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Epigenetics Changes in Breast Cancer: Current Aspects in India

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Abstract

Epigenetics is turning out to be one of the promising studies in cancer research. This review focuses mainly on how genetic and epigenetic factors like DNA methylation, histone modifications and various other genes can assess the promoter region of cancer related genes and provides a tool for cancer diagnosis and research. The objective of the review is to provide an overview of the literature with some recent developments providing insights into the important question of co-evolution of epigenetic changes in breast cancer progression and tumorigenesis. This review also comply study of different genetic changes existing in breast cancer. Further in this review focus on functioning of DNA methylation, including both normal, disruptions or abnormal role in human disease, and changes in DNA methylation during human breast cancer is also noted.

Keywords: Breast cancer; Epigenetics; Tumor; HER-2; BRCA genes

Introduction

Breast cancer is emerging fast as the leading cancer amongst females, especially in young females in metropolitan cities in India. Breast cancer as the name suggests starts in the breast tissues. The types of breast cancer that occur commonly are: Ductal carcinoma (cancer in the milk ducts) whose function is to move down milk to the nipple from breasts and Lobular carcinoma (part of the breast), called lobules [1].

In few cases, breast cancer can affect other vicinity of the breast. Depending upon the affected area this can be further generalized into two types invasive or non-invasive. Invasive means if the cancer has spread from lobule or milk duct to any other breast tissues. Non-invasive indicates that it is yet not spread to any other area of the breast. For the reason of its confined area to affect the non-invasive breast cancer is also called "*in situ*" and its further classified into two:

Ductal carcinoma *in situ* (DCIS)-(intra ductal carcinoma), inside the lining of the milk ducts. If this type of cancer remains untreated, it may progress to the invasive one.

Lobular carcinoma *in situ* (LCIS) - acts as a marker for invasive cancer in the same or both breasts.

Causes of breast cancer

Different factors results in manifestation of breast cancer can be: family history, Gender, age, genes like BRCA1 and BRCA2, alcoholism, menstrual cycle, drugs used for prevention of miscarriage like DES (di-ethyl stilbestrol), Radiation and sometimes Hormone replacement therapy which is done to get relieve from menopausal symptoms by replacing lower level of hormones can also affect to some extent [2].

But the most relevant factor of concern is defective BRCA1 and BRCA2 genes, some people may carry defective BRCA1 and BRCA2 genes [3], these genes function to produce proteins responsible for protecting body from cancer, any defect in these genes may contribute to abnormal production of cancer protecting proteins. Women with these defective forms of genes are at prone risk of breast cancer. They have an around 80% of chances of getting cancer.

In this review will further discuss role of BRCA genes in tumorgenecity.

Symptoms

It's difficult to notice any kind of early breast cancer symptoms. But as cancer further progress symptoms can be experienced:

Any hard lump or swelling in or the vicinity of armpit/breast, one can feel the uneven edges, and usually these lump does not hurt.

Sudden change in the morphology of nipples/breast- for example, redness, cancer dimpling, or wrinkles as that of an orange.

Fluid from the nipple–bloody, clear or yellow, like pus.

In the advanced stage of breast cancer symptoms may include the following:

- Severe to mild pain or discomfort in the breast
- Bone pain
- Weight loss
- Skin ulcers
- Swelling of the arm situated next to the affected breast

Diagnosis and treatment

Breast MRI- The first or easiest identification the breast lump can be done by this method by evaluating any change in the mammogram [4].

Breast ultrasound can also be done to know morphological changes like if it is a solid or fluid-filled lump.

Breast biopsy is done with ultrasound-guided, needle aspiration, open or stereotactic techniques in general.

CT scan is generally performed to evaluate cancer progression.

PET scan to check the early spread of cancer in other parts of body such as lungs, liver, lymph nodes etc.

Sentinal lymph node biopsy to confirm progression of cancer cells in other parts has.

