

Epigenetics and Familial Mediterranean fever

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Abstract: Throughout the last 20 years, the concept of auto-inflammation is developed, culminating with the finding of how gene mutations of Mediterranean Fever (MEFV) seemed to be causally linked to Familial Mediterranean fever (FMF). The autoinflammatory illnesses presently constitute a wide variety of disorders that have mutual signs of frequent fever, the incidence of hyper-reactive immune cells of hereditary origin, and indicators of inflammation that may occur systemically or specific to an organ with no autoimmunity specific infection. The key causes of the unregulated inflammation are the myeloid innate immune cells which mainly induced production of excessive inflammatory cytokines as IL-1 β and IL-18. Deficiencies through various signalling mechanisms regulating innate immune response, especially a single and even multiple inflammasomes hyperreactivity, remain the essence of pathological autoinflammatory phenotype. While FMF would be a monogenic autoinflammatory syndrome, it is genetically complicated and affected by environmental influences. Lately, epigenetic dysregulation has appeared to be a further cause of pathogenesis. Throughout this survey, we are addressing the epigenetic involvement pathways within (FMF).

Keywords: Autoinflammatory Diseases; Epigenetics; DNA Methylation; Familial Mediterranean Fever; Gene Expression; Microbiota

1. INTRODUCTION

Autoinflammatory disorders are a rising category of weakening and prolonged disorders with clear inflammation, which is sometimes systemic and appears through frequent fever periods. Hyperreactive innate immune cells are considered significant contributors to the pathogenesis of such illnesses. Furthermore, patients with an autoinflammatory illness show in their plasma high standards of the inflammatory cytokines and acute-stage proteins. Initially, the idiomatic autoinflammation has been used to characterize the existence of clearly uncontrolled inflammation periods within the lack of self-reactive T cells and/or elevated levels of auto-antibodies, and also without every observable infectious factor¹. Several autoinflammatory syndromes show systemically and/or organ-specific inflammatory characteristics

like frequent cyclic fever, arthritis, serositis, and/or dermal inflammation, innate immune cells stimulation and excessive production of IL-1 β , especially monocytes². Though at first the autoinflammatory idiomatic diseases just implemented on these typical inborn monogenic cyclic fever syndromes, like cryopyrin-associated periodic syndromes (CAPS) as well as FMF, this listing is extended yet to be an arising technologies implementation result, like following descent series, and includes a growing amount of recently characterized monogenic defects resulted from inflammation-associated genes mutation. The ample proof is that epigenetic dysregulation takes part in these diseases' pathogenesis³ (Table 1; showed by Stoffels and Kastner⁴).

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Table (1): Autoinflammatory disorders and evidence of epigenetic contribution to pathogeny

Mutated gene	Disease	Effector cytokine	Data on epigenetic regulation
Hereditary monogenic periodic fever syndromes			
MEFV	Familial Mediterranean Fever	IL-1 β	Yes ⁵
TNFRSF1A	TRAPS	IL-1 β	No
MVK	Hyper IgD syndrome	IL-1 β	No
NLRP3	Cryopyrin-associated periodic syndromes [familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, Neonatal-onset multisystem inflammatory disease/CINCA]	IL-1 β	Yes ⁶
NLRC4	NLRC4-MAS	IL-1 β /IL-18	No
PSTPIP1	PAPA	IL-1 β	No
NLRP12	FCAS2	IL-1 β	No
Antagonist deficiencies			
IL1RN	DIRA	IL-1 β	No
IL36RN	DITRA	IL-36	No
Complex autoinflammatory disorder			
	Behçet	IL-6/IL-1 β	Yes ⁷⁻⁹
	CRO/chronic recurrent multifocal osteomyelitis	IL-10/IL-1 β	Yes ^{10, 11}
	Crohn	IL-19/IL-3/IL-27	Yes ^{12, 13}

Note: Data are from "Old dogs, new tricks: monogenic autoinflammatory disease unleashed." by Stoffels M, Kastner DL., 2016, Annual review of genomics and human genetics.;17:245-72. doi: 10.1146/annurev-genom-090413-025334

Thus, individual subjective issues regarding health and illness should remain doubtful. Amongst patients, no test absolutely will determine the correct diagnosis. Cases sometimes require several tests that need an extended period, moreover the worry of meeting a practitioner¹⁴.

