Inflammatory Disease Emergence Linked to Epigenetic Factors

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A commonly discussed scientific concept is the nature vs. nurture debate, whether it is a person's genetic disposition or the environment they grew up in that makes them who they are. In healthcare, both are observed and play a significant role in the long-term health of patients. The emergence of epigenetics – "above/in addition to genetics" – has proven to be a key factor in altering gene expression without changing the corresponding DNA sequence, and is being studied for its lasting impact on human health. Inflammatory diseases remain one of the most lethal comorbidities across the globe, with virtually no understanding of the underlying processes and few long term treatment options, with no cures available. Increased cytokine production has often been observed in chronic inflammation, however, what lies beyond genetics and what contributes to the positive feedback loop of these conditions? This paper highlights possible explanations for the emergence of inflammatory diseases through the lens of the three major epigenetics factors: DNA methylation, histone modification, and non-coding RNA.

Introduction

The acute inflammatory response is the body's line of defense against invading antigens, such as viruses, bacteria, toxic chemicals, or foreign objects. When triggered, the immune system sends inflammatory mediators, such as hormones bradykinin and histamine, which causes blood vessels to dilate[1]. Dilation allows for more blood to flow and reach the target area aid the healing process. Additionally, the hormones irritate nerves to send pain signals to the brain. This ensures that the individual identifies the inflicted area and protects it. Inflammatory mediators promote the flow of fluids, including the migration of immune cells, through small blood vessels to sites of infection. Thus, common symptoms of inflammation include swelling, pain, heat, redness, or bruising[2]. Most humans experience inflammation throughout their lifetime when they catch a cold, scrap their knee, or get bit by a mosquito. However, the efficiency and level of immune response is dependent on a person's genetics and epigenetics.

Epigenetics is the study of how a person's behaviors and environment can affect the way your genes interpret DNA sequences. Throughout a person's life their genes will develop and accumulate epigenetic marks. Epigenetic marks are small markers that modify the function of genes. The epigenomes determine how much of the protein encoded by these genes is expressed. Their existence helps explain how genetically identical twins can express different behaviors, skills, or health despite sharing genetic information[3]. The epigenome can be affected by positive or negative influences – such as diet or surrounding environment. These influences leave an epigenetic signature, unique to each factor, that determines how easily the genes are expressed[3]. Unlike genetic changes, epigenetic changes do not alter your DNA sequence and their effects can be reversed[4]. Epigenetic processes are natural and essential to the way life has developed and evolved. However, adverse health and behavioral effects have arisen from defects within these processes[5].

This review will focus on explaining current research and understanding of the link between inflammatory diseases and epigenetic modification. Three main inflammatory diseases will be focused on throughout the article, namely psoriasis, inflammatory bowel disease, and rheumatoid arthritis. This review aims to explain the major types of epigenetic alterations –DNA methylation, histone modification, and non-coding RNA– and to bring further understanding of the underlying mechanisms of inflammatory diseases.

Inflammatory Diseases

Chronic inflammation refers to when the body continues sending inflammatory cells to "affected areas" even when there are no external antigens triggering the response. Unlike acute inflammation, which you might experience when you get a cut, this often is a result of the immune system fighting against the body's own cells by mistake, otherwise known as autoimmune disorders. With defects in immune regulations, chronic inflammation can occur throughout the body. A common example would be rheumatoid arthritis. This involves inflammatory cells and substances attacking joint tissues, and leads to periodic bouts of inflammation, called flare-ups. For those who have rheumatoid arthritis, inflammation causes severe damage to joints and discomfort or pain[6].

It has been observed that inflammatory diseases are commonly tied to certain human behaviors or characteristics such

as excessive alcohol consumption, high body mass index (BMI), lack of exercise or engagement in high intensity exercise, chronic stress, and smoking[7]. However, the exact triggers and causes of inflammatory diseases have yet to be identified, and a majority of inflammatory diseases have yet to be cured. Common inflammatory diseases include psoriasis, inflammatory bowel disease, and rheumatoid arthritis. Each disease has their own unique symptoms and affects different areas of the body, which will be explained further in the following sections.

Psoriasis

Psoriasis is a condition that speeds up skin growth[8]. Patients who are afflicted with psoriasis experience rashes with itchy, scaly patches. These patches are commonly located on the knees, elbows, and scalp. Symptoms appear in cycles, often flaring up for weeks or months before subsiding. The most common form of psoriasis is plaque psoriasis, characterized by patches of scaly, dry skin around the body. However, there are six other types, each exhibiting their own unique symptoms.

