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Epigenetic as a Novel Biomarker Associated with PAH Exposure and Breast Cancer Risk

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Abstract:
The pathophysiology and molecular pathways of breast cancer (BC) are still unclear, but it appears that BC is caused by the interaction between genetic susceptibility and environmental factors. Epidemiology studies have shown the increase risk of BC through polycyclic aromatic hydrocarbons (PAH) exposure. Environmental carcinogens induce disease pathways by altering the expression of specific genes that may be a consequence of epigenetic modifications. In order to understand the effects of PAHs in the BC risk, the epigenetic pathway may consider as an important key and likely play a role in BC initiation. Novel epigenetic biomarkers and treatments hold promise in the approch of personalized medicine. Here, we focus to review the epigenetic factors in relation to polycyclic aromatic hydrocarbons exposure that may influence BC risk.

INTRODUCTION

Overview of epigenetic modifications in BC Susceptibility

Breast cancer (BC) is the second malignancy that leads to death in women. It is heterogeneous with variable biological features on the molecular level(1). BC is considerably curable and outcomes improve in patients with early-detection, non- metastatic disease (2). Several factors such as age, family history, late-age pregnancy, early menarche, and late-onset menopause(2), high levels of estrogen during pregnancy(3), lack of breastfeeding, and alterations in gene expression patterns(4) can affect BC risk. Other factors that influence BC risk include: diet, life-style, and BC susceptibility genes (2). Remarkably, the accumulation of multiple, low- penetrant mutations can increase breast cancer risk(2, 5).

Various epigenetic abnormalities are present in BC. Epigenetic alterations including hypermethylation of DNA damage response genes (BRCA1 and hMLH1), cell cycle regulation and apoptosis (CCND2, CDKN2A/p16, RASSF1A, APC), p14(ARF), CDH1, MGMT, GSTP1, and cell signaling (ER and RARβ 2) are important in breast carcinogenesis(6) and elevate the risk of BC(7). Epigenetic modifications in ATM, MLH1, MSH2, and PALB2 are germline (8) and sometimes they carry with other germline mutations. Promoter hypermethylation of PALB2 was found in women who are the carrier for BRCA2 germline mutations (9). Multiple-case BC families with no identified genetic mutation may be caused by heritable DNA methylation marks(8). Heritable epigenetic in BC susceptibility genes which are derived from PBMC may be used as a guidance biomarker to predict BC risk with the unknown mutation. The normal breast tissue adjacent to the tumor location may show genes with promoter hypermethylation, such as RUNX3 and RASSF1A. The results indicate that the aberrant epigenetic modifications occur in the early stage of BC, and premalignant epigenetic alterations may be widespread from the tumor epicenter to the surrounding cells (10, 11).

Histone acetylation and methylation associate with BC(12-15). The studies demonstrated that acetylation of H3 lysine enhance in BC cells(16). The increase of the H4 acetylation can lead to abnormal expression of DNMT1 (17). Histone acetylation play important role in DNA damage response and determines the efficiency of DNA repair(18). Furthermore, HDAC1 can encourage cell proliferation by increasing the expression

of two LncRNAs, BC01600 and AF116637, in cancer tissue(19). Aberrant expression of the ncRNAs and their interaction with epigenetic proteins is shown in BC(20).

The level of epigenetic components such as methyltransferase (DNMT)-1 is increased in lymph node metastasis while DNMT 3a and 3b are elevated in severe stages. Other enzymes involved in epigenetic modifications are ten–eleven translocation (TET) family of methylcytosine dioxygenases. TET1 is inhibited by miR29 and subsequently, affects chromatin remodeling. In the progression steps of BC, TETs expression is decreased. Upregulation of TET1 promotes the expression of HOXA7/9 (21). Petr Novak and et al reported that the HOXA gene expression including HOXA1 to HOXA10 significantly decreases in BC tissue. This small epigenetic region is located at gene family clusters and inactivates by epigenetic microdeletions in BC (22).

