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Epigenetics and Rheumatoid Arthritis: Decoding the Interplay

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Abstract:- Rheumatoid arthritis, or RA, is a type of chronic inflammatory disorder that is defined by inflammation of the joints, pain, and joint degeneration. Thus, although genetic predispositions play a role in RA development, they are insufficient to explain differences in the disease's initiation and activity. Epigenomics, referring to changes in the phenotype of a gene or group of genes brought by modification of the DNA molecule without altering its base sequence, offers important information on RA's multifactorial etiology. The present article aimed at discussing the various epigenetic features in RA such as DNA methylation, histone modification, and non-coding RNA. These changes include, hypomethylation of the pro-inflammatory genes and hypermethylation of the anti-inflammatory genes and this promotes inflammation in the body specifically in RA. Other epigenetic abnormalities causing distortion of disease pathology include dysregulated histone modifications and non-coding RNAs. Knowledge of these epigenetic changes have brought about the intervention strategies in the form of epigenetic therapies. Azacitidine, vorinostat and miRNA based therapies are some of the classes of drugs which demonstrate efficacy in preclinical and clinical trials. That nevertheless there are some limitations that researchers are yet to embrace regarding specificity, delivery, and the true interactions between epigenetics. It is proposed that the further research should be concentrated on the development of precise or pharmacogenomic medicine approaches, the combination of genetic and epigenetic aspects of the drug treatment. In this context, the present review of the epigenetic targets and therapies clearly brings out the possibilities of im-proving RA management and the quality of life of patients through epigenetic interventions.

Keywords:- *Rheumatoid Arthritis, Epigenetics, DNA Methylation, Histone Modifications, Non-Coding RNAs, Pro-Inflammatory Genes, Anti-Inflammatory Genes, DNA Methylation Inhibitors, Histone Deacetylase Inhibitors, miRNA-Based Therapies, Autoimmune Disease, Inflammation, Gene Expression, Personalized Medicine, Epigenetic Therapies.*

I. INTRODUCTION

Rheumatoid arthritis (RA) is arthritis that is chronic and systemic, and is manifested by inflammation, pain and destruction and joint deformity. Influencing one percent of the population, RA greatly reduces the quality of life and, if left uncontrolled, can result in severe disability (Alamanos, & Drosos, 2005). Although there is genetic influence on RA development, it is not adequate to respond for onset and progress of the disease differences. Epigenetics, that is the modifications in the genetic programming of cells that are not coded in the strings of DNA but which can be passed to successive generations ,holds the keys to the intricate mechanisms of RA (Feinberg, 2007). This paper focuses on RA epigenetics and reviews how these modifications are involved in the development of the sickness, as well as potential treatment options for the diseases.

➢ *The Fundamentals of Epigenetics*

Epigenetic modifications regulate gene activity and expression through several mechanisms: Epigenetic modifications regulate gene activity and expression through several mechanisms:

- *DNA Methylation:*

Cytosine methylation mainly involves the attachment of one to three methyl groups in DNA molecule commonly at CpG dinucleotide and mainly functions to inhibit gene transcription (Bird, 2002).

- *Histone Modifications:*

Post-translational modifications including acetylation, methylation, phosphorylation, and ubiquitination that star alter histone structure and thereby gene activity (Chi et al, 2010).

- *Non-Coding RNAs:*

Such non-coding RNA molecules includes micro-RNA (miRNAs) and long non-coding RNA (lncRNAs) that modulate genes expression in post-transcriptional level (Bartel, 2004).

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II. MATERIALS AND METHODS

Pubmed, embase and the cochrane central register of controlled trials were searched to obtain articles related to epigenetics in RA. The identification process applied to the articles was based on certain terms, including 'rheumatoid arthritis' and 'epigenetics', 'DNA methylation', 'histone modifications', 'non-coding RNAs', 'epigenetic therapies'. The search was then narrowed by adding the words treatment and therapeutics. Furthermore, in order to make no omit any related work, the reference lists of the identified articles were carefully scanned for any other related research. This systematic approach was intended to obtain a broad number of research studies and clinical trials regarding to epigenetic processes and potential emergent treatments for RA

➢ *Epigenetic Mechanisms in Rheumatoid Arthritis*

- *DNA Methylation*

The studies also pointed out that DNA methylation was significantly different in RA which altered the expression of genes and it made the disease inflammatory (Richardson, 2003). Imbalance of DNA methylation in patients with RA includes hypomethylation of pro inflammatory genes and hypermethylation of anti-inflammatory genes.

