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Review Article

Epigenetics: A Bridge between Artificial Light at Night and Breast Cancer

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HSZ wrote the manuscript. AI, SHH, CA, MI and HSZ reviewed the literature. HAS approved the final draft. MK presented the concept of the study and finalized the manuscript.

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Abstract | The second most frequent cancer all over the world is breast cancer (BC). It is reported that only about 10% BC cases are attributed due to inherited genetic mutations while remaining 90% cancer cases are associated with environmental factors. Artificial light at night (ALAN) is considered one of the major environmental risk factors for breast cancer. It inhibits production of melatonin (MLT) from pineal gland which results in abnormal epigenetic changes that relates with an increased risk of BC. The most important ALAN-mediated epigenetic changes include methylation of DNA and acetylation of histone, which are significant for growth, development and progression of BC. DNA hypermethylation of promoter CpG islands inhibits transcriptional activity by methyltransferase enzyme which results in inactivation of tumor suppressor genes (TSG), while in hypomethylation, demethyltransferase enzyme causes the activation of oncogenes by promoting transcriptional activity. Contrary to DNA methylation, histone acetylation and deacetylation results in chromatin opening and closing, respectively; leading to transcriptional activation and inactivation of genes. Histone acetylation has been frequently detected in oncogenes while histone deacetylation in TSG. Collective data from various studies demonstrate that DNA hypermethylation and histone deacetylation of TSG lead to inactivation of TSG and activation of oncogenes. The purpose of this review is to discuss the evidence based relationship between ALAN and oncogenes expression through epigenetic remodeling by DNA methylation and histone acetylation.

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INTRODUCTION

Cancer remains the most important causes of death all over the world as compared to other non-infectious diseases. According to cancer statistical report, about 14.1 million cancer cases and 8.2 million deaths due to cancer were reported in 2012 (Khan *et al*., 2016). Later, in 2018, GLOBOCAN estimated 18.1 million new cancer cases and 9.6 million deaths due to cancer (Ferlay *et al*., 2018). World Health Organization (WHO) predicted 17.5 million expected deaths at the end of 2050 due to cancer (Khan *et al*., 2016).

Among all, the second most common cancer in women is BC and one of the important causes of death (Kaur *et al*., 2019; Torres *et al*., 2019). Over 1.5 million

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BC cases are diagnosed every year throughout the world. In 2018, about 2 million new BC cases were diagnosed (Zaidi and Dib, 2019).

ALAN increases the risk of BC due to suppression of MLT production (Stevens, 2005; Xiang *et al.*, 2019). However, MLT production increases in the absence of light (Hill *et al.*, 2009; Hill *et al.*, 2015). MLT is mainly produced and secreted by the pineal gland (Korkmaz and Reiter, 2008; Li *et al.*, 2017). In addition to pineal gland, it also synthesized by different organs like skin, gastrointestinal tract, retina, bone marrow, and lymphocytes (Hill *et al.*, 2015; Li *et al.*, 2017). Chemically, it is an indoleamine (N-acetyl-5-methoxytryptamine) and name (Mela-) is due to its effect on amphibians which blanch the melanophores and (-Tonin) because it is derived from serotonin (Basse and Arock, 2015). It is famous for 'night hormone' and supposed as 'Jack of all trades (Haim and Zubidat, 2015). It plays an important role in regulating the immune system and sleep wake cycle. It also acts as an anti-oxidative, anti-aging, anti-inflammatory and anti-cancer agent. (Bondy and Campbell, 2018; Amin *et al.*, 2019). The process of biosynthesis of MLT has been shown in Figure 1.