PAH and breast cancer

Interaction between environment and genetics plays an important role in tumorigenesis, and its evaluation improves the prediction of BC risk (23-27). Although a recently cohort study in China observed that there is not a correlation between BC and Indoor solid fuel combustion(28,29), Epidemiologic and experimental studies demonstrate that PAH exposure is associated with an increase in breast cancer risk (30,34-37). PAH a widespread chemical carcinogen in ambient environment pollution, enter the human body from a variety of sources including smoke from cigarettes and tobacco, inhaling gasoline and diesel-fueled, combustion of coal and coke, and eating grilled and smoked meats(38). These lipophilic compounds have been stored in breast fat and metabolized in breast epithelial tissues to deleterious state. So in this way, it can affect cellular morphology, division, and growth (39, 30). PAH biotransformation can bind to the DNA, forming covalent PAH-DNA adducts and also react with proteins such as hemoglobin and albumin (18, 31). DNA adducts can alter promoter methylation leading to abnormal gene expression, and ultimately tumorigenesis(32). PAH-DNA adducts reflect exposure to PAH, and they are presumed as an early effect marker for cancer(26). The level of PAH-DNA adducts is high in women who are at high risk due to cancer family history. The population-based cancer registry reports that early exposure to environmental factors, when the breast cells divide quickly, can enhance BC susceptibility (40, 24-26). A meta-analysis of 15 cohort studies showed that BC incidence is high among current and former smokers women, and there is an association between BC and active smoking(41). Two population-based case-control studies, demonstrated the association between residential exposures to PAH and BC risk(35-37). DNA repair capacity in response to PAH-DNA adducts can affect BC risk. Results showed an association between PAH-DNA adducts and BC risk in women who have a variation in in ERCC2 and XRCC1(DNA repair genes)(35). An invitro study showed that PAH effects on gene expression in ER-positive cell line(42).

In addition to genetic alterations, aberrant epigenetic patterns lead to the activation of oncogenes, downregulation of tumor suppressor genes, and reduction of DNA repair capacity, which are involved in cell transformation(43, 44). Epigenetic changes are involved in BC initiation and progression without changing DNA sequences(45). The germline mutation of high penetrance genes such as BRCA1/2 was a landmark biomarker for familial BC prediction, but the majority of BC occurs in women who don't have any germline mutation. In sporadic breast tumors, which constitute the main of BC cases, epigenetic mechanisms are involved in the downregulation of BRCA1 in the absence of mutations in the BRCA1 gene. Furthermore, in women who carry a mutated BRCA1 gene, silencing the wild allele by epigenetic modification may further enhance the BC risk(46). DNA methylation, histone modification, and non-coding RNA are the most epigenetic events that regulate the gene expression (43, 44). PAHs are capable of epigenome modification. PAH exposure through epigenetic modification may affects the telomere length shortening(47). Treatment of human cells with BaP or related metabolites causes promoter hypo- and hypermethylation and histone modifications, subsequently changes the expression of critical genes in cancer. (48). PAH alters DNA methylation in a number of genes through noncoding RNA (49). Methylation of genes are associated with the presence of PAH adducts in breast and breast tumor (50,51). Furthermore, Activation of AhR by PAH, which is initially bound to the HSP90, XAP2 and the HSP90-associated co-chaperone p23 protein, induces dimerization with ARNT. This process leads to the expression of the enzymes that are involved in a variety of functions, including chromatin structure remodeling, cell proliferation, loss of cell adhesion, and inflammation. (32).

The achievement of a biomarker for detecting cancer at an early stage is one of the main priorities in cancer research. Cancer biomarkers should have sensitivity and specificity in the clinical application level. Epigenetics can serve as a biomarker of the interaction between genetic predisposition and past and current environmental exposures. Such biomarkers can help to design preventive strategies and diagnose at-risk subgroups and personalized medicine (52). However it needs large-scale epidemiological Studies. Nowadays, blood-based epigenetic biomarkers have become an attractive and controversial subject for the assessment

of solid tumors. It should be noted that this kind of biospecimen cannot precisely reflect the modification of target tissue(some circulating molecules such as cell-free DNAs and RNAs (cfNAs), exosomes and non-coding RNAs, which originate from cancerous cells or solid tumors can present valuable information about tumor cells). In this regard, extensive efforts have been made to detect epigenetic biomarkers for the early diagnosis of BC(53). Therefore, to gain better insights on the effects of PAHs in the BC risk, the epigenetic pathway may consider as an important key. The studies of PAH-associated epigenetic alterations in particular susceptibility loci may provide valuable insight into the underlying biological mechanisms in PAH-associated carcinogenesis. In this review, we describe how PAHs influence the epigenetic modifications including DNA methylation, histone modification, and non-coding RNA and explain how specific epigenetic modifications might increase susceptibility to BC risk.

DNA Methylation

Methylation alteration at specific genes

DNA methylation is one of the epigenetic processes. PAH exposure has a potential role in gene silencing through hypermethylation at specific loci cancer(50, 51)and global DNA hypomethylation (54). Mammary cells can store and concentrate lipophilic aromatic hydrocarbons in breast fat. These cells metabolize the aromatic hydrocarbons into DNA-binding metabolites(55). Binding the PAH metabolites to nitrogenous bases can produce DNA adducts. Methylation of CpG islands increases DNA binding to reactant electrophiles(56-58). It has been shown that methylated CpG sequences at the exon 7 of the p53 gene increase the BPDE binding constant to G in codon 248(56). The linear regression model shows that DNA adducts formation is higher in CpG islands(58). Methylation of promoter CpG islands is associated with the repressive histone markers, including trimethylation of histone 3 at lysine 27 and 9. Cytosine methylation within the promoter can identify by methyl group-binding proteins (MBDs). finally, gene silencing promotes by recruiting co-repressor complexes with histone modification enzymes such as deacetylases (HDACs) (59). It is noteworthy that documents indicate that histone modifications is more rapid response to environmental effects, but DNA methylation mediates gene silencing over a longer time frame(60, 61).

