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Research Article

The Oxidative Stress Influence in Epigenetic Mechanisms and its Related with Diseases

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Abstract:
The present review was suggested to explain the effect of oxidative stress (OS) which promote by excessive generation of free radicals like reactive oxygen (ROS) or nitrogen species (RNS) from exo and endogenous factors in the cells in the epigenetic processing's included DNA methylation (DNAM), non-coding RNA and histone modification, these mechanisms regulate gene expression that might be affected in wide range of diseases, oxidative stress impact in epigenetic in different levels included promote nucleotide modification, inhibition or eliminated specific enzymes activity, structural changes of proteins in these pathways, nevertheless, the essential free radicals function in cell processing, it implicated in up and/or down regulation of some gene expression via epigenetic alterations. significant contribution of OS in epigenetic changes via different mechanism, particularly in absence of antioxidant defense, that effect in cell components, changes in some physiological markers like hormones, enzymes, regulatory factors lead to tissues changes and organ dysfunction.

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INTRODUCTION

Changes of histones, DNA sequences and non -coding RNAs, in addition to DNA sequence changes, Which result to the chromatin remodeling to enhance or obstruct level of gene expression. At the chromatin level the gene expression silencing is essential to the natural life of eukaryotic organisms and it is essential in the vital mechanisms controlling like genomic imprinting, embryonic development and differentiation[1], three main mechanisms of epigenetic regulation are demonstrated below:

DNA Sequences Methylation: One of the well-studied mechanisms in epigenetic is DNA methylation (DNAM).

Generally, it is genic silencing synonym, because it shapes of chromatin as an inaccessible state for the transcription process. In DNAM methyl group (CH3) was addition to carbon 5 of a cytosine, in general, regions rich with 5'-Cytosine-phosphate-Guanine-3' (CpG) dinucleotides found in asymmetric pattern in the genome and this motifs in the promoter regions of gene is known as CpG Island (CGI)[2,3]. About 30000 un methylated CGIs in the human genome, that warrants the potentially active constitutive genes configuration. The motif of methylation is involved in cell differentiation., therefore the methylation dysregulation lead to several diseases[4]. DNA-Methyltransferases (DNMTs) catalyzed DNAM process, There are four kinds of DNMTs, DNMT3A and 3B contributed in de-novo DNAM through development, DNMT1contributed in methylation patterns maintaining after replication of DNA and DNMTs represented in companied with de novo to induce chromatin remodeling complexes without catalytic site which is important in embryonic development[3,5]. This process is associated with the dosage compensation in mammals and genomic imprinting [6-9]. In spite of this silencing is made by DNAM, it is an important to use whole epigenetic machinery to correct process development.

Histone Modifications: The second epigenetic mechanism is Histone Modifications based on the chemical modification in chromatin. As well as of other proteins, posttranslational alterations involvement in proteins processing like acetylation, methylation, ribosylation, phosphorylation, sumoylation and ubiquitination[10,11]. Whose major function is DNA accessibility regulation, In general ribosylation and phosphorylation stimulate transcription of gene and euchromatin, while sumoylation promotes gene silencing and ubiquitination can has a dual role[12-21].

Non-Coding RNAs: A new demonstrates groups of epigenetic are regulators Non-coding RNAs (ncRNAs) that can control on gene expression without DNA sequence changes. Before ncRNAs discover, it considers as non -benefit sequences accumulated during evolution[22]. Nevertheless, the DNA Elements project Encyclopedia involved in the non-coding RNAs classification with known functions also detection of novel ncRNAs[23-25]. furthermore, ncRNAs are categorized into long ncRNAs (lncRNAs) and small ncRNAs which categorized to microRNAs (miRNAs), P-element Induced Wimpy -interfering RNAs (piRNAs) and small interfering RNAs (siRNAs).

The firs epigenetics concept was suggested by Waddington in 1939, who reported "the actual interplaying between genes and their products to phenotype into being"[26], Later further explanation was updating, Holliday[27] and Deans and Maggert[28] proved that epigenetic is gene expression regulation mechanisms without alteration in DNA sequences. These regulations are implemented via different pathways like DNAM, histone modifications and noncoding RNAs[29]. Reports have been proved that these processes are essential in the regulation of gene expression in the tissue, genomic imprinting and inactivation of X -chromatin. All these mechanisms work together to constructed "the epigenetic landscape" to demonstrate unique features and patterns division in cell types[30].

The first epigenetic mechanism that well understood is DNAM, although of DNAM is a stable epigenetic symbol, which may be token off resulted from passive or active demethylation activities. Passive demethylation can be implemented via multiple DNA replication cycles in the lack of methylation functional enzymes[31], DNMT enzymes downregulation[32]. DNMT cytologic localization[33] and DNMT recruitment impairment on DNA[34]. The 5mC elimination has been implemented via of 5-hyroxymethylcytosine formation, oxidized via the ten-eleven translocation (TET) enzymes. further processed were happened by thymine DNA glycosides forming a site would be repaired by the BER system or deaminated by AID deaminated produce 5 -hydroxymethyl uracil (5hmU), that removed by the TDG[35,36].