✓ *Pro-inflammatory Genes:*

Such as, hypo methylation of promoter region responsible for cytokines coding genes like IL-6 and TNF-α leads to their overexpression (Wada and Kanwar 1999). This overexpression sustains the inflammation within the ST and the tissue destruction leading to inflammation results in pain and functional disability.

✓ *Anti-inflammatory Genes:*

Aberrant DNA methylation of genes that is implicated in the regulation of Tregs is hypermethylation of foxp3 gene (Peeters et al . , 2011). Tregs have an important role as the major immunosuppressive cells that are involved in maintaining immunotolerance and avoiding autoimmunity. Because of epigenetic alterations, they exhibit reduced effectiveness in combating the autoimmune assault on joint structures.

- *Histone Modifications*

Thus, changes in histone modifications are also instrumental in the development of RA. They allow or prevent the genes from being turned on or off depending with the ease with which the DNA is made available to the machinery that encourages the transcription process (Kaeberlein et al., 1999).

✓ *Histone Acetylation:*

Histone acetyltransferases (HATs) enhance the acetylation status of histones and consequently allow the transcription of inflammatory genes by antagonizing the chromatin compaction. On the other hand, histone deacetylases (HDACs) take off the acetyl groups making the chromatin dense and the genes are turned off (Hsieh et al., 2013).

✓ *Histone Methylation:*

Histone methylation can be considered as a transcriptional activator if used in right context or that of a repressor. The studies have shown that, malfunctioning histone methylation in RA can cause the alterations of genes related to immune response and inflammation (Zhou et al. , 2017).