Epigenetics as sure providing modern thoughts to improve the clinical and diagnostic approaches in addition to eliminating the difference between environmental influences and hosting genetics. Epigenetics possesses the possibility of being utilized as a biomarker of illness identification and treatment, illness observation, as well as therapy reaction. Over the last years, pharmacogenetics has gained vast attention also epigenetic drug (epidrug) improvement has made considerable progress¹⁴.

2. DEFINITION OF EPIGENETICS

Epigenetics is a review of mitotic (and possibly meiotic) genetic modification in gene expressions due to variations within DNA series¹⁵. But other

epigenetics' principles are profound even do not require hereditary. For example, the US National Institutes of Health (2009) stated through their final venture that epigenetics shows the two genetic differences within genes activity and expressions (through offspring of cells or persons) and steady, prolonged-term modifications in the curative capacity concerning cell which are unnecessarily hereditary. Irrespective of the right definition, epigenetic mechanisms that steadily modify genes expressions types (and/or transport modifications in cell splitting) are believed to contain: DNA methylation, modulations of histone, chromatin remodeling and also the non-coding RNAs¹⁶.

3. SIGNIFICANCE OF EPIGENETIC STUDY

The detection and usage of epigenetic biomarkers own the possibility of affecting the treatment and clinical outcomes positively¹⁷.

Biomarkers are linked to how the disease develops and even the final diagnosis. Some biomarkers could also be possible curative goals or show that seeking these aims should start^{18, 19}. Possible markers foundation is just the initial stage because those signs have to be proven and convinced like a credible and statistically accepted image of a certain disease. The epigenetic biomarkers were previously integrated into different clinical fields and are utilized in the prophylaxis, and management of malignancy, disorders of autoimmunity, in addition to neurological and cardiac problems¹⁴.

In fact, we can find many merits of epigenetic biomarkers. Firstly, those signs show a modern trend in which molecular characters relate to genic and environmental influences that develop diseases²⁰.

Epigenetics supply useful biomarkers that do not rely on DNA series only. The epigenetic biomarkers, specifically those associated with DNA methylation, place out the DNA and RNA on the basis of checking sequences and may supply a different settlement profile¹⁷. Investigation of epigenetic biomarkers may be performed on samples from blood, tissue, body fluid, and excretions generally obtained during surgical operations¹⁴.

Moreover, the epigenetics disturbance may be tested within the genome context, before and even at the beginning of the disease in comparison with the RNA and protein-based testing in which abnormalities seem at comparatively delayed phases and sometimes in lower quantity or concentrations¹⁴.

4. EPIGENETICS MECHANISMS

4.1. DNA Methylation and DNA hydroxymethylation

Adding the methyl group onto the 5'carbon location of cytosine into cytosine-phosphate-guanosine (CpG) dinucleotides will significantly decrease DNA access for RNA polymerases transcription factors and, leading to suppression of transcription (**Figure 1A**). The DNA methyltransferase (DNMT) enzymes are accountable for keeping methylation. The DNA re-methylation is fundamental throughout cell split to transcribe the epigenetic code to the reproduction of the daughter cell. However, the *de novo* methylation to formerly functional genes' silence may contribute to the gene system's regulation. DNMT1 and DNMT2 are accountable for the re-methylation of DNA through the cell division^{21, 22}, while DNMT3a and 3b insert modern methyl categories into already unmethylated DNA²³. The condition is perhaps extracomplicated, and differentiation between conservation and *de novo* DNMTs is probably not justified or has an excessive simplification such as DNMT1 is actually implicated in the daughter strands methylation for

and may be alternative to illness prognostic factors the duration of the cell division and the organizational areas' *de novo* methylation²⁴.