Based on the above diagnosis procedure cited, treatment is based on few factors promising early detection, including: Type and stage of the cancer- like stated early non-invasive or benign breast cancer can be treated more easily than the invasive one which has high chances of affecting other organs as well. Another factor is cancer sensitivity to certain hormones like estrogen or progesterone which are found to maintain sexual functionality in women. Thus hormone sensitive cancer is further classified as ER or estrogen positive (like normal cells have estrogen receptors on their cell surface which regulates their growth likewise cancer cells can also have estrogen receptors in their cell surface signaling cell growth of tumor cells), progesterone positive, or ER negative (in this case no hormone is sensitive and cannot be targeted for blocking hormones). Among these hormones the most sensitive one is estrogen hormone which has capacity to grow breast tumor [5].

Some women may have HER2-positive breast cancer. *HER2* genes (Human Epidermal growth factor Receptor 2) produces HER2 proteins that helps breast cells in proper growth, division, and repair process. Due to abnormal function and have too many copies of this gene, amplification of breast HER2 genes takes place making more number of HER-2 receptors leading to overexpression of HER-2 proteins causing uncontrolled division and growth of breast cells forming tumor. It's found that HER-2 positive breast cancer contributes 25% of all other forms of breast cancer [6].

Summarizing all the previous discussions regarding the progression and focusing on the diagnosis procedure, cancer treatments can be systemic or local. Systematic treatment involves administration of oral drugs or into bloodstream (which reaches cancer cells throughout the body) such as chemotherapy, HRT (Hormone Replacement Therapy) and Target Therapy. Depending upon the invasion local treatments may include either surgery, radiation, or many more. Surgery can be lumpectomy or mastectomy depending upon the site of cancer as lumpectomy removes lumps and mastectomy removes some or all nearby structures of breast. The other two emerging scope of treatments i.e., HRT (Hormone Replacement Therapy) and Target Therapy involves replacement or blockage of some specific proteins leading to cancer. As discussed earlier HRT is a promising approach for treatment of ER positive or PR positive breast cancer having receptors for the same to fuel growth of tumor [5,6]. Both these hormones (ER and PR) help in growth and division of normal cells. Blocking these receptors can be an effective treatment in early or metastatic cancer preventing death by breast cancer. Use of drugs like tamoxifen after lumpectomy is one of the best examples cited to prevent metastatic tumor. Tamoxifen is a drug which blocks estrogen receptors hence estrogen cannot bind to cancer cells. This type of treatment ensures lower chances of reoccurrence of cancer and affecting the other breast too. Another promising inhibitor is aromatase inhibitors (als). In cases of post-menopausal women or women with non-functional ovaries or surgery removing ovaries estrogen is still produced by an enzyme called aromatase present in fat tissue, these als can block aromatase receptor stopping them to make estrogen. Tamoxifen with also is proved to be most effective one in preventing reoccurrence of breast cancer in post-menopausal women.

Another scope is to target certain cells, tissues, genes or proteins helping in growth and survival of cancer cells. This type of treatment is called as Target therapy. This therapy is helpful combatting HER2 positive breast cancer, ER or PR positive cancer where only these specific cells will be targeted with administration of target drugs [7].

Prognosis

New or improved treatments can help patients fighting breast cancer to live longer. However, its reoccurrence or progression to other body parts even with treatment is questionable. Sometimes, cancer can reoccur even if the tumors are removed totally and surrounding nodes are found to be cancer-free. Several factors accounting recurrence of cancer are:

- Tumor location and rate of its invasion
- Hormone receptor-positive or -negative
- Gene expression and epigenetics
- Tumor markers, such as HER2
- Size and shape of the tumor
- Rate of tumor growth

Depending upon these and many other prognosis criteria effective treatment is decided. But problem arises in most of the cases as the cancer has spread beyond lymph nodes affecting other parts also. So, an early prognosis is always better option because as the cancer stages progresses its invasion becomes more vigorous, ultimately leading to death. Therefore the need to understand the genetics and epigenetics involved along with factors like environmental factors which are involved in DNA methylation and histone modification at the tail is mandatory [6,7]. The reason behind why DNA methylation is affected than normal in breast cancer cell will help to diagnose early stages of cancer.