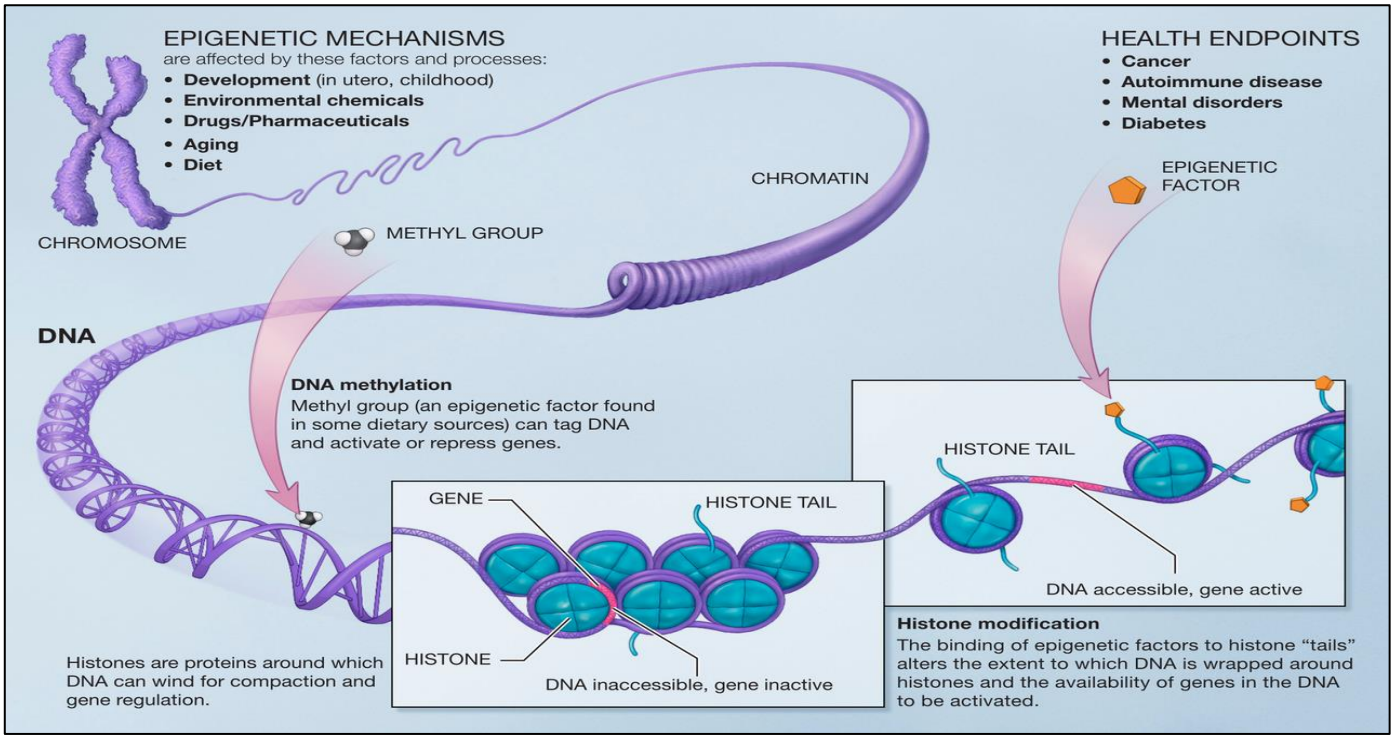

Fig 1 The Location of Epigenetic Changes within Chromosomes, Depicting Direct Methylation of DNA or the Histones that Bind to the DNA Sequence (https://nebula.org/blog/wp-content/uploads/2020/12/epigenetics1)

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- *Non-coding RNAs*

Among the ncRNAs, has miRNAs and lncRNAs are considered as the main regulators of gene expression in RA.

✓ *MicroRNAs (miRNAs):*

Such sRNA can also bind to target mRNAs and prevent them from being translated or cause them to be degraded. These dysregulated miRNAs including miR-146a and miR-155 are available in RA synovial tissue and exert an ostentatious impact on inflammatory conditions exerting their effects by moderating mRNAs of the managing proteins associated with immune responses (Guan et al. , 2015).

✓ *Long non-coding RNAs (lncRNAs):*

lncRNAs may bind with DNA, RNA and proteins associated with the alteration gene expression. For instance, HOTAIR, a comparatively documented lncRNA, is overexpressed in RA and it will participate in changing the chromatin constructions from the purpose of favouring the release of inflammatory genes (Batista and Chang, 2013).

➢ *Epigenetic Therapies for Rheumatoid Arthritis*

The recognition of epigenetic alterations in RA has spurred interest in developing targeted therapies. These therapies aim to modulate epigenetic marks and restore normal gene expression patterns.

- *DNA Methylation Inhibitors*

Drugs that inhibit DNA methyltransferases (DNMTs) can reverse the hypermethylation of genes involved in anti-inflammatory pathways. By demethylating these genes, DNMT inhibitors can restore their expression and function, potentially alleviating the autoimmune response in RA.

- *Histone Modification Modulators*

✓ *HDAC Inhibitors:*

HDAC inhibitors can increase histone acetylation, thereby suppressing the expression of inflammatory genes. Preclinical studies have shown that HDAC inhibitors can reduce inflammation and joint damage in animal models of RA.

✓ *HAT Activators:*

While less explored, activating HATs could potentially enhance the expression of anti-inflammatory genes, offering another avenue for therapeutic intervention.