DNA methylation may be modified via Ten-eleven transmit methylcytosine dioxygenase (TET) proteins that transform the methyl group to the hydroxymethylcytosines²⁵. So, the DNA hydroxymethylation seemed to be a medium within the method of intense DNA methylation of the copied suppressed genes to a demethylated case in uncovered and copied actively chromatin²⁶. Hydroxymethylated CpG positions are unaffected by DNMTs, thus from DNA methylation²⁷. The lack of TET proteins and hence hydroxyl diversions suppression may lead to high DNA methylation standards. Therefore, hydroxymethylation seemed to be a separate steady epigenetic condition²⁵. DNA hydroxymethylation sounds to be an active epigenetic condition²⁵. DNA hydroxymethylation sound to be an active epigenetic sign and identifies with raised gene expressions in comparison with methylated DNA²⁶ (Figure 1A).

4.2. Histone modifications

DNA is enfolded around histone protein groups, octamers including both transcribe of every histones H2A, H2B, H3, and the three dimensions that regulate its formation and access to the copied combination and H4. The histone proteins may be changed in their N-terminal amino deposits, which intermediates modifications through their electric ration and thereby determine the chromatin access to the copied combination²⁹. A number of histone alterations were recorded, involving acetylation, methylation, or citrullination (**Figure 1B**). Instances for "silencing" histone changes contain H3K tri-methylation (H3K9me3), histone 3 lysine 9 di-methylation (H3K9me2), and even H3K27me3, while histone 4lysine 16 acetylation (H4K16ac), H3K4me3, H3K18ac, H3K27ac, and also H3K56ac seem to be activating reproduction signs³⁰⁻³³. As noted, histone alterations and CpG methylation are linked throughout methyl-CpG-binding proteins (MBD)³⁴. Those proteins induct two histone deacetylases and methyltransferases that lead to silencing throughout the alteration of histone^{34,35}. Furthermore, histone tail alterations may let and even prevent the DNMT3linkage³⁶.

4.3. Non-coding RNAs

The non-coding RNAs (ncRNA) seem to be active molecules of RNA but without translation into protein, also they are included in numerous biological procedures. According to nearly 1–2% in the individual genome encoded a protein, we have had very little information about the remaining

