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Review Article

The Role of Epigenetic Mechanism In Pathogenesis of The Osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is one of the musculoskeletal disorder defined by the degeneration of cartilage, sub-chondral bone remodeling and tenderness of the synovial membrane. The disorder is multifactorial disease of the joints or knees, which is considered to be linked with ageing, environmental, hormonal, and genetic factors linked with the progression and beginning. **Objective:** To assess the role of epigenetics in the pathophysiology of osteoarthritis. **Methods:** Literature was searched through PubMed, Googlescholar, Sciencedirect by using the MeSH words of osteoarthritis, Musculoskeletal disorder, Epigenetic mechanism in osteoarthritis. In this review, we discussed our emerged understanding of epigenetic mechanisms in pathogenesis of OA that can be used by joint tissue to ensure homeostasis and find possible therapeutic targets in the prevention of disease. **Results:** The micro RNA fields have most advanced in OA, probably because micro RNAs are essential genes as a result of manageable by standards molecular methods. The severity of difference between these two (Dicer & miR 140 null animal) apparently indicated the additional more crucial miRNAs remains to emerge or be identified. **Conclusions:** The recent studies showed that many mechanisms play an important role in the pathophysiology of OA and lead to a new researches avenue or therapeutics. The micro RNA fields have most advanced in Osteoarthritis (OA), probably because micro RNAs are essential genes as a result of manageable by standards molecular methods.

INTRODUCTION

Today with the advancement of molecular biology, osteoarthritis is thought to be a multifactorial disease [1]. Osteoarthritis (OA) is one of musculoskeletal disorder defined by cartilages degeneration, sub-chondral bone remodeling and tenderness of the synovial membrane [2]. It disturbs millions of peoples aged up to 55 years or above, frequently leading to the physical weakness and also reducing life's quality [3]. It badly affects hands, the knees, and hips. It's more common in the women [4]. While OA is to related with aging, it has also linked with a number of both non-modifiable and modifiable risk factor such as lack of exercise, obesity, genetic disposition, the thickness of bone, gender or sex, occupational injuries, and trauma [5]. While the exact cause and the pathophysiology of OA has not completely clarified, the disorder is multifactorial disease of the joints or knees, which is considered to linked with ageing, environmental, hormonal, and genetic factors linked with the progression and beginning [6].

Epigenetic mechanisms: Epigenesis is a term that was firstly devised by a scientist Waddington 50 years ago, to state how genotypes bring out to different phenotypes, then there is a view that is primarily different from the definition of 'without a change in the basic DNA sequence results in the heritable phenotypic transmission' that is mostly used nowadays [7]. Today epigenetic mechanisms typically consist of DNA methylation of CpG dinucleotides and post-transcriptional modifications of histone proteins and also include non-coding RNAs (such as microRNAs)

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that mediate gene-silencing [8]. Epigenetic mechanisms are formed to be found in several taxa, of which the DNA methylation is one that has been broadly studied in the mammals which occur at CpG dinucleotides. It is also found that in mammals, DNA methylation can occur outside the sites of CpG, which has been reported in embryonic stem cells as an example. However, cytosine is specifically methylated to 5-methylcytosine, later it was found that it can also be transformed to the 5-hydroxy-methylcytosine, which play a crucial role in the epigenetic [9].