Oxidative Stress (OS): the redox state disturbance that proved implicated in different disease Oxidative stress is known as OS, the disequilibrium between free radicals included ROS or RNS and the antioxidants defenses mechanisms in the biological system[37]. ROS are higher activity molecules including different chemical species, like hydrogen peroxide (H_2O_2), superoxide anion (O_2-) and hydroxyl radical (OH). These active molecules can be interaction with cell components as well as proteins, lipids and DNA, RNA cause metabolic pathway alteration, molecular damage which implicated in different diseases pathogenesis[38]. The main source of ROS is mitochondria resulted from electron transfer via ATP generation[39,40]. High level of ROS also generated from exogenous factors like ultraviolet irradiation and radioactivity. Cell used antioxidant defense mechanisms to prevent harmful effects of OS., these mechanisms are including enzymatic and non-enzymatic pathways. As well as glutathione

peroxidase, glutathione-S-transferase P1, superoxide dismutase, sulfiredoxin, peroxiredoxin and catalase[41]. the non-enzymatic molecules consist of vitamins C, E, A and glutathione which have low molecular weight[42].

The Correlation Between Oxidative Stress and Epigenetics: Oxidative stress was happened as a results of ROS accumulation., evidences found that its increased with age and it is accompanied with cell repair machinery decline, which will causes high level of DNA lesions lead to mutations like in the epigenetic state disruption. several examples of tight interconnection interplays between the OS effects and the epigenetic landscape are discussed below, as well as ROS can effect on the methylome via the oxidized DNA damage formation by pyrimidine and 5-methyl cytosine (5mC) hydrolyzation, regarding to similar structure with the epigenetic signals associated with 5-hmC that can be interfered[43]. the DNA demethylation can be affected also via TET-mediated hydroxymethylation and DNA oxidation[44]. Indirectly, ROS can change the epigenetic system activity because histone-modifying enzymes related to intracellular essential metabolites levels like Fe, Acetyl-CoA, ketoglutarate, NAD+and S -adenosylmethionine, proving that the alteration in epigenetic are strong associated with global energy levels and cellular metabolism the cell[45], Thus OS can globally effect on the cell more than one levels, like DNA and histone modifiers, that will impact in the epigenetic landscape directly.

Oxidative Stress Effect on DNA Methylation: The DNA methylation alterations are generated from OS mainly according to the function and activity of DNMTs changes. Numerous reports in cancer proposed that the OS induction mediated by H2O2 raised DNMT1 activity and linking to the tumor suppressor genes promoters[46]. Furthermore, OH stimulate a global hypomethylation according to the interference of DNMTs-DNA linking capacity[47]. it has been found that high OS state stimulate catalytic cycle changes of iron and inhibition TET family DNA demethylases, thus DNAM levels was increasing[48]. More cited studies indicated that high OS situations stimulated via ROS generation increase levels of 8-hydroxydeoxyguanosine (8-OHdG) which promote a conformational modification which change the state of chromatin from active to repressive state[49]. furthermore, 8-OHdG prevent DNMTs-DNA binding, results to a global genome hypomethylation[50,51].

Additionally to the directly DNA modification , ROS also impact DNAM pattern, that associated with transcription repression, the primary methylation In mammals are targeting cytosines in CpG dinucleotides. In spite of CpGs are methylated genome-wide, regions with high density of CpG dinucleotides are especially hypomethylated[52]. the category of DNAM enzymes included DNMTs and the demethylases, DNMTs used S-adenosylmethionine (SAM) to methyl group transfer to C, while TETs oxidize 5-methyl cytosine (5-mC) to 5 -hydroxymethyl cytosine (5-hmC) in an Fe(II)-, ascorbate, O_2-dependent reaction and a-ketoglutarate[53,54].

In some disease pathologies global DNA hypomethylation has demonstrated, most islands (CpG) are hypermethylated[55-58], these methylation is changed included specific hypermethylation and global hypomethylation which have been proposed to be related to oxidative stress.

However, the direct 5-mC oxidation to form 5-hmC cans consequence to DNA demethylation. 5-hmC prevents maintenance of Methyltransferases DNMT1, therefore, suitable inheritance of methylation motif blocking and caused indirect demethylation of CpG region[59].

An approach of DNA hypermethylation under OS is TET proteins inhibition. As Fe(II)- and a-KG-dependent dioxygenases, it can be inhibition by iron oxidation. Through the catalytic cycle, Fe(III) and Fe(IV) is oxidized from Fe(II)[54] which regenerated by ascorbate[53]. In condition of OS, this regeneration is concerned, consequence to enzyme inhibition and global 5-mC levels increasing[60]. Likewise, 5-hmC is important eliminated in SY5Y neuroblastoma cells exposure to OS[61]. Moreover, in murine cerebellar granule cells, TET1 knockdown lead to cell death, reporting that OS caused TET1 inhibition could be involved in the pathogenesis of some disease[62].