genome till current times. Besides that, the RNA

world was sometimes dependent on outcomes of

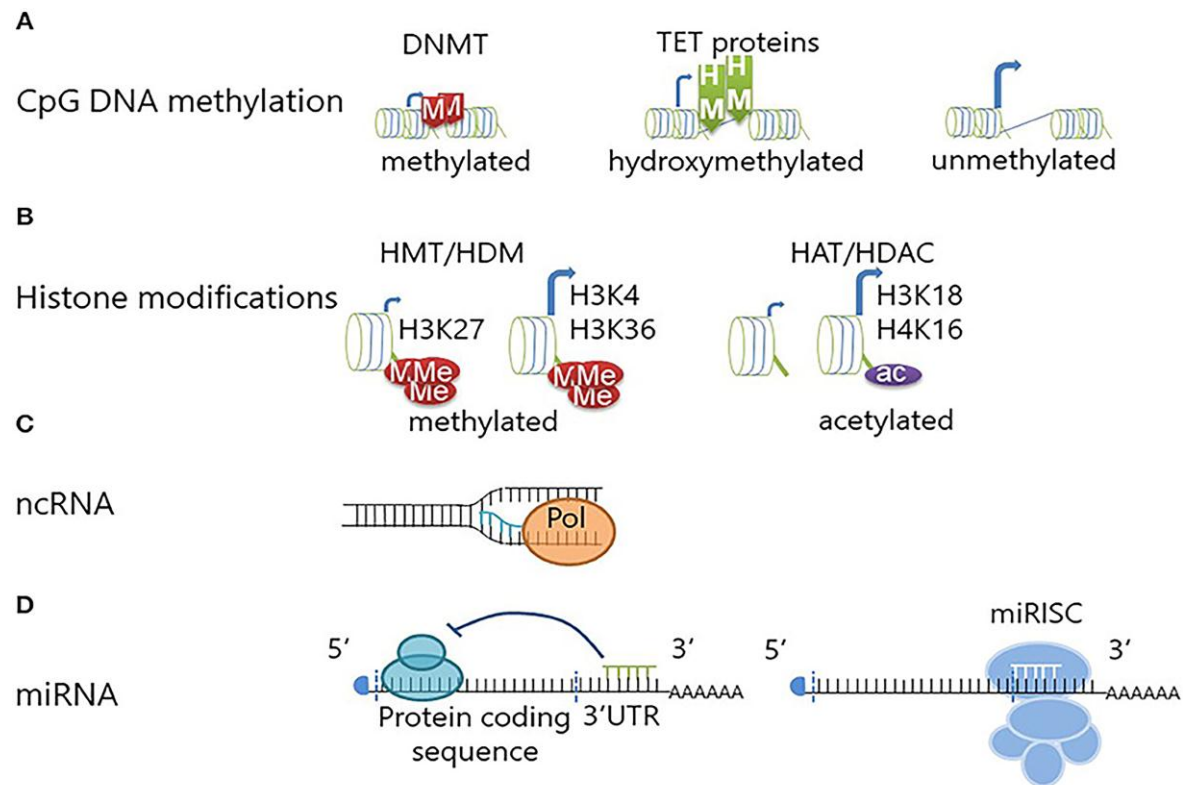


Figure 1: Epigenetics mechanisms. (A) DNA methyltransferase (DNMT) enzymes generate (*de novo*) DNA methylation at CpG dinucleotides. DNA Hydroxymethylation is achieved through oxidation of methylated CpG DNA and mediated by Ten-eleven translocation methylcytosine dioxygenase (TET) proteins. (B) Histone methyltransferases (HMT) can add (one to three) methyl groups to histone amino termini. (C) The transcription of non-coding RNA from intergenic or intronic regions can promote coding mRNA transcription by providing an open chromatin formation. (D) Short micro-RNAs (miRNA) can mediate transcriptional repression through inhibition of the ribosome when binding to the 3'UTR region of mRNAs. Also, miRNAs can stimulate the mRNA degradation through initiation of the miRISC complex²⁸. Copyright note: From “The role of epigenetics in autoimmune/inflammatory disease,” by Surace AE, Hedrich CM, 2019, *Frontiers in immunology*. 10:1525. (<https://doi.org/10.3389/fimmu.2019.01525>).

protein-coding mRNA research. Noncoding RNAs were assessed to be "evolutional junk RNAs"^{37, 38}. The RNA nature without coding is analyzed within two groups according to the numbers of nucleotides in the RNA molecule. The non-coding RNAs of up to 200 nucleotides are known as tiny or short ncRNA, while over 200 nucleotides are classified as long ncRNA. To the management of the nature of biological functions, ncRNAs are important. Worldwide, researchers are interested in identifying biological mechanisms or systems where the ncRNAs directly or indirectly operate through study for their roles. The non-coding RNA group (piwi-interacting RNA, small nucleolar RNAs, small interfering RNAs, microRNAs, circular RNAs, antisense RNAs, long intergenic non-codingRNA, in addition to other types) include various sections, however many studies throughout the literature are concentrated on miRNAs and long RNAs that not coded^{37,39} (Figure 1C).