DNA methylation: DNA methylation is defined as adding the methyl (CH3) group at cytosine base which results in5-methylcytosine (5mC). However, its oxidative derivative, 5-hydroxymethylcytosine (5hmC) forms which lead to many succeeding steps to unmethylated cytosines [10]. DNA methylation is modulated by the enzyme DNA-methyl transferases (DNMT1,-3a, -3b). However, DNA methylation occurs at the CpG dinucleotides that are clustered close to the gene promoters and suppression of genes expression is also caused by them [11]. The localized grouping of CpG dinucleotides occur in some areas which are named as Cp-G island where the DNA-methylation normally occurs. CpG islands regions are very conserved methylated parts that are present in a close concurrence (up to 2kb) of the Cp-G island where tissues specific methylated DNA appears [12]. For the functional importance of the DNA-methylation, the genomics localization of Cp-G site is very crucial. In enhancer and promoter's regions on the genes, the methylation has linked with silencing of gene, but methylation is linked with increased gene expression in gene body [13]. However, many different studies explored that methylation changes of oncogenes comprehensively deliberated then altered methylation. Roach has identified modifications in the methylation of genes promoter regions such as ADAMTS-4, MMP13, MMP3, and MMP9. In the promoter site of such enzymes, the entire proportion of non-methylated sites in the OA cartilage seems to be increased. DNA hypomethylation position by OA chondrocytes is linked with messenger RNA (mRNA) and protein expression of ADAMTS-4 [14]. It is studied that worldwide estimation of methylation in normal and OA cartilage is uniform and shows that some promoters of gene remain hypomethylated during chondrogenesis. Kim et al. ha currently stated that expressions of SOX9 in OA cartilage is decreased and are concerned to improve the methylation status of the promoter. These alterations inhibit the binding of regulating factors such as NF-Y and CREB [15]. DNA methylation is involved in transcriptional modulation of growth differentiation factor-5, which is a factor in synovial joint development, repair and maintenance. It has been proved that genetic consequence of the OA predisposition SNP rs143383 is controlled epigenetically with methylation on DNA [16]. The RUNX2 (Runt-related transcriptional factor-2) is perilous for the osteoblast distinction and formations of bone. Studies indicate that transcription of Runt related transcriptional factor-2 (RUNX2) gene has been modulated by methylation at Cp-G sites and also determined the RUNX2 accessibility in Osteoarthritis cartilages for trans-activation of the genes, and MMP13 [17]. Clustered regular inter-spaced short palindromic repeats and CRISPR linked with protein 9 nucleases (CRISPRCas9) based epigenome correction tool have enabled targeted Cp-G methylation on promoters of the two loci such as IL6ST and BACH2 [18].

Histone modifications: Histone modifications modify the chromatin assembly, generating 'open' and 'closed' states, and these variations regulate gene expression under specific conditions [19]. Working approximately with the methylation of DNA, histone modifications include phosphorylation, acetylation, ubiquitination and methylation [20]. These modifications regulate the expression of gene by regulating the transcriptional factors or machinery. Recent researches indicated that acetylations and de-acetylation of histone proteins plays a crucial roles in pathophysiology of Osteoarthritis by disturbing chondrocyte catabolic and anabolic process. Histone (C2H30) acetylation enhances gene expression by allowing the transcriptional factors or components to approach to transcriptional-machinery. Histone acetylation has modulated by the histone's acetyl-transferase. Histone deacetylation is considered to be involved in suppression of expression of the gene. Histone de-acetylation is modulated by enzyme HDAC (histone de-acetylases) [21]. The two categories of deacetylases are classical HDACs, which use a zinc-catalyzed deacetylation mechanism and sirtuin deacetylases, which need NAD+ to eliminate acetyl groups. Various transcriptional activators or repressors serve as HAT or HDAC. HDAC inhibitors (HDACi) have been modified to treat various neoplasms. These molecules also hold the ability to treat rheumatoid arthritis in animal models [22]. The development of OA is linked with a number of HDACs expressions and stimulation. Another publication shows that stimulation of these HDACs increases cartilage demolition. For example, HDAC4 null mice showed unusual chondrocyte hypertrophy and successive early ossifications in chondrocostal cartilage [23]. These results found that HDAC4 has a chondroprotective role in inflammatory situations. Present study indicates that HDAC4over-expression decreases interleukin-1b (IL-1b) expressions and prevents RUNX2 and MMP-13 expressions in doses dependent way [24]. In OA patients, the expression of HDAC7 increased which may contribute to cartilage degradation by improving the MMP-13 gene expression. Inhibitions of the