Study the genome-wide DNA methylation in mice lung tissue has been shown that the promoter region of Pten and Tpd52l1 are respectively hyper- and hypomethylated, in DBC exposure(62). PTEN is one of the most frequently mutated genes identified in DCIS and IDC subtypes with hypermethylation(63). The meta-analysis study introduces it as a valuable biomarker for the diagnosis of BC(63). Tpd52l1 belongs to the tumor protein D52 gene family and is implicated in BC(64). Tpd52 family plays a role in cell proliferation and calcium signaling. It can be assumed that this result may not show methylation patterns for all tissues, but PAH may also influence the genes mentioned in breast tissue.

BaP can modify BRCA1 methylation patterns in ER+ BC (MCF-7) cells(42). Study of tumor tissue biopsy from patients with invasive or in situ breast cancer revealed that BRCA1 promoter methylation was high among invasive cancers and premenopausal cases and it frequently elevates mortality(65). Breton and et al. found that methylation patterns of receptor tyrosine kinase and receptor tyrosine phosphatase change as a result of maternal smoking(66). Another study in adolescents who were exposed to cigarette smoke in during pregnancy showed that methylation was enhanced in the promoter and 5'UTR(untranslated region) of brain-derived neurotrophic factor(67). In contrast, a cross-sectional study conducted in PAH-exposed brick makers, DNA methylation of P53 and IL-12 was inversely associated with PAH exposure(68). Study in animal models revealed that prenatal PAH over-exposure leads to an increase in the PPARγ expression in offsprings which regulate through the decrease in DNA methylation. Activation of peroxisome proliferator-activated receptor γ (PPARγ) plays an essential role in the proliferation and invasion of breast cancer cells(69). Therefore, through enhancement of the PPARγ via epigenetic alteration, PAH may increase BC risk. Promoter methylation of APC and RAR-β genes, as well as PAH-DNA adducts, elevate the risk subtype of ER+/PR+ BC (50). Additionally, the LIBPCS study found that the source of PAHs can influence the methylation of the specific genes.

PAH exposure is associated with impaired Treg function that is the result of altered methylation of the Foxp3 promoter(60). Kohli and et al. found that tobacco smoke exposure increases methylation of IFN-gamma in T effector cells and FOXP3 in T regulatory. They noted that cigarette smoke, along with other chemicals like nicotine and particulate matters may contribute to epigenetic alterations(70). Treg cell ablation accelerates the tumor progression and increases tumor growth in early-stage, in contrast, Foxp3+ Treg cells accumulate in advanced BC(71). FOXP3 is expressed in a variety of normal and cancerous cells in addition to Treg. FOXP3 downregulation is associated with cancer development in BC. Evidence shows that FOXP3 is a tumor suppressor gene in the breast. HER2 and SKP2, two oncogenes in breast cancer, are repressed by FOXP3. HER-2 protein is a transmembrane receptor for growth factor, which is present in 15-20% of invasive breast cancers. SKP2 has a role in ubiquitination and degradation of the cdk-

inhibitor p27 and its expression increase in 50% of breast cancers(72). So, it may be considered that PAH by epigenetic alteration of FOXP3 in breast tissue and immune cells conducts tumorigenesis.