4.4. MicroRNAs

MicroRNAs (miRNAs) are small (ranging from 18 to 25 nucleotides), endogenous non-coding RNAs; they are efficient in the evolution and accountable for post reproduction organization of gene expressions⁴⁰. It is suggested that most of the protein-encoding gene expressions in the individual genome are managed via 2654 ripe miRNAs (miRBase, <http://www.mirbase.org>) specified to date⁴¹. The miRNAs may have many goals, while genes may be controlled with many miRNAs. Thus, miRNAs own significant impacts on eukaryotic organisms' cellular and developmental courses; miRNAs may have complete and even weak linkage to the 3' translated area (3' UTR) in target genes within the mature sequences of mRNA, instantly damaging mRNA or causing translation inhibition⁴². But, it is assumed that the 3' UTR areas well as the 5' UTR (near the cap site) is perhaps targeted by

miRNAs, so contributing to miRNA-mediated post-transcription regulation⁴³. In addition, several works have indicated that miRNAs may facilitate transcription genes activating (TGA). miRNA is included within genes activating via linking to the goal genes' mRNA and inducing a protein combination containing transcribed activators^{44,45} (**Figure 1D**).

Long non-coded RNAs (LncRNAs) are formed from two protein-encoding (e.g., H19 and TUG1) and DNA areas that are not coded. LncRNAs seem to be capable of regulating the gene expressions included in several cellular systems' regulation with their complicated structures⁴⁶. Moreover, in contrast to miRNAs, LncRNAs may be poorly protected while comparing the nucleotide sequencing among species⁴⁷.

Long uncoded RNAs have proven strongly developed but differentiate within various forms of cells and tissues. Lately, a sum of 14,880 lncRNA transcripts was recorded via the GENCODE consortium gathered through the ENCODE venture, containing 9277 human origins generating from the gene's position 5362 LncRNAs, and 9518 intergenic LncRNAs (LincRNAs)⁴⁸. The detection of LncRNAs has supplied an important development in the classification of RNA-based processes in controlling gene expressions. LncRNAs may organize the transcription function of a certain gene or a certain chromosomal area. The best-known case, Xist, a 17-kb X-chromosome transcription, is the main controller of polycomb-suppressor complexes (PRC) to combine compound parts and initiate X-chromosome inhibition⁴⁹. On the contrary, LncRNAs like MALAT1 and H19 are efficient within lipid and carbohydrate metabolism in addition to protein combination and dissolution^{50, 51}.

5. EPIGENETICS AND GENE EXPRESSION

Proteins transcription, translation, and sequent modulation are transmitted genetic data from the DNA copy from the archive to the short-lived RNA transporter, generally with sequent protein generation. Though each cell in the organism has basically the same DNA, cell kinds and roles are different due to discrepancies of quality and quantity in their gene expression. Subsequently, gene expression management is at the centre of uniqueness and evolution. Gene expression types that characterize distinguished cells are shaped throughout evolving and retained as cells divided by mitosis. Therefore as well as genetic material, cells gain material that is not encoded in the DNA nucleotide subsequence, which has been referred to as epigenetic information⁵².

6.EPIGENETICS OF AUTO-INFLAMMATORY DISORDERS:

Familial Mediterranean Fever is considered the commonest inherited autoinflammatory disorder (MIM #249100). It's an autosomal recessive disorder that principally impacts individuals in the eastern Mediterranean basin and thus its name. The International FMF organization defined mutations causing the disease in 1997. The mutations were found to occur in the MEFV genes on chromosome 16p⁵³. MEFV encoding for pyrin, a significant complex of inflammasomes that interacting with caspase-1 and other inflammasome compounds to organize IL-1 β generation^{54,55}. Although the consistency of MEFV as the cause of FMF was for more than 20 years, pyrin function has been discussed. Previous research on mice demonstrated that pyrin prevents caspase-1, and the researchers recommended an anti-inflammatory function to pyrin⁵⁶. Different studies showed pyrin assembling an inflammasome compound and act as a pro-inflammatory⁵⁷⁻⁵⁹. Finally, it may be demonstrated that homozygous obtain-of-role pyrin mutation in mice causes pyrin inflammasome activation and acute inflammatory phenotypes via producing two pyrin-imperfect and knock-in mice that have mutated human B30.2 domains⁶⁰. The system of pyrin inflammasome activity had been defined in 2016. It may be manifested that the pyrin inflammasome is organized through RhoA-dependent phosphorylation. Phosphorylated pyrin interacting with chaperone proteins 14-3-3 to keep pyrin dormant. Dysregulated interaction among 14-3-3 and pyrin results inactivation of pyrin inflammasome^{61,62}. FMF is featured by abdominal and chest pain, frequent fever, in addition to arthritis⁶³. FMF diagnosis sometimes depends on the phenotypical Tel Hashomer⁶⁴ or Yalcinkaya-Ozen standards⁶⁵ and may be aided with genetic investigation⁶⁶. In 20% of cases with an FMF phenotype, a second mutation of the MEFV gene may not be observed⁶⁷.