Understanding on Breast cancer so Far

Breast cancer is one of the most common cancers in the world. Globally, it constitutes about 9% of all new cancers [1]. It is known to be the second most common cancer among females, while in the metropolitan cities like Delhi and Mumbai the rank is of the commonest cancer [2,3]. Mammography is the most prevalent screening strategy for breast cancer detection known till date which is a very painful and costly procedure. Hence focusing on identifying novel screening or diagnostic strategy for risk assessment, early detection and prognosis is much more important. Breast cancer onset and its progression is a multiple step process that result from epigenetic and genetic changes [4]. Amongst the epigenetic mechanisms involved is the altered expression of multiple genes due to changes in the methylation status of CpG islands in their promoters and often coding regions too [5-8]. Epigenetics is defined as "phenomena which regulate gene expression through a mechanism to produce changes in cells and the body" [9,10]. Since aberrant gene methylation is one of the earliest molecular alterations that occur during cancer, therefore it is emerging as a promising strategy for early detection of cancer. Recent studies suggest that methylation profiles of cancers are tumor type and ethnicity specific [11,12]. There are several studies on methylation profiles of breast cancer patients from western population [13-16]. However, to our knowledge there is no study or less study in the Indian population till date. The term epigenetics was first coined by a British geneticist and embryologist Conrad Hal Waddington in 1940, to describe the study of the causal analysis of development. Epigenetics is the study of changes occurring in gene expression without any change in gene sequence. These heritable changes are result in chemical changes and addition of methyl group to cytosine bases and are referred to as DNA Methylation (Figure 1).

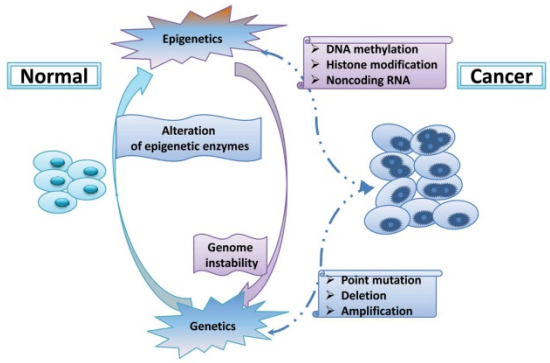

Figure 1: Schematic presentation of epigenetics in breast cancer. Source Credit: Epigenetic regulation and cancer (Review) [17].

DNA methylation

The most common epigenetic tool for gene expression is DNA methylation. DNA contains four base pairs adenine, guanine, cytosine and thymine. Methylation or addition of methyl group to C5 (5th carbon) of cytosine is catalyzed by DNA methyl transferase. In most of the cases these methylated cytosines lie near to CpG i.e., guanine base. Methylation is a global process in mammals compare to others. As CpG stretch is found in entire genome, methylation can take place anywhere. But in some stretch where CpG content is more (1 kilobase), like CpG island, if methylation occurs it will cause silencing of tumor suppression genes thus leading to cancer. Normally DNA accessibility and chromatin compaction by methylation ensures proper gene response towards developmental stages and tissue types. These epigenetic signals are maintained by cell divisions which can ensure appropriate regulation, activation and repression of gene. Therefore DNA methylation plays a vital role in regulation of gene expression, it is heritable with a mechanism of propagation through cell division [18-20].

With DNA methylation, other mechanisms including ATP-dependent chromatin remodeling or non-coding RNAs, histone tail modifications, play an important role in chromatin compaction and gene regulation, but their heritability is less clear. One of the most studied area is the genomic instability caused in combination to DNA methylation, histone modifications especially acetylation and methylation in nucleosome remodelling and gene expression in breast cancer cells. These modifications take place in the histone lysines. While there is no proper understanding of how both genetic and epigenetic changes can influence gene expression, and thereby tumor evolution, it is very unclear how these mechanisms may influence each other, and how these cumulative changes may influence and co-evolution of gene expression during tumorigenesis [19].