Alteration at global methylation

Long interspersed nuclear elements-1 (LINE-1) belong to classI retrotransposable elements that are the most abundant elements of classI in the DNA. LINE-1 reactivation can affect cellular functions, such as epithelial cell differentiation programs, cellular adhesion, inflammation, metabolism, induction EMT(73, 74). LINE-1 elements length is 6–7 kb and they have 500000 copies in the human genome. It consists of two open reading frames (ORFs); ORF1 and ORF2, which are involved in duplication and transposition of elements(75). DNA methylation at the 5' position of cytosines by DNA methyltransferases (DNMTs) is an important mechanism for LINE-1 silencing. Although LINE-1 is active during early embryogenesis, its activity is suppressed when cells initiate the differentiation program. The content of PAH-DNA adducts is opposite to global DNA-methylation. Also, there is demonstrated that BaP induces DNA hypomethylation of Short interspersed nuclear elements (SINEs) and Long terminal repeats (LTRs) elements(77). Pavanello and et al analyzed the methylation status of specific genes and repetitive elements including, Alu and LINE-1 in PBLs isolated from coke-oven workers. They reported that the global methylation level in the PAH-exposed group is significantly higher than the controls. Also, the levels methylation of the tumor suppressor including, p53 and HIC1 in Coke-oven workers decrease in comparison to the control group. Moreover, the methylation status of Alu and LINE-1 has a significant positive correlation with anti-B[a] PDE-DNA adduct and 1-pyrenol, conversely, p53 methylation is negatively correlated with 1-pyrenol and anti-B[a] PDE-DNA levels(78). Inconsistent with Pavanello; Ivo Teneng (79) and Boissinot et al (80) Jin Yang (99)showed that LINE-1 methylation is reduced in-vitro and in PAH-exposed individuals, respectively. Ivo Teneng et al demonstrated that BaP exposure enhances transcriptionally active chromatin markers such as H3K4me3 and H3K9ac and reduces the interaction of DNA methyltransferase-1 (DNMT1) with the LINE-1 promoter(79). Also, they explained that the first event that induces by BaP is histone modifications that happen with short term exposure, but long-term impact includes DNA methylation. HDAC1 performs an important role in the proteosomal-mediated degradation of DNMT1(50). Also, they found that LINE-1 hypomethylation response is not just tumor cell-specific, but exists in primary cells. in contrast, Claudia Knothe et al. demonstrated that LINE-1 methylation is a tissue feature(81). Differences in the extent of LINE-1 methylation between these studies may be caused by differences between cell types and length of chemical exposures.

BaP-induced AhR activating regulates LINE-1 expression via the TGFβ/ SMAD2/SMAD3 axis(82). SMAD proteins add four acetyl groups on histone 3 using histone acetyltransferases (HATs) P300 and CBP and induce gene transcription(83). Reduction in global DNA methylation causes genomic instability and initiate the early stage of cancer(84). PAH exposure by decrease LINE-1 methylation may promote its mobility. New somatic LINE-1 insertions have been demonstrated in several epithelial cancers. LINE-1 insertion may lead to the disruption of key cancer genes, and finally, initiation of BC, although it exerts retrotransposition-independent functions(82).

Overall, Repetitive sequences that are extremely methylated, undergo hypomethylation in transformed cells, whereas unmethylated promoter of coding genes (especially tumor suppressors) and noncoding RNA with tumor-suppressor features become hypermethylated and silenced in cancer cells through PAH. Methylation of genes can determine the cancer subtypes. In addition to the type of tissue, the duration of PAH-exposure, the selected method, and study design and capture exposure at the biologically relevant time are also the effective factors in carefully examining the level of methylation of genes. Although PAH- related DNA methylation seems to play a critical role in the initiation of BC pathophysiology, limitations such as, lack of highly exposed and unexposed populations for comparisons, and using blood samples or non-breast cell lines that may have a different response with breast cells, can influence the validation of the results. Moreover, studies have failed to establish clear relations between PAH adducts and hypermethylation or hypomethylation, suggesting that other mechanisms may be involved.

Histone Modification

Histone acetylation

Decrease histone acetylation

Histone modifications modulate the chromatin structure, and subsequently, cause to inhibit or activate gene expression(2, 85). Histone modifications including acetylation and methylation are the most subject studied in breast cancer (86-92). Methylation and acetylation changes are usually found in lysine residues that are present in different positions of histones H3 and H4, whereas phosphorylation changes occur in threonine or serine amino acids (94). Xiangzhi Li and et al reported that MYST1 protein, a histone acetyltransferases, markedly decreased along BaP-induced DNA damage repair in HELF cells. They considered that maintenance of genome integrity is depended of MYST1 level(116).

BaP exposure leads to reduction histone H3k14 acetylation in the StAR promoter region in neonatal animal models which persist to the adult stage. This epigenetic alteration damages sperm count in the long term (95). Sadikovic and et al by invitro studies showed that histone acetylation levels on the promoter region of genes such as MBD2,HDAC1, MBD3, ATRX, and METT5D1 were decreased in BaP-treated cells which are were involved in chromatin remodeling(59).

Increase histone acetylation

The study showed that cigarette smoke condensate (CSC) CSC enhances C/EBP-b level and this henomenon subsequently elevates the expression of LncRNA LOC554202 and miR-31 through increased levels of H3K4Me3 and H3K9/14ac marks in the promoter region of LOC554202(96). Treatment the BC cell lines by BaP leads to hyperacetylation in NAB2, TMF1, BRMS1L, GADD45B, BAX, CYP1B1. These hyperacetylation genes are included cancer-, DNA damage-, transcription-, and detoxification- associated genes(48). CBP/P300 is increased in Cigarette smoke-treated cells and results in the various of acetylating processes(97). Invitro study confirmed that activation of HAT p300 enhances the transcriptional activity of Wnt/β-catenin target genes which is correlated with BC (98).