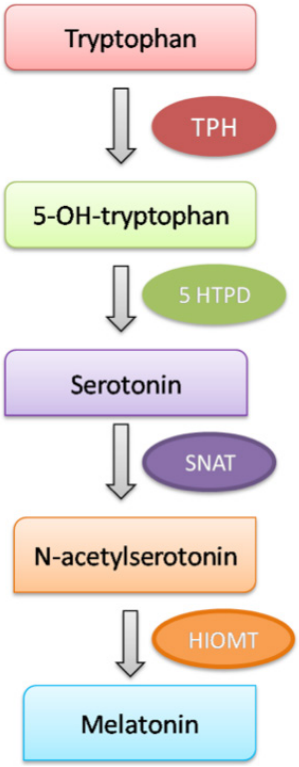

Figure 1: Synthesis of MLT. MLT synthesis takes place in pineal gland. Pineal glands uptake tryptophan and converts it into MLT through five enzymes catalyzed reactions. The diagram represents the sequential reactions and enzymes involved in biosynthesis of MLT. TPH: Tryptophan hydroxylase, 5-HTPD: 5-Hydroxytryptophan decarboxylase, SNAT: Serotonin N-acetyltransferase, HIOMT: hydroxyindole-O-methyl transferase).

The production of MLT is controlled by the suprachiasmatic nucleus with the help of the pineal gland, which affects clock genes and reduces cancer (Blakeman *et al.*, 2016; Zubidat and Haim, 2017; Giudice *et al.*, 2018). During the day, the concentration of MLT reduces whereas its concentration increases at night. By exposure of ALAN, the normal action of MLT disrupts due to its less production (Sharma *et al.*, 2010) which cause abnormal epigenetic changes that enhances the BC risk (Haim and Zubidat, 2015).

In 1942, C. H. Waddington first introduced the idea of epigenetic (Hasan *et al.*, 2015). It controls genetic alternation without changes in sequence of DNA nucleotides (Kochan and Kovalchuk, 2015). Two major ALAN mediated epigenetic changes include methylation of DNA and acetylation of histone that are important to growth, development and progression (Lujambio and Esteller, 2008; Bondy and Campbell, 2018). These modifications are also increasing the chances of BC (Salavaty, 2015) by activation of oncogene and interruption of the role of particular TSGs (Lee and Muller, 2010). MLT regulates alternations in tumor cell. It performs anticancer activity by down-regulation of oncogenes and up regulation of TSGs. It also causes methylation and deacetylation of the oncogene (CYP19) that reduces BC. As a result of deacetylation, chromatin condenses and suppresses the binding of transcriptional factor which require for activation of oncogenes. Moreover, MLT also reduces BC by methylation of other oncogenes (Early Growth Receptor 3 and POU4F2/Brn-3b) and unmethylation of TS glypican- 3(GPC3) (Lee *et al.*, 2013). Epigenetic mechanism relates to inactivation of TSG and activation of oncogenes and these modifications affect genes expression (Haim and Zubidat, 2015).

Effect of ALAN at MLT secretions and estrogen production

ALAN influences the normal daily pattern because it contains light with different spectrum and wavelength (Keshet-Sitton *et al.*, 2016). It decreases the concentration of MLT by the retinohypohalamic pineal region. Decrease in MLT results in increase level of estrogen, which also increases the risk of BC development (Blask *et al.*, 2011; Dauchy *et al.*, 2014; Bauer *et al.*, 2013). It is thought, the main reason of BC risk is lifetime load with estrogen (Stevens, 2009; White *et al.*, 2017).

Effect of ALAN on methylation of tummor suppressor genes

Among epigenetic alternations which are induced by ALAN, the most important is DNA methylation, and it is more common form of molecular fluctuations in human cancer. In DNA methylation, a methyl (–CH3) group shifts to the 5th carbon (5C) of cytosine from Sadenosyl- L-methionine (Fang *et al.*, 2003; Mahmood and Rabbani, 2017; Pfeifer, 2018). Enzyme (known as DNA methyltransferase) involves the shifting of –CH3