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HDAC-7 in-vitro result in inhibition of the inflammatory factors induce expressions of Mmp-13 [25]. Moreover, levels of HDAC1 and 2 have been reported to be elevated in OA cartilage [26]. A nuclear factor like-2 (Nrf2) is a principal transcriptional factor that regulated the anti-oxidant defense systems. Acetylation of Nrf-2 increases its transcriptional ability and down-stream targets and this acetylation has shown to deliberate protected in the animal's models of inflammatory and oxidative stress-related disease [27]. Many current Nrf2 activators were instigating in various cruciferous vegetables such as cabbage exhibiting anti-inflammation and antioxidant events [28]. Remarkably, HDACs (histone de-acetylases) inhibitors, tri-chostatin A, and sodium-butyrate inhibit MMP13 expression and block the dissolution of tissues. As a result of HDACi action the chondro-protective role of HDACi is also reinforced by the reduced damage to cartilage which was detected in in-vivo models of inflammatory arthritis. However, mechanisms by which HDACi modulate suppression of cytokines-induced metalloproteinase expression remain unknown [29]. Another study reported that H3K27me3 demethylases regulated in vitro chondrocytes activities in the Osteoarthritis (OA) by TGFb inhibitions induced expression of gene. Targeted the H3K27-me3 de-methylases inhibition could provide a potential in OA (Osteoarthritis) therapeutics [30].

Non-coding RNAs miRNAs: Micro-RNAs are single standard RNA of 19 to 25 nucleotide that negatively modulate post-transcriptional gene expression. They can regulating expression of gene via binds with 3'- UTR (untranslated region) of targeted mRNA which is partially or completely complementary to mature miRNA [31]. Micro RNAs are transcribing from the miRNAs genes as pri transcript (primary transcript) in nucleus. After being transported in to cytoplasm, hairpin structure of pri-miRNA cleaved by protein Dicer and matured into micro RNA [32]. miRNAs are involved in many biological methods, such as developmental, pathophysiological & physiological process and they regulated, change the expressions of several genes. After binding to target sequence, they silence genes either by breakdown into their specific targeted mRNAs or by preventing gene translations. About 500 human miRNAs have been defined earlier [33]. Most of the studies published in last many years widely studied role of micro RNAs by identifying many miRNA candidates which plays a crucial roles in the homeostasis of cartilages and Osteoarthritis pathogenesis. Studies indicate that blocked expression of miR-107, miR-146, miR-148, and miR-149 in the cell was also significant in initiation and development of OA. Existing evidence proved that altered level of miR-145 was linked with matrix metabolism in OA [34]. Over-expression of miR-483-5p can inhibit some members of MAPK (mitogen-activated protein kinase) pathway, elucidate that matrix production increased in human chondrocytes [35]. miR-27a seems to be the most studied miRNA in OA, current indication has reported that expression's on MMP13 in Osteoarthritis the cartilages in comparison to the normal's cartilages has to regulated by the miR-27 [36]. miR 92a 3p modulates cartilage specific gene expressions in chondrogenesis and deprivation by targeting HDAC2 which shows that histone hyperacetylation has an impact on increased expression of extracellular matrix (ECM) [37]. In cytoplasm miRNA can direct binds with anabolic and catabolic mRNAs where they regulating post-transcriptional expressions of genes and suppress translation. Another study has shown that miRNAs have a regulatory impact on expression of the anabolic and catabolic genes in Osteoarthritis (OA), which occur upstream previous to their transcription. miRNAs targets upstream signaling pathway such as WNT or beta Catenin pathways, NF kappa-B pathway, SDF1or CXCR4 pathway and SIRT1or p53 pathway, which was found to regulated by micro RNAs in chondrocyte during progression of Osteoarthritis [38]. MiR-365 is involved in catabolic processes: it's up regulating in Osteoarthritis chondrocytes cultures has induced by inhibitions of its targeted genes histone de-acetylase 4 (HDAC4). Additionally, miR-365 is a negotiator of the inflammatory responses [39]. Hypoxia inducible factor-1α modulates chondrogenesis by modulating SOX9 expression as well as autophagy and apoptosis in chondrocytes [40]. MiR-222 reduced the chances of chondrocyte apoptosis and extracellular matrix degradation via targeting HDAC4. Followers of the TNFRSF (TNF-receptor super-family) are imperative inducing the apoptosis via activation [41]. Autophagy is a biochemical process of the maintaining homeostasis in normal cartilage [42]. microR-181 is differential expresses in the cartilage of Osteoarthritis patients which downregulate the expression of BCL2. Thus, miR-181 could be use as potentially therapeutic targets in OA treatment [43]. In OA patients we found circulating miRNA signature by using high resolution miR-array. Three signature miRNAs were found which are miR-671 3p, miR-140-3p and miR 33b 3p, which act as potentially biomarkers to the estimation of Osteoarthritis probability and development [44]. In spites the facts that numbers of miRs and research papers are involves in the pathogenesis of OA has increasing significantly, not any miRNAs bio-markers had been identified which can be used in the initial detection of the diseases, because OA is a heterogeneous multifactorial disease. However, the above described miR signatures differently respond to stimuli in the initiation and development of OA. Additionally miRNAs based