Alteration in acetylation level has been found in many human cancer such as renal cell carcinoma prostate , lung , gastric , and BCs(99). There is correlation between DNA methylation and histone deacetylation in H3 and H4, and it is suggested that these modification together may be part of a process for tumorigenesis(43). Chromatin modifications provide appropriate conditions for inhibiting the cellular DNMTs activity. These results lead to reducing in cytosine methylation within the target gene that is visible after one replication cycle. Global histone acetylation pattern of histone 3 at lysine 9(48), lysine27 , and lysine18 are changed by BaP exposure. H3K18ac and H3K27ac are located at TSS of the AhR gene and involve in the regulation of the transcriptional activation(100).

Although histone acetylation and deacetylation is critical in normal growth and development, pattern alterations in result of PAH may contribute in tumorigenesis and be predictive biomarkers for BC risk and its phenotype. Also, most studies are reported base on Invitro investigation or blood sample from patients. Studies of PAH-related histone modification patterns and related component as well as target genes that are regulated with these processes, will provide precise inform about possible carcinogenesis of PAH. However, it is still unclear how modifications trigger in histone.

Histone methylation

Histones can be methylated in lysine and arginine residues by two major families of histone methyltransferases(HMTs). One of the most well-known KMTs is EZH2. This enzymes directly are targeted by miRNAs(101, 102) and LncRNAs(103). miRNAs affect gene expression mainly by regulating KMT expressions(104-107) and act as a tumor suppressor miRNAs. These miRNAs are negative regulators of EZH2. The result of their performance leads to suppress the cell invasion, metastatic tumor phenotype(107), and cell proliferation (101)and versus promote apoptosis(104) and decrease cell viability(105). PAH treatment causes the enhancement of expression of epigenetic genes such as DNMT and EZH2(108). In this regard, PAH may regulate the EZH2 expression through inhibition expression of these miRNAs. upregulation of EZH2 has been found in BC. As will be mentioned in the LncRNA section, recruitment and connection of EZH2 by LncRNAs has been determined in the BC and enhance the methylation.

It is found that H3K36me3 modification elevates at the MGMT and MLH1 gene regions in peripheral blood lymphocytes (PBLCs) Coke oven workers exposed to PAHs(18). Also, it is revealed that H3K36me3 is associated with the DNA damage and Urinary 1-hydroxypyrene (1-OHP). Histone modification occurs in response to the PAH exposure and leads to increase expression of DNA repair genes. Therefore, decreasing H3K36me3 modification during PAH exposure may induced malignancy. Furthermore, the H3K4me3 modification negatively correlates with the degree of PAH-induced DNA damage. It is suggested that modifications of H3K4me3 may be involved in the regulation of DNA repair (18), but Genes mediating DNA damage response is unknown.

Co-exposure to PAH and other carcinogens synergistically activate AhR to up-regulate the expression of SUV39H1 methyltransferase and causes to downregulation of SOCS3 ,and subsequently, enhance the Akt and Erk1/2 activation to promote cell transformation(109).

BaP exposure leads to a significantly decreased NR2E3 as well as its target gene, estrogen receptor(110). NR2E3 is a nuclear receptor and regulates transcription of several genes, which involved in development, differentiation, and survival. The expression of NR2E3 causes longer survival in BC patients(111). Tilak Khanal and et al identified that PAH inhibits NR2E3 homodimerization and leads to NR2E3 releasing from ER promoter regions. Then, histone modifications promote through recruiting the LSD1 as a histone demethylase of H3K4me2 and decreasing H4ac in the promoter region of ER(110). These histone modifications are as markers for the

activation transcribed promoter region. It seems that PAHs are not only associated with BC risk but also mediate abnormal epigenetics that will affect BC patients' survival in the future. Collectively, how these post-translational modifications which control diverse chromatin functions can pass to next generation cells is remain unclear. Histone modifications are regulated by various enzymes that may be affected by PAH. Histone abnormalities can impair gene regulation. It is suggested that DNA adduct may play an important role to recruit the histone modification enzyme in CpG islands of promoter regions and enhance the tumor suppressor genes methylation. Depending on the location of histone and types of epigenetic modifications, the PAH impact can have a variety of results.

