibitor, meaning that it is not specific for any specific Sirtuin.

Nicotinamide is a form of vitamin B3 that facilitates the NAD+ redox homeostasis. NAD+ can be used as a substrate for non redox enzymes like the sirtuins, and the product of the reaction would be nicotinamide. Hence the administration of nicotinamide takes advantage of the feedback inhibition associated with this reaction, meaning that the product of the reaction will inhibit the enzyme when its levels are too high. Since it is feedback inhibition, this administration is only effective for a certain duration of time, and this is sort of a blessing and a curse. On one hand, constant administration of nicotinamide is required to continue inhibition of the sirtuins. However, on the other hand, there has been some research into using nicotinamide to stimulate sirtuin(Hwang 2017). Nicotinamide has an interesting ability to create conditions within the cells and tissues that would stimulate sirtuin. Therefore, some scientists have theorized the use of nicotinamide as a fine tuning device for the amount of sirtuin in tissues(Hwang 2017).

There are some drawbacks to nicotinamide, there has been shown to be inhibitory chemicals with competitive potency. This means that nicotinamide may not work well with other specific inhibitory chemicals such as 2-anilinobenzamide derivatives (Hwang 2023).

The possibility of using feedback inhibition in order to inhibit certain HDACs can serve as an important thought to keep in mind in future research. However, the takeaway is the importance of class 3 HDACs and their possibility of aiding further research into other classes.

Class 4 HDAC

HDAC 11 primarily has power over the immune functions of the body. However there have been many associations in breast cancer related to this HDAC. First, high HDAC11 expression has been associated with estrogen receptor and Human Epidermal Growth Receptor 2 negative status. Meaning that high HDAC11 expression has been associated with quite fatally serious forms of breast cancer. Second, there has been research in a cell line called SKBR3 into

a specific tumor suppressor gene that HDAC11 regulates called Aplysia ras homolog I(ARHI). ARHI also regulates apoptosis and autophagic cell death. Scientists identified *ARHI* as a gene under HDAC11's control through siRNA knockdown, and this gene is suppressed when HDAC11 is overexpressed which cements HDAC11's role in cancer(Zhao 2023).

An HDAC inhibitor is Elevenostat which is a hydroxamate based inhibitor geared specifically towards inhibiting HDAC11.

In general, Class 4 HDACs serve an important role in the development of breast cancer as well. Despite the fact that it may not play as big of a role as other classes such as class 1 or class 2, the combination of treatment of class 4 and other classes is viable for increasing the effectiveness of treatment. Especially its control over ARHI and the importance of regulating a gene that has such a big impact on cell death.

Pan-HDAC Inhibitors

The portion will be about pan-HDAC inhibitors, or inhibitors that are non-specific towards certain classes of HDACs. One example of a pan-HDAC inhibitor is vorinostat that generally has antiproliferative and proapoptotic agents. It has not been used for breast cancer in a living human body, however has proven effective in other cancers in vivo such as lymphoma(Xue 2016) by allowing the expression of p21, a tumor suppressor gene, and therefore stopping the cell cycle and the G1 checkpoint. Another pan-HDAC inhibitor would be panobinostat which has been shown to induce apoptosis in both non-TNBC and in TNBC cells. It has also suppressed proliferation and metastasis in mouse models. It has also upregulated *APCL* transcription and expression which allows for ubiquitination and degradation of damaged proteins(Qin 2019). Meaning that damaged proteins will be broken down.

Both vorinostat and panobinostat have been shown to downregulate FOXA1, growth factor; upregulate p21 and p27, tumor suppressor factors; and downregulate Bcl-2, a survival protein(Wawruszak 2021). This means that growth of the tumor will be downregulated, there will be more suppression of the tumor, and allows for apoptosis to come into play. However all of these were only studied on TNBC cell lines such as MDA-MB-231. These 2 pan-HDAC inhibitors have also prevented metastasis by inhibiting matrix metallo-proetinase 9(a protein involved in the degradation of the extracellular matrix)(Maccallini 2022). Essentially by preventing the over degradation of the extracellular matrix, metastasis is prevented.

The importance of having pan-HDAC inhibitors is clear, and being able to treat a patient more generally may be useful if the perpetrating class is not found at first.

Chimeric Compounds

There have also been studies into chimeric compounds which have the ability to simultaneously modulate 2 or more targets. This has proven to possibly be an important fix to a problem in which HDAC inhibitors in general are not effective against solid tumors in hematological cancers(Maccallini 2022). Therefore the use of chimeric compounds could both manage the epigenetic scene while also managing solid tumors.

In general chimeric compounds are most effective because they have a predictable pharmacokinetic profile, there would not be any drug drug interactions, and in general it makes it easier on the patient when it comes to what and when to take it(Maccallini 2022). However, there have been some side effects present with chimeric compounds due to interactions with antitargets.

An example of a chimeric compound that will be discussed is pyrimethamine which is both an antiparasitic –using its ability to inhibit DHFR(dihydrofolate reductase)– and also regulates a specific oncogenic transcription factor called STAT3. STAT3 is activated in many

cancers because it is in charge of increasing cell proliferation and inhibiting apoptosis. On top of that pyrimethamine has been shown to upregulate p38(tumor suppressor factor), and downregulate Bcl4(survival factor).

Chimeric compounds have an important role in ensuring that certain side effects will not be an issue due to a lack of drug drug interactions, and preventing patient or physician error when it comes to taking a treatment.

An overview of all inhibitors mentioned in this paper is presented in Table 1 below.

HDAC inhibitor name	HDAC Class inhibited	Function
Trichostatin A(TSA)	Class 1(specifically HDAC 1)	Returns normal levels of ER-*α*
Entinostat	Class 1	Upregulate vasculogenic mimicry, convert ER negative tumor to ER positive tumor
BAS-6	Class 2	Selectively kills apoptotic resistant cells
Nicotinamide	Class 3	Inhibits sirtuins using feedback inhibition
Elevenostat	Class 4	Inhibits HDAC 11
Vorinostat	All Classes	Antiproliferative & Proapoptotic
Panobinostat	All Classes	Antiproliferative & Antimetastasis
Pyrimethamine	DHFR & STAT3	Antiparasitic, and inhibits STAT3

Table 1: List of inhibitors and their targets

Discussion

Histone deacetylases play an important role in both breast cancer and cancer in general. These proteins have an important impact on the control of tumor suppressor genes as well as control over a variety of genes that control proliferation and cell growth. Control of HDACs using HDAC inhibitors is essential in order to prevent the over suppression of certain genes like cylindromatosis tumor suppressor gene or under suppression of certain genes like *FOXA1*. The targeting towards specific HDACs that is able to be achieved using class specific HDAC inhibitors is going to be essential in future years. This in combination with possible tissue specific treatment would be revolutionary in the medical world.

HDAC inhibitors also have a lot of potential to become more potent against cancer. There has been research in HDAC inhibitors, such as Tucidinostat, into deriving compounds in order to make the treatment that balances effectiveness and ensures minimal toxicity to normal cells(Maccallini 2022). Additionally the use of HDAC inhibitors in combination with other treatments such as the letrozole treatment in combination with entinostat has great potential. There is so much that HDACs and HDAC inhibitors have to offer to increase the survival rate of

not only breast cancer patients, but all cancer patients in order to make cancer no longer the second highest cause of death in the world.

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