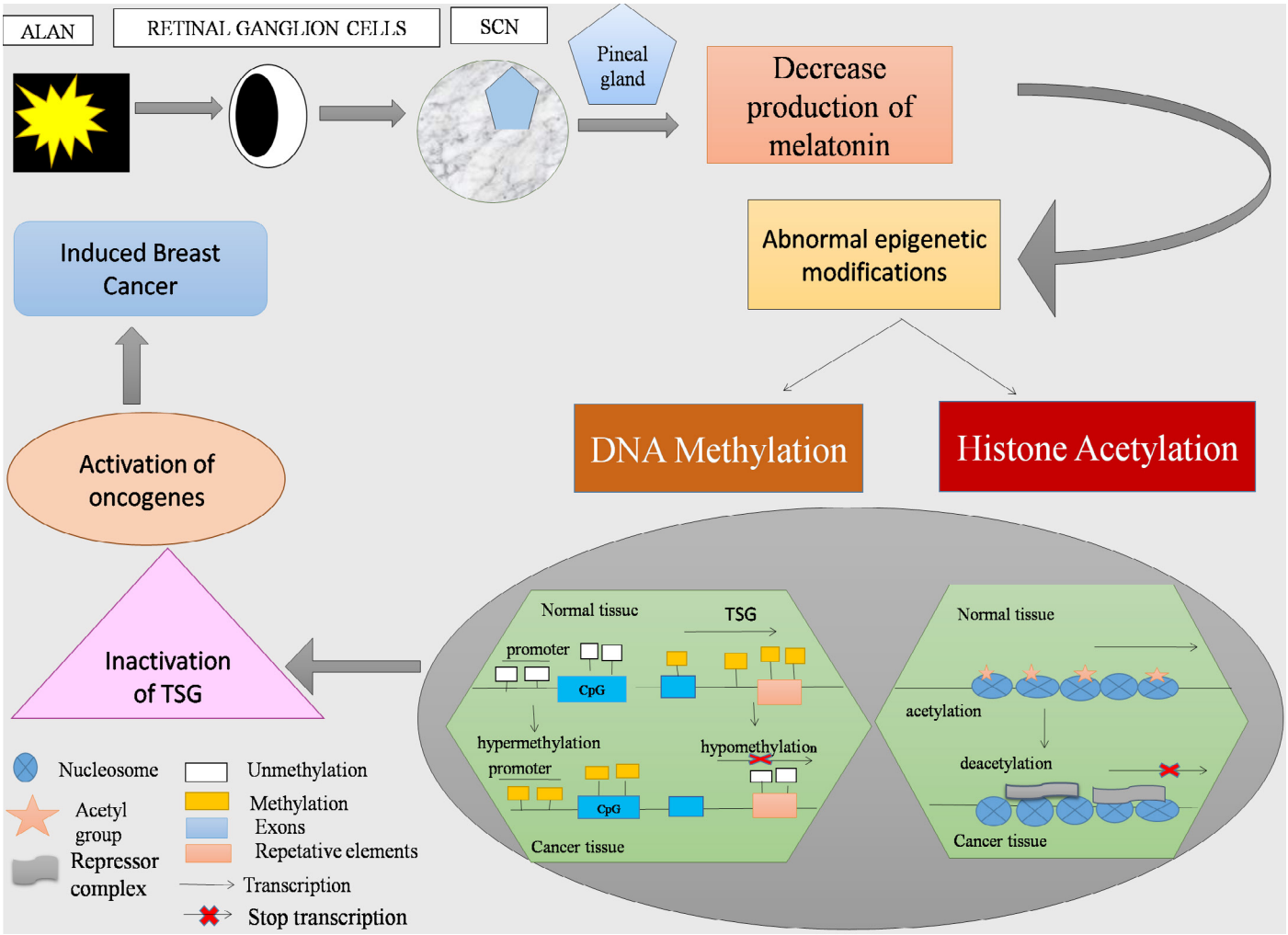

Figure 2: ALAN induced BC: MLT synthesis take place in pineal gland at night, however; ALAN reduced its production which results in abnormal epigenetic changes including DNA methylation and Histone acetylation. The promoter region is unmethylated and acetylated in normal tissue of TSG while it is methylated and deacetylated in cancer tissues. As a result, TSG become inactive and oncogenes become active leading to BC induction.