Histone phosphorylation

Histone phosphorylation by PAH may enhance the target genes transcription which, initiates the tumorigenesis that should experimentally be confirmed. exposure to BaP induce DSBs in mammalian cells which is detectible by Phosphorylation of histone H2AX (γH2AX)(phosphorylated at Ser139) (112). γH2AX is significantly increased in BaP -treated ApcMin/+ cells compared to control, and this assay, confirm an effective genotoxic effect of B(a)P on cells(113). Moreover, several studies demonstrated that exposure of complex mixtures containing PAHs can increase histone phosphorylation markers such as γH2AX, even it is detected in short-term exposure (114-118). Phosphorylation performs by PIKK leads to localize DNA damage response proteins. Then, γH2AX recruits the HATs, HADCs, chromatin -remodeling and –modification complex, and kinase, in sites of DNA damage. In the following, histone H2B is phosphorylated, but H3 phosphorylation on Thr-11 removes by CHK1. This phenomenon is implicated in the regulation of gene expression that is involved in the cell cycle (119). These results indicate that elevation of γH2AX by PAH exposure may reveal mark for aberrant expression of the genes involving in the cell cycle, and implicate in tumorigenesis. tobacco smoke exposure can induce the phosphorylation of HDAC2 on serine/threonine residues and subsequently its degradation carry out with proteasome(120). Scholars reported that lower miR-24-3p expression is associated with plasma BPDE–Albumin adducts. On the other hand miR-24-3p negatively regulates the H2AX(121), thus it may be speculated that PAH by epigeneticaly reduction the miR-24-3p expression promotes DNA-damaging. Wang FP and et al studied the PBLC of coke oven workers. They reported that the H3Ser10 phosphorylation level in the PAH-exposed group is higher than the control group. They also found the correlations between DNA damage and H3Ser10 phosphorylation(122).

However, very few studies have been performed on the role of PAH on histone phosphorylation and BC risk, and frequently research evaluates the histone phosphorylation that is associated with DNA damage. The assess of histone phosphorylation may reflect early PAH-induced DNA damage although, further studies are needed to understand and confirmed the influence of this modification.

Non-coding RNAs(ncRNA)

These group of RNAs are consisted of, micro RNA (miRNA), long noncoding RNA (lncRNA), small-interfering RNAs (siRNAs), piwi-interactingRNA(piRNA), and small nucleolar RNAs. Noncoding RNA have potential to regulate gene expression through different mechanism such as heterochromatin formation, disruption of translation, DNA methylation and histone modification. noncodingRNA cause gene silencing or enhancing expression (123). Aberrant miRNA expressions have been identified in the in BC (124). Beside epigenetic modification in noncoding RNA, it is considered that interaction between noncoding RNA and epigenetic component can promote alteration in gene regulation. Environmental factors can induce binding of LncRNA to histone modification and promote oncogenesis(69). Here we review LncRNA and miRNA(125,126).

Long Non-Coding RNAs

Long noncoding RNAs(LncRNA) are defined as a class of ncRNAs with a dimension of more than 200 nucleotides, which transcript mostly by RNA polymerase II (RNA pol II)(153). Evidence demonstrated that they are involved in a diverse spectrum of biological function in normal cells, so aberrant expression of them can play critical roles in the development of human diseases (127-129). Characteristics including early appearance, stability in biological fluids, tissue specificity have emerged LncRNAs as important biomarkers for health risk assessment (126). Alteration of LncRNA expressions is found in environmental chemical–induced carcinogenesis and cell malignancy (49, 126). LncRNAs are considered one of the essential epigenetic modifiers. LncRNAs interacts with chromatin remodeling complexes and can recruit them to the regulation of gene expression(49, 131).

LncRNA MALAT1

MALAT1 is capable of associating with PRC2 (histone methyltransferase), and subsequently impacts the gene transcripts. MALAT1 binds to the EZH2 subunit and recruit PRC2. PRC2 is composed of EZH2, RBBP4/7, SUZ12, and EED subunits and performs two/trimethylation in histone3 at lysine 27. Similar to MALAT1, LncRNA ANRIL can bind to EZH2(103) and it is suggested that these LncRNAs

may be a scaffold to chromatin-remodeling complex for regulating the expression of genes(132). A study of PBLCs samples from PAHs-exposure workers showed that the expression of MALAT1 was higher in PAHs-exposed group compared to the control group (49). Moreover, this transcript level is elevated in tissue of BC patients. Also, MALAT1 expression levels are correlated with tumor stage and lymph node size and is introduced as a valuable marker of a breast cancer diagnosis (133). This LncRNA is oncogene that could promote proliferation, metastasis, and tumor formation in cells (134-136). Cell-cycle dysregulation leads to uncontrolled cell proliferation that is the main event in cell transformation. Environmental impacts on genes associated with cell cycle may change susceptibility to tumor progression.