The objective of the review is to provide an overview of the literature with some recent developments providing insights into the important question of co-evolution of epigenetic changes in breast cancer progression and tumorigenesis. This review will also include some studies of different genetic changes existing in breast cancer. Further in this review focus on functioning of DNA methylation, including both normal, disruptions or abnormal role in human disease, and changes in DNA methylation during human breast cancer is also noted (Figure 2).

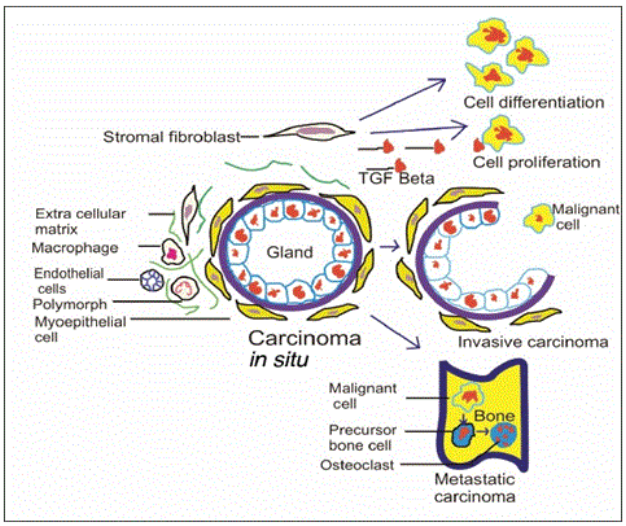

Figure 2: Possible effects of epigenetic changes in tumour microenvironment. Source Credit: Epigenetic changes in tumor microenvironment.

Role of DNA methylation in tumorigenesis: DNA methylation is an epigenetic process involved in many regulations of many processes like gene expression, inactivation of X chromosome, imprinting, chromatin organization and silencing of retroviral and transposable DNA elements. DNA methylation is a cellular process which is the addition of a methyl group to the fifth position of a cytosine forming 5-methylcytosine. These methylated cytosines are present in the DNA of all types of cell [19]. Moreover, this methylated cytosine can be found in grooves of DNA, inhibiting proper transcription. Proteins called DNA (cytosine-5) methyltransferases mediates DNA Methylation. There are five different types of DNA methylases, i.e., DNMT1, DNMT2, DNMT3a, DNMT3b, DNMT3L. DNMT1 has an increased methylation in hypermethylated DNA and it is assigned as a maintenance methyl transferase, DNMT2 is highly conserved and widely distributed with no methyltransferase activity, others like DNMT3a and DNMT3b are *de novo* methylate DNA in human cells with specific preferences for DNA regions, fifth enzyme DNMT3L is homologous to DNMT3 but have no catalytic property rather are associated with *de novo* methyltransferases in establishment of maternal imprinting patterns during development [20,21].

DNA methylation in noncoding regions maintains transcriptional silencing however DNA methlytion in coding regions lead to abrupt changes like epigenetic modifications [22,23]. Therefore this particular functionality of DNA methylation is the need for stringent regulation. Disruption or alteration of methylation which are gene specific leads to many human diseases and one of them is breast cancer.

As malignant cells show major disruptions in their DNA methylation profiles manifesting as hyper-methylation of gene promoters, global hypo-methylation, and increased rate of mutation at methylated CpG dinucleotides is observed. Hyper-methylation of CpG islands in gene promoters has been the most important studied research area of DNA methylation in cancer, approximately half of all human genes promoters are associated with CpG-enriched regions (0.5-5 kb) called CpG islands [24]. Thus, making it possible that

substantial number of human cancers arises through suppressor epigenetic gene silencing mechanisms that inactivate both alleles. Because of this, chromatin-remodelling drugs may provide a novel strategy for cancer prevention and treatment.