When experiencing psoriasis, it has been observed that white blood cells, specifically T-helper lymphocytes, become overactive. This results in an overproduction of cytokines, triggering the inflammatory process throughout the body. Starting at the skin level, blood vessels will widen and white blood cells will begin to accumulate. This triggers rapid proliferation of keratinocytes[9]. Healthy keratinocytes, the main cells in the outer layer of the skin, take about a month to divide, mature, and migrate to the skin surface. However, patients with psoriasis go through this entire process in three to five days, resulting in rapid production and accumulation of skin cells.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) encompasses two conditions– Crohn's disease and ulcerative colitis (UC). Patients with IBD will commonly experience chronic inflammation in their gastrointestinal (GI) tract[10]. This will often manifest physically in patients as abdominal pain, cramping, bloating, changes in bowel movement, increased gas, or mucus in stool.

The normal microbiome composition in a healthy GI tract is a diverse ecosystem filled with a plethora of bacterial species[11]. Gut associated lymphoid tissue (GALT) and the microbiome along with other immune cells associate to perform a number of symbiotic functions[12]. Autophagy is one of these critical processes in the maintenance of the GALT, responsible for the breakdown of pathogens, antigen processing, and immune cell homeostasis. However, when this process is altered, bacteria in the GALT begin to reduce, possibly triggering the beginning of inflammatory disorders.

Additionally, many of the immune cells are located within the intestinal lamina propria, including T, B, natural killer cells, macrophages, and neutrophils[13]. The lamina propria is the connective tissue within the intestine that aids in the formation of the mucous membrane. When the inflammatory response is triggered, activated immune cells enter the intestinal mucosa and produce high levels of interaction between proinflammatory molecules. These high levels will ultimately lead to intestinal mucosal inflammation, and in the case of IBD the inflammation is chronic.

Rheumatoid Arthritis

Rheumatoid arthritis, or RA, occurs when the immune system mistakes healthy cells as pathogenic and attacks them – usually at the joints— causing periodic inflammation and swelling.

RA develops as a combination of an inflammatory process – synovitis – and the infraction of tissue boundaries, contributing to how widespread the condition is throughout the body. Researchers have identified multiple cell populations in the joints, which they believe may play a role in the development of RA[14]. Significant cell types identified in the blood samples of RA patients included immune cells and other structural cells that build connective tissue in the joints. Through their identification of these cell types, they were able to trace cells that produced inflammation promoting molecules within the joints. These cells are under further research to understand and explore their role and how scientists can possibly control their production to reduce the symptoms of RA.

There are increased efforts focused on the identification of the cause of RA, however concrete causation has yet to be found.

Current Treatments

It is thought that the over production of inflammatory cytokines and the triggering of inflammatory processes, including the recruitment of neutrophils and monocytes are essential in the hyper-function in the inflammatory process[15]. Thus, a common treatment option for patients are aminosalicylates.

Aminosalicylates are a group of drugs that can help to control the symptoms of IBD and include balsalazide, mesalazine, olsalazine and sulfasalazine. They are primarily utilized to help prevent and curve inflammation flare-ups and regulate the immune inflammatory response. Each aminosalicylate contains 5-aminosalicylic acid (5-ASA). 5-ASA is believed to change the way in which cells release cytokines, possibly reducing their production to counteract the existing surplus. Unlike other treatment options–which will be further ex-

plored— aminosalicylates are not immunosuppressants, and subsequently have not been found to be associated with an increased risk of infection or cancer[16]. This unique characteristic makes aminosalicylates a more popular treatment choice to decrease the risk of any adverse health outcomes. However, aminosalicylate has been found to cause headaches, nausea, abdominal pain, loss of appetite, vomiting, rash, fever, diarrhea, and/or pancreatitis.

When treating rheumatoid arthritis, a different approach is used. Often disease-modifying anti-rheumatic drugs, or DMARDs, are used to ease the symptoms and progression of the condition. Their function is to reduce the effects of released chemicals during immune attacks to the joints. Methotrexate is a specific DMARD that is usually the first medication to be prescribed when a patient is initially diagnosed[17]. Methotrexate stimulates adenosine release in fibroblasts. Adenosine will then accumulate and as an anti-inflammatory agent there is a reduction in T-cell activation and down-regulation of B-cells[18]. Due to the anti-inflammatory properties of methotrexate, it is not only utilized for rheumatoid arthritis, but also for psoriasis and Crohn's disease treatment.