LncRNA HOTAIR

HOTAIR, inhibits the expression of p21, via EZH2-mediated histone trimethylation and leads to defection in the cell cycle induced by cigarette smoke extract (CSE)(137). furthermore, the findings confirmed that CSE is involved in malignant transformation through axis IL-6/phospho-STAT3 /HOTAIR(138). In-vitro studies revealed that tri methylation of histone3 at lysine27 , as a biomarker in response to DNA damage, had been upregulated through HOTAIR(100). It is considered that HOTAIR may be presented as a prediction factor of PAH-induced DNA damage and genotoxicity. Moreover, the long intergenic RNA HOTAIR expression in BC cell lines recruits the PCR2 to altered trimethylation on histone H3 lysine 27 , leading to modulating the cancer epigenome and silencing of metastatic suppressor genes(20). The increased expression of HOTAIR has been found in the PAHs-exposed subjects in comparison to the control group (49).

LncRNA TUG1

It has been demonstrated that the TUG1 expression increase in male coke oven workers. This elevation is associated with the level of PAH exposure(49). TUG1 is upregulated in breast cancer and can encourage cell proliferation and metastasis and inhibits apoptosis in human BC tissue. RNA sequencing analysis demonstrated that TUG1 expression is increased in HER2-enriched and basal-like subtypes in comparison to luminal A (139, 140). In contrast, evaluation of TUG1expression in BC tissues and cell lines showed that TUG1 was down-regulated and correlated with clinicopathological features(141). However, differences in the number of studied subtypes and number of samples can affect the overall results of TUG1 expression, although studies provide a novel biomarker in early diagnosis of BC in the clinic.

LncRNA H19

H19 is a multifunctional LncRNA, which plays an important role in growth control(109). H19 is increased in BC tissue compared with normal tissue and expression level of it is associated with proliferation, invasion, and metastasis (142). This LncRNA regulates gene expression in BC at epigenetic modification.

Lin Y and et al in a case-control study, found that elevation of H19 expression can increase the risk of breast carcinogenesis, moreover, the association was more significant in ER+, HER2-, and ER+HER2- molecular subtype of patients(143). Ye Fu and et al found that BaP treatment and H19 repression inhibits DNA-adducts formation. Also, they revealed evidence that H19 binding to S-adenosylhomocysteine hydrolase (SAHH) may inhibit methylation the LINE-1 in BaP-treated cells. Global methylation level has a negative correlation with BaP-induced DNA damage. In this research, they did not evaluate which type of DNMTs would be influenced during the interaction between H19 and SAHH in invitro, although another study had been revealed that H19 downregulation enhanced DNMT3B-mediated methylation(144). Aberrant H19 expression can be involved in diverse malignancies such as liver cancer(90), pancreatic cancer(91), gastric cancer(92), and tumorigenesis like breast cancer (94).

In addition to the above mentioned, epigenetic alteration-induced by the environmental factors in the promoter region of LncRNA may distinctly regulate their expression. Despite the suggestion of lncRNAs as novel diagnostic and prognostic tools it is important to note, that the aberrant expression of LncRNA is still controversial and can similar in a variety of cancers. Therefore, evaluation of LncRNA expression along with other epigenetic alterations in the susceptible genes can be useful as biomarkers for cancer risk prediction of environmental exposure such as PAH.

microRNAs

MicroRNAs (miRNAs) are noncoding RNA of ~22–23 nucleotides in length that regulate gene expression by pairing the mRNAs of protein-coding genes(92). The miRNA profile anomaly exists in every stage of BC, from beginning the tumorigenesis to metastasis. miRNAs act as tumor-suppressive or oncogenic that affect the cellular signaling pathways of proliferation, apoptosis, epithelial–mesenchymal transition (EMT), angiogenesis, growth, and metastasis. Also, miRNAs can provide valuable information about BC subtyping, treatment monitoring, diagnosis, and prognosis(91). A class of miRNAs that are known epi-miRs(145) can interact with epigenetic modification factors, such as DNA methylation and chromatin remodeling, to regulate gene expression in response to environmental stimuli. Because of the potential for one miRNA to target multiple gene transcripts, some epi-miRs perform

two functions in the breast. For instance, when the miR-22 targets HDA4, KAT5, TET1, TET2, and TET3, it acts as an oncomiR while by targeting the KDM7B and HDAC3, it affects as a tumor suppressor miRNA(112).

Environmental pollutants may change miRNA expression patterns(146) (96) (121, 147). BaP increased the expression of the miR-483-3p in the primary culture of rat hepatocytes while the AhR inhibitor decreased the level of the corresponding miRNA(148). Xiaoxi Huang et al showed that the expression level of miR-483-3p is significantly was reduced in BC cell lines(149) while other study reported that miR-483-3p expression was increased in BC cell lines(150) that their variety results can due to using different methods. miR-483-3p targets cyclin E1 and decreases MCF-7 cell proliferation(149). CyclinE1 forms a complex with CDK2 and then promotes entering the cell cycle from G1 to S phase(151). These results suggest that miR-483-3p may serve a role in tumorigenesis of BC.Other study demonstrated that the expression of miR-142-5p is downregulated after exposure to BaP (152) and negatively associated with plasma BPDE-albumin adducts(121). miR-142-5p downregulation is observed in luminal A/B BC subtypes while upregulation of miRN-142-5p is reported in HER2+ and Basal-like BC subtypes(91).miR-143-3p is linked to downregulate the genes expressed in cells that are treated by BaP. miR-143-3p upregulated diminishes proliferation and migration via modulating the MAPK7 in BC cell lines(153). Increase expression of miRNA-25 through PAH-activated AhR have a putative role in the regulation of tumor suppressor genes such as p53(154).