group and three members of this family are known (Yang et al., 2001). Both DNMT3A and DNMT3B are de novo methyltransferases (Korkmaz et al., 2009) whereas DNMT1 is the continuation methyltransferase and during cell division, it equally transfers the methylation patterns (Lujambio and Esteller, 2008). It is well-known enzyme relates to methylation of DNA and promotes apoptosis (Kochan and Kovalchuk, 2015).

DNA Methylation is the most important mechanism in epigenetic alternations which is involved in regulation of genetic programming and enhances the progression of different types of cancers, including BC (Pouliot *et al.*, 2015; Zubidat and Haim, 2017). These alterations occur only to a cytosine and guanosine sequence in the DNA, known as CpG dinucleotide. These regions are primarily present at the promoter and there is generally no methylation in normal cells (which permit the active gene transcription) while in cancer cells these CpG promoter region are methylated which results in silencing of various TSGs and pro-apoptotic genes (Basse and Arock, 2015; Wajed *et al.*, 2001).

Several kinds of alternation in DNA methylation can take place in cancer, such as hypermethylation in gene-locus resulting in the inactivation of TSG, or hypomethylation of the distinctive genes and repeated sequences (Basse and Arock, 2015). Hypermethylation is the term used for more methylation while hypomethylation for less methylation (Ehrlich, 2002; Blask *et al.*, 2003). These alternations act as a biomarker for identification as well as treatment of cancer (Radpour *et al.*, 2009).

In case of BC, the expression of circadian genes is deregulated. Reports indicated hypermethylation on promoter of PER1, PER2, CRY1 and BMAL genes in BC (Kuo *et al.*, 2009; Shanmugam *et al.*, 2013; Salavaty, 2015). In long term shift workers, Cry2 (related to circadian genes) is hypermethylated on promoter region (Zhu *et al.*, 2011; Steven and Zhu, 2015). Glypican-3 (GPC3), a tumor suppressor gene is aberrantly methylated in MCF-7 BC cell lines. Upon treatment of MCF-7 cells with 1nM MLT, significant increase in the expression of GPC3

gene was observed. The findings suggest that MLT could modulate methylation pattern of this tumor suppressor gene (Lee *et al.*, 2013). In long term shift workers, the miR-34b promoter region is aberrantly methylated which enhanced the BC risk due to ALAN exposure (Liu *et al.*, 2015). Report indicated the relationship between DNA methylation of TSG (BRCA1, BRCA2, TP53, CDKN2A) and night shift workers. It graphically showed the expression of methylation decreases from number of years in these TSG. Results indicted that in night shift workers, BRCA1 and TP53 are hypomethylated compared with non shift workers (Carugno *et al.*, 2019). Hypomethylation of p53 and BRCA1 has been assumed to be induced to counterbalance defects in circadian cell cycle regulation and thus could indirectly increase the risk of cancer.

Effect of ALAN on methylation of oncogenes

Oncogenes included those genes that enhanced cell proliferation and survival (GRØNBÆK *et al.*, 2007). Several types of genes in BC changed the level of their expression due to unusual methylation. In cancer cells, the genome is globally hypomethylated or unmethylated that caused the instability of chromosome, and failure of genomic imprinting might result in the upregulation or more expression of proto-oncogenes (Jovanovic *et al.*, 2010; Hasan *et al.*, 2015). In several proto-oncogenes, the promoter region is hypomethylated or not methylated leading to uncontrolled cell proliferation, cancer progression and development of treatment resistance. The main epigenetic mechanism of BC is the activation of oncogenes due to inactivation of TSG that cause the cancer, including BC (Basse and Arock, 2015).