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therapeutic options are delayed because of the heterogeneity of disease. Clinical trials should be taken for some of these miRNAs which provides the auspicious therapeutics targets.

Other non-coding RNA: Extensive disturbances in miR expression have chiefly focused on significance of ncRNAs to OA. Thus, we are beginning to study and understand about involvement and nature of other ncRNAs in Osteoarthritis (OA), piwi interaction's RNAs, snoRNAs (small-nucleolar RNAs) and long-non coding' RNAs (lncRNAs). In last's year an insight to have special role in the Osteoarthritis that appeared for first time. Small nucleolar RNAs (SnoRNAs) mediated enzymatic modification of the other species RNA, such as rRNAs, by formation of ribonucleo-protein complexes with enzyme. These alterations involve pseudo-uridylation and ribose-methylation [45]. PiRNAs make RNA protein complex with the Pi (piwi) proteins, also linked the both epi-genetic and post transcriptional genes silence genetic compounds [46]. PiRNAs are existing in the germ-line cell's and held function in the part to silences retro-transposon [47]. LncRNAs are greater than 200 nucleotides and are involved and may be vital in various biological methods like in diseases and development. Dysregulated lncRNAs expressions plays a significance roles in the inflammatory related disorders and have been demonstrate as beings associated with progression of OA and damaged cartilage [48]. Last published data suggests that lnc-RNA DANCR (Differentiations Antagonizing Non-Proteins Coding RNAs) was recognized to promote chondrogenesis by upregulating SMAD3 and STAT3 [49]. Research on the epigenetic of the OA is still inception but recent studies show that many mechanisms will plays an important roles in patho-physiology of OA and will leads to a new researches avenue or therapeutics. The micro RNA fields have most advanced in OA, probably because micro RNAs are essential genes as a result of manageable by standards molecular methods. Dicer null mice demonstrated the importance of micro RNAs in large bone formations, while deletion in single micro-RNA; miR140 have clear development phenotypes with an initial on-set of OA. The severity of difference between these two (Dicer & miR 140 null animal) apparently indicated the additional more crucial miRNAs remains to emerged or identified. Conditionally the null animals, includes iR-140 form, still needed to generates renowned the act of the micro-RNAs in developments and diseases. Various other disputes also remains, particularly in term of the micro-RNA targets identification, these targets are more probably to identifying the new pathway which involved in progression of OA. Therapeutically the miRNAs specific inhibitors, modified lock nucleic-acids have to be previously undergoing in evaluations and can expected to explore in OA

CONCLUSION

To date epigenetic function of the lncRNAs in reaction to inflammations and potential to regulate the chondrocytes homeostasis are unknown completely; it also expected that the interests of research in present field will be essentially increases over coming's years and provides with new therapeutics target to treatment the cartilage degenerations.

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