Hongyi zhang reported that miR-7 as a tumor suppressor could indirectly repress the STAT3 expression. They showed that miR-7 identified the 3'UTR of KMT1E and resulted in the suppression of STAT3. STAT3 downregulation leads to inhibition of c-myc, TWIST, and miR-9 expression in BCSC cell that subsequently decreases the EMT and metastasis. Moreover, they found that HOTAIR via PRC2 indirectly inhibits the miR-7expression. Due to PAH impact on HOTAIR regulation(155), it may be considered that PAH by targeting miRNA and LncRNA plays epigenetic alteration roles.

Some miRNAs bind directly to the 3'UTR of mRNA and subsequently, downregulate ESR1 expression (156-158). it is reported that miRNA-148a reduces DNMT1 expression that outcome is upregulation of ER expression(159). Some PAHs have estrogenic or antiestrogenic activities, because of their structural similarities. They can bind to both ERs, affecting their cascade signaling and increasing the risk of BC(160). Estrogen Receptorsα (ERα) and Estrogen Receptorsβ (ERβ) are two different isoforms of ERs that execute estrogen biological functions. They can trigger genomic and non-genomic signaling cascades. In the genomic pathway, ERs dimerize after binding with hormone and then bind to regulatory elements of target genes(161). During non-genomic signaling, they involve in the activation of the proteins. The ER expression dominantly is regulated by the epigenetic processes including, ER promoter hypermethylation and histone deacetylation. The invitro study demonstrated that ERα expression can be induced by epigallocatechin-3-gallate (EGCG) as a DNA methyl teransferase (DNMT) inhibitor as well as trichostatin A (TSA) as an HDAC inhibitor in ER-negative breast cancer cells(163). It is reported that BaP exposure may disrupt the expression of BRCA1 in ER+ MCF-7 cells (164). In this regard, the epigenetic components that regulate ER expression may present as a predictive factor for PAH- related breast cancer risk. In total, epidemiology studies need to reflect PAH-specific miRNA signatures that may act as epimiR, and miRNA biosynthesis. Involved enzyme in miRNA prossess may undergo dysregulation and leads to abnormal miRNA expression profiles(165).

CONCLUSION AND PERSPECTIVE

Personalized medicine makes decisions about drug treatment and disease management, based on some cancer genes harboring genetic changes. It predicts the patient response to specific anticancer drugs. Moreover, associated data, such as the levels of RNA, proteins and various metabolites. PAH epigenetically regulates some breast cancer-related genes, which contribute to the initiation of the pathogenesis of breast cancer. Epigenetic modification may do histone changes prior to the DNA methylation. Epigenetic modification, as biomarkers, can help to design preventive strategies and diagnose at-risk subgroups and premise of personalized medicine. Although studies have revealed that exposure to environmental pollutions may alter epigenetic modifications, many studies have used cigarette smoke, which includes a mixture of several substances or BaP alone. It has been shown that hypo- or hypermethylation at multiple promoter regions in breast tumors and LINE-1 hypomethylation in the blood of controls are associated with PAH source. PAH directly or indirectly by the production of activated metabolites can cause DNA adducts formation and subsequently genetic mutation. PAH may influence methyl modification through different pathways. PAHs change methylation modification by interacting with the AhR receptor and activating downstream genes. Another mechanism is the recruiting non-coding RNA, and subsequently, enzymes that are involved in the methylation process. Other mechanisms that involve in methylation is PAH-DNA adducts formation. Base on the number of methylated cytosines and its positions, DNA-adducts formation in CpG islands may induce hypo/hypermethylation in the promoter regions. Due to the low methyl groups in the promoter region of

suppressive genes, it seems that the formation of PAH-adducts and the created structure, may recruit the methylation compounds, which cause gene silencing. It is recommended that changing the length time of PAH-exposure, dose-response, diet, and the use of antioxidants may decrease the effects of PAH on epigenetic modification. Although the relationship between PAH-DNA adducts, PAH exposure, and BC susceptibility have been identified, there are still many unresolved questions about the effective mechanism of the PAH. Overall, a better understanding of epigenetic might open options for breast cancer prevention and follow up through the development of biomarkers reflecting exposures to PAH pollutants and predicting the risk of future breast cancer.

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