Oncogenes such as POU4F2 and ERG3 showed different methylation patterns and were up-regulated in BC cell lines. Treatment of BC cells with 1nM MLT, halted the growth of BC cells by down-regulating above said oncogenes via increased methylation. (Lee *et al.*, 2013). CLOCK (related to circadian genes) is hypomethylated on the promoter region in shift workers. (Zhu *et al.*, 2011; Steven and Zhu, 2015). Other independent studies conducted in CLOCK which showed slightly more methylation in BC cases compared with healthy control (Erdem *et al.*, 2017). ALAN showed different results from the methylation of TSG and oncogenes. The results are shown in Table 1.

Effect of ALAN on acetylation of tummor suppressor genes

ALAN caused changes in usual acetylation pattern of TSG (Haim and Zubidat, 2015). The balance between histone acetylation and deacetylation is necessary for controlling the expression of genes. Histone acetylation is promoted by histone acetyl transferases enzyme (HAT) that is concerned with activation of gene transcription, whereas histone deacetylation or hypoacetylation is promoted by another enzyme called histone deacetylase (HDAC) which is associated with repression of gene transcription (Suzuki et al., 2009; Cohen et al., 2011; Li et al., 2013). Changed expression or gene mutations that encode histone deacetylation or hypoacetylation have been associated with induction of cancer while both these promote the abnormal transcription of leading genes and controlled the main functions of cells such as cell propagation, regulation of cell-cycle and apoptosis (Ropero and Esteller, 2007).

Table 1: Effect of ALAN on methylation pattern of genes in BC.

Gene/ Protein	MLT	Normal function	Methylation-Pattern	Effect	Activation/ Inhibition	References
Per 1	↓	TS	-CH3↑	BC	Inhibition	Kuo *et al.*, 2009
Per 2	↓	TS	-CH3↑	BC	Inhibition	Kuo *et al.*, 2009; Shanmugam *et al.*, 2013
Cry1	↓	TS	-CH3↑	BC	Inhibition	Kuo *et al.*, 2009
BMAL1	↓	TS	-CH3↑	BC	Inhibition	Kuo *et al.*, 2009
EGR3	↓	Onco	-CH3 ↓	BC	Activation	Lee *et al.*, 2013
POU4F2	↓	Onco	-CH3 ↓	BC	Activation	Lee *et al.*, 2013
GPC3	↓	TS	-CH3 ↑	BC	Inhibition	Lee *et al.*, 2013
CLOCK	↓	Onco	-CH3 ↓	BC	Activation	Zhu *et al.*, 2011; Steven and Zhu, 2015
CLOCK	↓	Onco	-CH3↑	BC	Activation	Erdem *et al.*, 2017
Cry2	↓	TS	-CH3↑	BC	Inhibition	Zhu *et al.*, 2011; Stevens and Zhu, 2015
mir-34B	↓	TS	-CH3↑	BC	Inhibition	Liu *et al.*, 2015
BRCA1	↓	TS	-CH3 ↓	BC	Inhibition	Carugno *et al.*, 2019
BRCA2	↓	TS	-CH3 ↓	BC	Inhibition	Carugno *et al.*, 2019
CDKN2A (p16)	↓	TS	-CH3 ↓	BC	Inhibition	Carugno *et al.*, 2019
TP53	↓	TS	-CH3↓	BC	Inhibition	Carugno *et al.*, 2019
ESR1	↓	Onco	-CH3↓	BC	Activation	Carugno *et al.*, 2019
ESR2	↓	Onco	-CH3↓	BC	Activation	Carugno *et al.*, 2019

↓: Downregulation; ↑: Upregulation; TS: Tumor Suppressor; BC: Breast Cancer.

Table 2: Effect of ALAN on acetylation pattern of genes in BC.