Familial Mediterranean Fever patients with identical genotypes can present various phenotypes of the disease. This disparity could be because of other altering genes, epigenetics, or environmental influences. The first hint of the environmental effects on FMF was the discovery of the absence of minor amyloidosis amongst Armenian FMF cases in the USA⁶⁸. In case of moving to Europe, the eastern Mediterranean patients are known to have a less dangerous disease⁶⁹. The environmental influences might affect the presence of different phenotypes among FMF patients. One of these factors might be the living country^{70,71}. They may be based on genetic factors coupled with a region of specific influences such as nutritional patterns, privation, working environments, as well as environmental matrice

pollution. These findings are important, particularly to the assessment of the human capability of amyloidosis⁷¹. A previous study of FMF cases from 14 communities found that the residence state was the key factor evaluating the elevated risk of amyloidosis rather than the MEFV genotype⁷¹. In addition, a contrast among Turkish kids who have FMF staying in Turkey or Germany revealed a higher extreme disease trend for those in Turkey, showing the climate as a clear influencer of the FMF phenotype⁷⁰.

Additionally, previous studies comparing cases with identical history staying in Turkey or Germany have enabled environmental impact assessment of FMF intensity, where variables of the environment can cause over 12% of phenotypic variance^{72,73}. Besides, advances in DNA methylation of the MEFV reasoned FMF genes were reported to minimize MEFV expressions through FMF environmental leukocytes in 51 FMF cases relative to 21 healthy regulations. These results underscore the environmental effects on serious FMF disease^{5,74}.

7. EPIGENETICS AND MICROBIOTA

Although FMF seems to be a monogenic disease, epigenetic influences as well as microbiota could perform a function in the FMF pathogenesis or phenotypic expressions. It is enticing to estimate that interactions of host-microbe could be significant to this inherent immune system disease. Khachatryan *et al.* have shown that microbiota's structure and ramification varied through cycles with and without attack, also between FMF cases and healthy controls⁷⁵. Microorganisms can influence FMF because pyrin is an NLRP3 component that is a receptor for pathogen recognition⁶⁹. It has been demonstrated that pyrin reveals virulent pathogenic activity. Cross taking of the inherent immune system and commensal gut bacteria (microbiota) also could influence (or could be influenced by) the case inflammatory state. Microbiota composition and divergence varied through the attack and attack-free times also between FMF cases and stable controls⁶⁹.

Throughout that case, impacts of the environment influencing the gut microbiota may play apart in defining the start and intensity of disorders of the innate inflammatory pathway in the sense of a monogenic disease. Gut microbiota can also be a cause for the initiation of AA amyloidosis, which is one of the morbidity factors in FMF patients⁷⁶. However, dependent on the MEFV genotype, various standards of basic status activating of pyrin could likely affect the intestinal homeostasis in the gut giving a complex inter-individual risk of developing chronic inflammation. Microbiota metabolites are able to modulate other inflammasomes under this light⁷⁷. In the host gut, the