Both methylation patterns., global hypomethylation and CpG islands hypermethylation can be implemented by DNMTs relocalization. The repair proteins discriminate 8-oxo-dG and induce DNA Methyltransferases DNMT1 maintenance, that made a structure with the de -novo DNA Methyltransferases DNMT3B, the histone H3K27 Methyltransferases and EZH2 SIRT1 deacetylase[63,64], which is mainly induce CpG island promoter regions activity, when present high level of 8-oxo-dG and DNAM and H3K27me3 enhancing H3K4me3 and H4K16ac levels were reducing. Take together, DNMT3B, DNMT1 and SIRT1 are missed from other genomic location. thus, low expressed genes CpG islands were hyper methylated in an in vivo under OS exposure, while housekeeping genes were unaffected[63].

Effect Over Histone Modifications: Histones are extensively changed when exposure to free radicals and

are glutathionylated in a redox-sensitive way, that impact its stability and folding like their capability to be post-translationally changed. Since histones are the most chromatin proteins, any alteration in abundance, post-transnational modification (PTMs) or structure will have acute effect on the chromatin global structure, gene expression effectiveness, genome replication and stability, several reports are also clarified that OS promote alteration modified in histones methylation and acetylation as it represents over the maintain the chromatin state enzymes. OS generate via H_2O_2 can induce histone alteration complexes to inhibit active tumor suppressor genes. In spite of OS impacting histones posttranslational modifications which involved in chromatin regulation, it does not effect in the similar manner according to the variant sensibility to the OS of the Histone Methyltransferases, HDMs and HATs.

In a same way to DNAM, one of the notable alteration is histone deacetylases (HDAC), that eliminate their activity by cigarette smoke[65]. The patients with COPD demonstrate lower level of HDAC2 activity that raised acetylation in histones H3 and H4 of the NF-kB promoter therefore pro-inflammatory genes dys -regulation[66].

Oxidative stress Effect on Non-Coding RNAs: The regulation of transcription depended on non-coding RNAs is also change in diffident manner by OS, as it has demonstrated in modifications of histones and DNA. To yet, there are several microRNAs whose their generation changes due to cellular OS changing[67,68]. like, in epithelial cells miR-200c is up-regulated as consequences of increasing ROS that lead to elevate senescent cells and apoptotic via the its target gene ZEB1action[69]. some miRNAs is stimulate by transcription factors that are sensitive to elevated ROS level like miR-27a/b miR-506 , miR-200 and miR-206 via its target genes[70,71-73]. furthermore, the miRNAs processing from primary structure is regulated by DGRC8-Drosha complexes which eliminated the processing capacity of DGRC8 by OS, that observed on Fe(III) for its action and therefore corresponding mature miRNA is down regulated[74].

some miRNAs implicated in the detoxification pathway of NRF2-ARE, according to its natural inhibitor KEAP1 or the targeting of NRF2, or indirect action of genes which regulate the previous signaling pathway, like, NRF2 expression is inhibited by miR-101 in breast cancer cells to activate its sensitivity to suppress proliferation and OS[75]. in esophageal squamous cell carcinoma miR-432-3p directly linked to the coding region of KEAP1 to down regulating and transcription of downstream genes up-regulating of the NRF2-ARE pathway[76]. In neuroblastoma cells miR-7 relieves the OS via targeting KEAP1[77]. in different cancer cell miR-200a linked to the 3 UTR sequence of KEAP1 causing degradation of its mRNA[78-80].

On the other hand, Several miRNAs Expression have been clarified to be changes under OS, Magenta in vitro experiment have estimated ROS impact in the miRNAs levels in the endothelial cells. Study found that human umbilical vein endothelial cells Exposure to H2O2 causes significant miR-200c and miR-141 up-regulation. Yu[81] have clarified the miR-200c role in the ROS-associated apoptosis regulation.

miR-21 is one of the miRNA types with role in the response to OS which miRNA has been found to be stimulated via ultraviolet b in cell line via ROS-mediated MAPK pathways[82]. Conversely, human umbilical vein endothelial cells miR-21 has proved to ROS homeostasis interrupted and antioxidant responses disturbance in cellular glucose variability[83]. miR-145 is up-regulated through OS is. Moreover, lncRNAs have been found to be associated with OS, like level of cancer-associated lncRNAs were increased in the some disease like myocardial infarction.

CONCLUSIONS

According to the information mentioned above, oxidative stress effect in chromatin at different levels included DNA, histones, structural DNA-binding proteins and histone modifiers. As well-known that OS is implicated in disease pathogenicity. However, belong to the mechanisms of epigenetic affected by OS, the direct association of OS in disease has not demonstrated, the chromatin alterations mediated by ROS have significant impacts in initiation and progression of some diseases. From these literature review can be concluded the significant ROS role in DNAM included global hypo methylation and specific gene hypermethylation and methylation enzymes, regarding to histone, its affected by ROS or NOS at methylation acetylation and phosphorylation. Oxidative stress also effected and affected by non-coding RNA included microRNA and LncRNAs in addition to other types of RNA, other epigenetic mechanisms also undergo the OS changes. Further investigation need to be implemented for more information's particularly in common diseases.

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