Acetylation and methylation of histones in breast cancer

DNA methylation and histone modifications: Gene silencing by methylation is associated with chromatin modifications in DNA packaging. The two important components of chromatin which regulates gene expression are DNA methylation and histone proteins. These two components regulate proper expression of genes in humans. Chromatin is made of nucleosome, a protein made of complex DNA structure composing an octamer of four core histone proteins such as H2A, H2B, H3 and H4 wrapped around by a 147-bp stretch of DNA. Histone tails are known to undergo various tail modifications such as methylation, acetylation, phosphorylation, ubiquitination and sumoylation to regulate key cellular processes such as transcription, translation, replication and cell/DNA repair. During normal development process and in tumorigenesis both DNA methylation and histone modifications affect each other reciprocally. Histone methylation may regulate DNA methylation process or after DNA replication DNA methylation can serve as a template for certain histone modifications. Similarly any modification in N-terminal group in lysine in histones by acetylation or deacetylation catalyzed by enzyme histone acetyalse (HAT)/deacetylase (HDACs) removes their positive charge or acetyl group resulting in an open chromatin structure triggering gene silencing. HDAC family is catgorised into zinc dependent (classes I, IIa, IIb, and IV) and zinc independent which require NAD+ for their catalytic activity (class III, also called sirtuins) [25]. Some of these enzymes like HAT, histone methyl transferases (HMT) or HDACs can be regulated to change chromatin structure and re-express aberrantly silenced genes associated with growth inhibition and apoptosis of cancer cells, because these enzymes are recognized to be a component of nucleosomal remodelling complexes regulating chromatin structure and gene expression. These facts revels that inhibition of class III HDAC by a pharmacologic inhibitor can help in regulation of breast cancer as HDACs are involved in global hypo-acetylation of histone H4. Acetylation of H4 histone at K6 position occurs as a hallmark in early tumorigenesis.

Histone methylation: Histone methylation process involves large number of chromosomal remodelling complexes. Enzyme Trithorax group of histone methyltransferases, such as SET1 and MLL have been noted to catalyze dimethyl- and trimethyl- H3K4 modifications. These H3K4 methylated forms then interacts with Chd1 which is a component of Spt-Ada-Gcn5-acetyltransferase (SAGA) complex with HAT activity to modulate chromatin structure to euchromatin state. These Trithorax group has been known to implicate transcriptional activation of regulatory genes so, their action is balanced by a group of enzymes called polycomb group (PcG factors). PcG factors are associated with silencing of both normal and cancerous cells. They modulate the methylation process of H3K27 [25]. Numerous studies suggest the fact that these PcG factors have a critical role in abnormally silencing of tumor suppressor genes in cancer cells. There are four different PcGs discovered yet in mammals i.e., PRC1, PRC2, PRC4. Most commonly PRC4 exists in stem cells, embryonic cells, cancer and progenitor cells in association with SIRT1 which is a class III HDAC. During lysine methylation of H3K27 the functionality of PRC complexes is guided by a histone lysine methyltranferase EZH2, methylation of H3K27 stabilizes the binding of PcG complexes to mark long term gene silencing. This methylated H3K27 is often present in the promoter region of DNA hypermethylated and silenced cancer genes. Further investigations are mandatory to receive and understand better comprehension in this context.

Some other genes involved

Most inherited cases of breast cancer are found with two abnormal genes: BRCA1 (BReast CAncer gene one) and BRCA2 (BReast CAncer gene two) [21]. Every human have these BRCA1 and BRCA2 genes. The main function of the BRCA genes is to repair cell damage and keep breast cells growing in a normal pace. But if any abnormal or mutated gene is passed from generation to generation, the genes won't function normally and the risk of breast cancer increases. Abnormal BRCA1 and BRCA2 genes may account for up to 10% or 1 out of every 10 cases of all breast cancers. Women diagnosed with breast cancer due to abnormal BRCA1 or BRCA2 are supposed to have a family history of breast cancer, ovarian or any other cancers. Women with these genes abnormality have 80% chances of getting affected by breast cancer during their lifetime. Men who have BRCA1 gene are at a higher risk of prostrate cancer. Men with abnormal copy of BRCA2 genes are 7 times more vulnerable to prostrate cancer than normal men. Other genes that are associated with breast cancer include:

ATM: The Ataxia telangiectasia mutated (ATM) gene (serine/threonine kinase) helps damaged DNA repair. DNA are the carrier of genetic information in cells. Person inheriting two abnormal copies of this gene causes the disease ataxia-telangiectasia, a rare disease which affects brain development. Inheriting one abnormal copy of ATM gene has been reported to an high rate of breast cancer in some families because of the abnormal gene stopping cells repairing damaged DNA.

p53 (also called as TP53 gene): The p53 gene play an important role in providing instructions to the body to make a protein which can stop tumor growth. Inheriting an abnormal p53 gene causes Li-Fraumeni syndrome, a disorder that causes people to develop soft tissue cancers at a young age.

CHEK2: The CHEK2 gene also works similar to p53 gene guiding to generate a protein that supress tumor growth. An inherited abnormal CHEK2 gene can also cause Li-Fraumeni syndrome or it can double breast cancer risk.

PTEN: The PTEN gene regulates growth of the cell. Abnormality in PTEN gene, results in Cowden syndrome, which is a rare disorder causing higher risk of both benign (not cancer) and cancerous breast tumors, as well as growths in the thyroid, uterus, ovaries and digestive tract.

CDH1: The CDH1 gene makes a protein that helps cells bind together to form tissue. An abnormal CDH1 gene can cause stomach cancer in early age. Women found with an abnormal copy of CDH1 gene are at an increased risk of invasive lobular breast cancer.

The AR, BARD1, BRIP1, ATM, CHEK2, DIRAS3, NBN, ERBB2, PALB2, RAD50, and RAD51 genes are associated with breast cancer. As the above listed genes are less involved in genetic mutation their study is still less considered [21].

Current Approaches

As studied earlier in normal cells DNA methylation is conserved of cytosine by- DNMT1, a DNA methylase. DNA methylation primarily occurs in the promoter region of CpG islands containing a sequence of around 1kb with high frequency. Silences this gene expression by

methylation of CpG islands in promoter region is said to be a normal event occurring to regulate gene expression in cell. However due to abnormal or vigorous DNA methylation of tumor suppressor genes, neoplastic transformation is resulted. This type of aberrant DNA methylation occurs in every step of cancer, and genes are silenced. Still the involved mechanism is less understood. By studying previous research articles we can understand some hypotheses related to aberrant DNA methylation. As there are two alleles of tumor suppressor genes both of them is to be suppressed prior to tumor formation. In Recent years many tumor suppressor genes are identified by using chromosomal analysis that shows loss of heterozygosity (LOH). The molecular events leading to aberrant methylation are still not understood. But there are several hypotheses which are to be tested like infidelity of DNMT1 an aberrant promoter hypermethylation. Methylation occurs prior to DNA replication with to ensure passing of the identical methylation pattern of the parental cell to each daughter cell. *De novo* methylating enzymes DNMT3a and DNMT3b can be involved in aberrant DNA methylation. These enzymes use unmethylated DNA template for embryonic development. It is still unknown that what is controlling the enzymes specificity, but in case if a wrong target of CpG sequence is taken, it will contribute to abrupt gene silencing by methylation. A faulty repair mechanism of aberrantly methylated DNA can be another mechanism responsible for gene hyper-methylation. A human DNA demethylase has the potential to function as a repair enzyme, to correct abrupt methylation of CpG sequences [23]. Those factors which control DNA methylase template specificity have not been identified and its further research will clarify its role in the cell growth, differentiation and regulation. Another event is to produce abnormal hyper-methylation of CpG islands by chromosomal remodelling and resulting abrupt methylation of lysine-9 of histone-3 in nucleosomes by enzyme histone methyltransferase. According to one review on tumorigenesis, Vadakedath and Kandi have found gene silencing by DNA methylation of cancer related genes [26]. These cancer-related genes and genomic screening of aberrant methylated CpG islands associated with different types of tumors [27-30] are indicative of the epigenetic changes in tumorigenesis. Another factor to be considered is lysine acetylation by enzyme histone acetylase (HDAC), withdraws positive charge of lysine which result in an open chromatin structure, facilitating gene transcription. The enzyme histone de-acetylase acts as removing the acetyl groups from lysine, as a result reverse transcription takes place resulting in silencing of gene expression. Aberrant de-acetylation of histones in nucleosomes is probably due to dysregulation of the specificity of HDAC and may be associated with neoplastic transformation.