microbiota plays an important role and is vulnerable to variants of genes and environment, either in health or disease. Being a type of uncommon hereditary autoinflammatory monogenic disease, FMF presents a history of intermittent inflammatory variants, having a significant effect on innate immunity. The microbiota is particularly susceptible to these inflammatory variants. Additionally, unique autoinflammatory reactions in FMF can be controlled. FMF symptoms can also be susceptible, and this emerging problem needs further consideration as an environmental, genetic interactivity model. Gut microbiota is potentially a crucial element in the determination of the FMF phenotype. Plenty of microbiota and its form in FMF cases can be based on genetic and environmental factors, though it has a secondary function. In contrast, environmental factors may be crucial in the long run in shaping the nature of the condition and the symptoms onset (i.e., AA amyloidosis). In FMF patients, future research should investigate gene-environment interactions. In addition, potential beneficial effects resulting from external gut microbiota modulation need further research into how complex probiotic therapies could enhance symptoms and development of microbiota without affecting the valuable impacts of the main curative choice in cases with FMF⁷⁸. Growing proof is accumulating the function of intestinal microbiota in bile acid bioconversion within inter-individual differences leading predisposition to infection, converted metabolism and immune reaction. So, the genetic factors can be one of the factors deciding the intestinal microbiota profile in subjects with FMF^{79, 80}.

8. SUMMARY AND CONCLUSIONS

Epigenetics perform an unbiased but essential function in autoimmune/inflammatory pathophysiology disorders. Histone alterations, non-coding RNAs, and also the CpG DNA methylation, are the greatest proofs. However, we recently just begin understanding this and the processes by which epigenetic activities cause disease. Full interpretation of epigenetic disease aetiology is difficult as epigenetic conditions are highly complicated and occur accompanied by other epigenetic signs. They are unsteady and rely on several changes, containing cell cycle and exterior influences involving the immunologic micro-environment. A number of epigenetic alterations, implied reasons, and their participation in the pathophysiology has been approved, and other changes can cause a minor condition in regularity autoimmune/inflammatory illness and outstanding inflammation.

Nevertheless, secondary epigenetic changes could affect inflammatory reactions, and their curative target may further regulate inflammation and tissue spoil. But, aside from cancer therapy, "epigenetic therapies "recently still" science fiction" in the immunology and rheumatology domain, as aim-directed implementation is recently unavailable. Epigenetic alterations are complicated, as well as not targeted methods are related to genome-wide modifications, which can cause severe side-effects, even worsening the disease. Therefore, current studies are justified in offering a further detailed view of epigenetic causes of inflammation and unregulated immune, and their fundamental molecular reasons.

Just one complete image of epigenetics in the systemic inflammation will aid in:

(i) Understanding the typical autoimmune/inflammatory diseases pathophysiology.

(ii) Delivering molecular contributors for changeable manifestations, disease intensity, and results within associated individuals who have the phenotypically changing illness, and (iii) offering other goals into the study for vital signs in addition to individual and target-directed therapies.

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List of Abbreviations:

CAPS : cryopyrin-associated periodic syndromes
DNMT: DNA methyltransferase
FCAS2: Familial cold autoinflammatory syndrome-2
FMF : Familial Mediterranean fever
H3K27me3: histone 3 lysine 9 tri-methylation
H3K9me2: histone 3 lysine 9 di-methylation
H3K9me3: H3K tri-methylation
H4K16ac : histone 4 lysine 16 acetylation
LincRNAs : intergenic LncRNAs
LncRNAs : Long non-coded RNAs
MBD: methyl-CpG-binding proteins
MEFV : Mediterranean Fever
MicroRNAs (miRNAs)
mRNA: messenger RNA
MVK : Mevalonate Kinase
ncRNA : non-coding RNAs
NLRC4 : NLR Family CARD Domain Containing 4
NLRC4-MAS:NLRC4-Related Macrophage Activation Syndrome
NLRP12: NACHT, LRR and PYD domains-containing protein 12
NLRP3 : NOD-, LRR- and pyrin domain-containing protein 3

PAPA syndrome: Pyogenic Arthritis, Pyoderma gangrenosum and Acne

PRC : polycomb-suppressor complexes

PSTPIP1: Proline-Serine-Threonine Phosphatase Interacting Protein 1

TET: Ten-eleven transmit methylcytosine dioxygenase

TNFRSF1A : TNF Receptor Superfamily Member 1A

TRAPS: Tumor necrosis factor receptor-associated periodic syndrome

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