Gene/ Protein	MLT	Normal Function	Acetylation/ Deacetylation	Effect	Activation/ Inhibition	References
P53	↓	TS	Deacetylation	BC	Inhibition	Proietti *et al.*, 2014
CYP19	↓	Onco	Acetylation	BC	Activation	Korkmaz *et al.*, 2009
ER	↓	Onco	Acetylation	BC	Activation	Saha and Corsi, 2007
c-MYC	↓	Onco	Acetylation	BC	Activation	Saha and Corsi, 2007
STAT3	↓	Onco	Acetylation	BC	Activation	Xiang *et al.*, 2019
BRCA1	↓	TS	Deacetylation	BC	Inhibition	Hill *et al.*, 2009
BRCA2	↓	TS	Deacetylation	BC	Inhibition	Hill *et al.*, 2009
Per 1	↓	TS	Deacetylation	BC	Inhibition	Hill *et al.*, 2009
Per 2	↓	TS	Deacetylation	BC	Inhibition	Hill *et al.*, 2009
Ku-70	↓	TS	Deacetylation	BC	Inhibition	Hill *et al.*, 2009
MMP	↓	Onco	Acetylation	BC	Activation	Bondy and Campbell, 2018

↓: Downregulation; ↑: Upregulation; TS: Tumor Suppressor; BC: Breast Cancer; Onco: Oncogene.

For alternations in chromatin, most important mechanism is the adaptation of histone acetylation and deacetylation. These adaptations cause epigenetic changes due to alternations in expression of gene and cell development which may affect carcinogenesis and propagation (Cui *et al.*, 2018). In cancer, the functions of histone deacetyltransferase are not only limited to their involvement to histone deacetylation, but also played an important role in deacetylation of non-histone proteins. For instance, in vivo and in vitro study, Histone deacetyltransferase 1 linked with the p53 (that is tumor suppressor) and deacetylated it (Ropero and Esteller, 2007).

MLT exhibited anticancer effects in BC. It decreased the MDM2 expression and increased acetylation of p53 in MCF-7 cell lines (Proietti *et al.*, 2014). MLT via its receptor MT1, activated the RORα that controls the expression of SIRT1 (histone deacetylases) and BMAL/ CLOCK. CLOCK (histone acetyltrasferases) acetylated PER1/2 and other DNA repair genes BRCA1, BRCA2, P53 and Ku-70 which reduced the development of cancer due to acetylation activity. Hill *et al.*, have explained, how BRCA1, BRCA2, p53, Ku70, PER1 and PER2 deacetylated and induced BC due to ALAN (Hill *et al.*, 2009). The findings showed below recommend that ALAN causes more expression and abnormal recruitment of histone deacetyltransferases in promote regions could be a regular event in cancer development and progression, resulting suppressed transcription of tumor-suppressor genes.

Effect of ALAN on acetylation of oncogenes

ALAN decreased the production of MLT and enhanced phosphorylation and acetylation of oncoprotein (such as STAT3) that over expressed in BC (Xiang *et al.*, 2019). Hyperacetylation of Proto-oncogenes results in activation of proto-oncogenes while hypo-acetylation of tumor suppressors genes is frequently localized to promotor region causing the genes to be silenced (Audia and Campbell, 2016).

MLT has been reported to decrease the expression of CYP19 protein which is frequently overexpressed in BC cell lines. MLT exhibits oncostatic effects via deacetylation of CYP19 (Korkmaz *et al.*, 2009). In addition, MLT induced hypoacetylation and decreased the activity of matrix metalloproteinase (MMP). Increased expression of MMPs have been noted in various types of tumor which mainly facilitate metastasis (Bondy and Campbell, 2018). CLOCK (histone acetyltransferases) promotes acetylation of different genes such as c- myc and ERα that induce BC due to acetylation (Saha and Corsi, 2007).

The collective findings published previously recommended that ALAN causes the more expression and abnormal recruitment of histone acetyltransferases in promoter regions ehich could be regular event in cancer development and progression, resulting in activation of oncogenes. ALAN mediated acetylation of TSG and oncogenes has been shown in Table 2.

Conflict of interests

The authors declare there is no conflict of interest.

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