Burden of various diseases always hampered the progress of human civilization especially in the third world countries [31,32]. Advanced techniques are being utilized to understand various disease conditions, chronological alteration of disease causes for various life threatening diseases including infectious diseases such as malaria [33-36], different bacterial diseases such as tuberculosis and others [37-39], viral diseases such as Dengue, Chikungunya, West Nile etc. [40,41], diabetes [42] and obviously different types of cancers.

Nano carrier based treatment

In the present scenario various types of cancer remained a global major concern. Hunt is on for novel therapeutics to battle against this merchant of death. On the technical ground, promising Nano carriers with several therapeutic and technical benefits such as protection of the drug till reaching the proper delivery time and organ, avoiding other hazardous interaction in the body, optimal penetration and distribution profile maintenance are being attempted and received approval from authorities as therapeutics for cancer treatment [43].

Lipid metabolism and apoptosis based approaches

Altered lipid metabolism rate, especially sudden rise in cholesterol, fatty acids and phospholipids in cancer cells could be used as an excellent marker for cancer diagnosis and therapeutic purpose [44].

Lipidomics based studies have been attempted to provide a glimpse on the difference in lipid profile of normal and cancer cells [45]. Attempts have been made towards cancer associated induced apoptosis as a therapeutic approach. In this regard assessment of various cell signalling process associated to cell death or apoptotic process has been investigated. Targeting ribosomal DNA transcription process has been a recent attempt in this aspect [46].

Tweaking natural immune system

Natural immune system follows multiple options to eradicate and halt cellular system to progress towards cancer. Such immune checkpoints are kept on hold by various receptors and ligands, therefore, preventing a natural immune system to function against probable cancer induction. Latest drugs such as anti-PD-L1, nti-CTLA-4 is under intensive investigation which can help in overcoming the immune checkpoints and provide the cellular system a natural way of eradicating cancer.

Conclusion

Epigenetics is an emerging field of study. In India epigenetics studies are very less as compared to other countries like U.S.A, U.K, and Japan. It serves a promising future in drug designing for breast cancer and early detection of tumors. Hypermethylation occurring in the promoter region of genes related to cancer provides a tool for cancer diagnosis. Construction of biomarkers can be used for diagnosis purpose. Suppression of the genes causing tumorigenesis by histone acetylation or aberrant methylation has been reported. Epigenetic events are reversible therefore finding targets for inhibition of histone deacetylation and DNA methylation. 5AZA a specific inhibitor of DNA methylation, demonstrated to reactivate few cancer-related genes which are silent in human tumor cells. Both 5AZA and HDAC inhibitors can act as single agents in clinical trials for patients diagnosed with cancer. Phase I studies on the combination of these epigenetic agents are under development. There seems that the future prospects of this form of cancer epigenetic therapy are to be followed with great interest. These epigenetic changes provide being potential targets for intervention in therapeutics by inhibitors of histone deacetylation and DNA methylation. By combining these epigenetic agents, the synergistic activation of tumor suppressor genes and the synergistic *in vitro* antineoplastic activity provides an interesting potential for the cancer chemotherapy. From the study of related genes in estrogen metabolic pathway we can find out mechanism involved in aberrant DNA methylation in breast cancer. Distinct epigenetic change starts from initiation of tumor, and extends to growth induction; invasion and metastasis, epithelial mesenchymal transformation, and histone modification pose a path for discovery of new treatments in breast cancer. Vast research is going on occurring of aberrant methylation and the pathway involved in such deviations. Such efforts will unlock the key for prognosis of breast cancer and lead the path for future deep understanding.

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