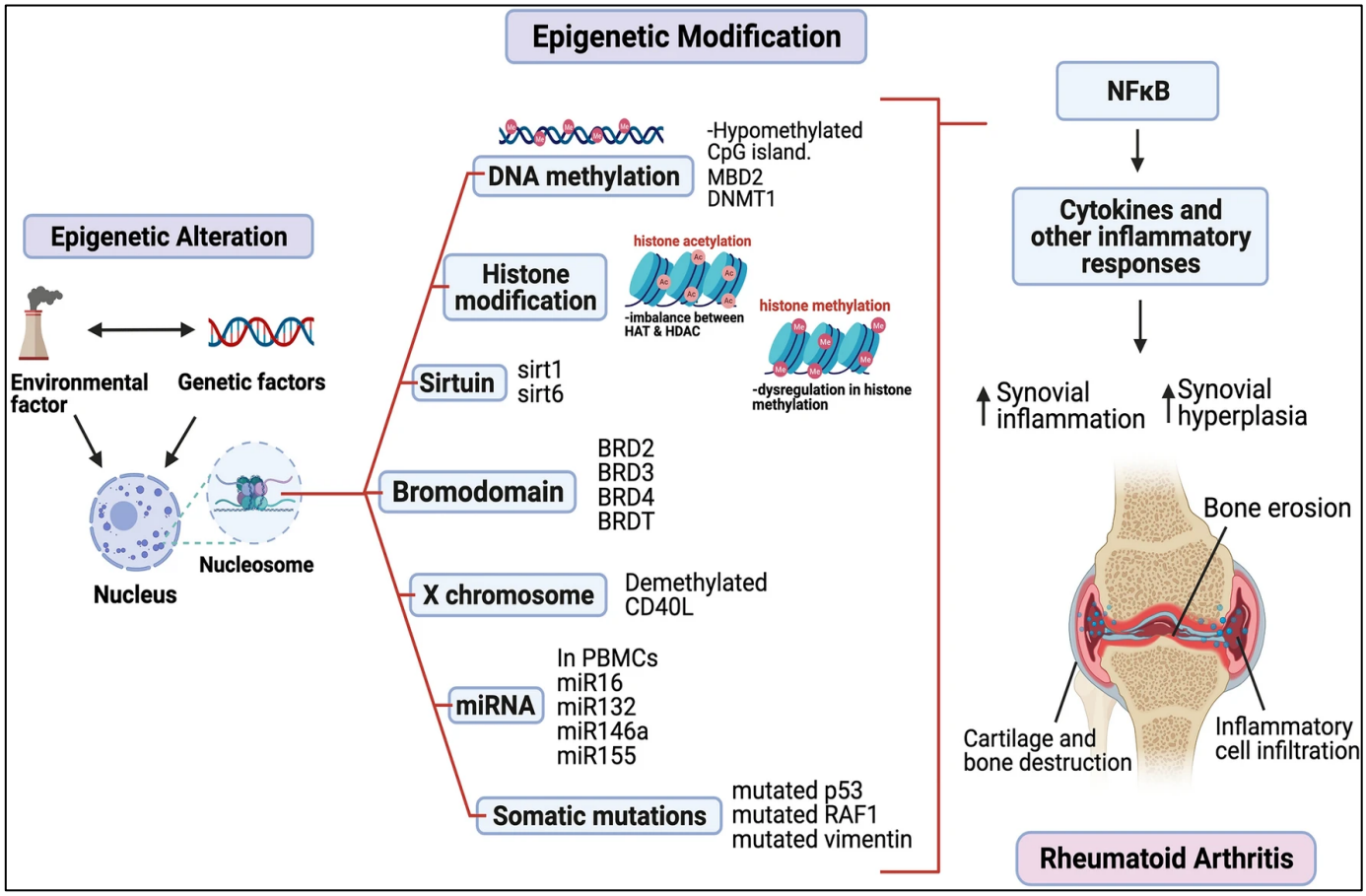

Fig 2 Schematic Representation of Different Types of Epigenetic Alterations Involved in the Development of Rheumatoid Arthritis (https://www.researchgate.net/publication/353473017/figure/fig1/AS:1050047173099520@1627362163153/Schematic-representation-of-different-types-of-epigenetic-alterations-involved-in-the.png

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- *miRNA-Based Therapies*

The therapies of dysregulated miRNAs in RA are also being worked out.

These include:

✓ *miRNA Mimics:*

Artificial or synthetic miRNAs which mimic the effects of downregulated miRNAs in RA and thus brings back their capability on gene regulation (Ebert & Sharp, 2010).

✓ *miRNA Inhibitors:*

Mirgulators for blocking the activity of upregulated miZIP coding for damaging proteins and for preventing the anti-apoptotic function of L-miR-21 (Ebert & Sharp, 2010).

➢ *Challenges and Future Directions*

While the potential of epigenetic therapies is immense, several challenges need to be addressed:While the potential of epigenetic therapies is immense, several challenges need to be addressed:

- *Specificity and Delivery:*

Most epigenetic modifications are noted to be cell type-specific; hence, the delivery systems should be well-targeted to minimize off-target impacts and toxicity.

- *Dynamic Nature of Epigenetics:*

Epigenetic modifications are dynamic and described as plastic, which means that the epigenome is not static but it undergoes constant change due to the endogenous and exogenous stimuli, hence the treatment process may require accurate timing and dosing.

- *Comprehensive Understanding:*

In order to comprehend the most efficacious targets of treatment in RA, it is urgently important to extend the knowledge of the connection between genetic and epigenetic profiles.

There is a need for further investigations to identify proper delivery systems for the drugs; the systems should be very accurate so that the epigenetic drugs will access the right cells, likely through nanoparticles or specific viral vectors. moreover, using epigenetic with genetics and the environment will create opportunities for one-of-a-kind treatment which will be known as personal treatment to the patient.

III. CONCLUSION

Epigenetics is the study of how genetics and the environment interact to influence the development of rheumatoid arthritis. In the case of canine T-ALL, epigenetic mechanisms play a significant role in understanding the disease. Researchers are exploring various pathways to treat the condition by shedding light on these mechanisms.

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