Topical corticosteroids are common in psoriasis and other inflammatory skin conditions. They are steroids applied directly to skin that reduce redness, swelling, scaling, and itchiness. A popular example of corticosteroids is hydrocortisone. To reduce inflammation, typically hydrocortisone will bind to glucocorticoid receptors[18]. Glucocorticoids are steroid hormones that are created by the adrenal glands and are often used as immunosuppressive agents at a pharmacological level. Thus, as hydrocortisone activates glucocorticoids, pro-inflammatory genes are inhibited and anti-inflammatory genes are promoted.

Biological therapies, such as aminosalicylates that target tumor necrosis factor-*a* (TNF-*a*), originated in the late 1990s to maintain remission in inflammatory disease[19]. After initial activation by macrophages, TNF binds to TNF receptors I and II (TNFRI and TNFRII). This leads to a chain reaction of inhibition of regulatory T-cells and eventually induction of apoptosis[20]. However, approximately two third of patients with IBD will become non-responders during TNF-α inhibitor therapy.

Additionally, after heavy reliance on topical corticosteroids, patients often experience steroid withdrawal syndrome. This disorder often manifests as red, inflamed skin that becomes increasingly itchy and flaky. Symptoms come and go periodically and it can last months to years after steroid use[21].

Overall, these therapies hold moderate to significant risks for patients without providing either long term relief or alleviation of inflammatory symptoms leading researchers to understand the underlying mechanisms which cause these diseases such as improved treatment options and cures.

Epigenetics

In Greek, the prefix "epi-" refers to "in addition to". Therefore, "epigenetic" literally means "in addition to genetics." Now, in modern medicine and research the term now encompasses any process that alters gene activity, but not the physical DNA sequence. These alterations, although not transcribed in DNA, can still be heritable to offspring. However, it has also been found that after inheritance there is still possibility to reverse its effects.

The three main epigenetic factors focused on in this paper include: DNA methylation, histone modification, and non-coding RNA.

DNA Methylation

DNA methylation involves the addition of a chemical group to DNA. This group is usually added to regions of the DNA that promote transcription factor binding for DNA expression leading to a decrease in expression of the protein encoded there. In contrast, chemical groups can be removed through a process called demethylation. DNA methylation and demethylation is a common cellular process to regulate gene expression.

When a methyl group is transferred to the C-5 position on a cytosine ring, DNA methylation is likely beginning. This process is frequently assisted by DNA methyltransferases (DNMTs). Changes caused by DNA methylation are often heritable, and primarily occur in somatic cells and in CpG locations, known as CpG islands. These locations tend to be near transcription start sites, making them easily accessible to be methylated. Only about a quarter of this process occurs in a non-CpG location[22]. When dysregulated, DNA methylation can contribute to diseases and malignancy development.

Regulation of methylation derives from: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L. They aid in the silencing and inactivation of various genes and sequences[23]. These regulators play an important role in genomic integrity. If impeded or altered the body can experience chromosome instability and tumor advancement.

DNMT1 is responsible for the heredity that often comes from methylation, replicating methylation patterns in daughter strands. DNMT2 catalyzes the methylation of position 38 in tRNA[24]. DNMT3A and DNMT3B perform methylation during development[25]. DNMT3L increases the ability of methyltransferases to bind to methyl groups and stimulate their activity in vivo[26].

On a molecular level, there have been six different types of modified DNA bases linked to enhanced gene transcription[27]. DNA methylation is hypothesized to regulate certain pathophysiological processes such as imprinting, genome instability, and chromosomal translocations[28]. When methylated promoters are silenced, DNA methylation will follow the patterns

of gene expression and provide insight into the development of disease. Therefore the observation of DNA methylation may act as a reliable biomarker for early disease diagnosis.

Histone Modification

Histones are proteins that pack DNA tightly in a cell and create organized structures called chromatin in the nucleus. When DNA is wrapped tightly around histones it cannot be accessed by transcription factors. This makes it unavailable for protein expression and turning "off" that gene. Thus, instead of turning the genes "off" and "on" they will utilize chemical groups to change whether a gene is unwrapped or wrapped. Histones can restructure chromatins even after being modified through acetylation, and methylation[29].

Histone acetylation changes this chromatin structure, which depending on if the structure is open or closed, regulates gene expression. It is commonly associated with promoting transcription, as it is targeted when recognized and bound to DNA sequence-specific transcription factors that recruit histone acetyltransferase (HAT) cofactors[30].

Histone methylation modifies amino acids in a histone protein through the addition of methyl groups. This process is catalyzed by methyltransferases and demethylases. In comparison to acetylation, it is generally more complex as one methylation site is linked with permissive chromatin (euchromatin) and repressive (heterochromatin)[31]. Additionally, methylation marks recruit proteins that maintain chromatins, otherwise known as effector proteins.

Non-coding RNA

DNA instructions produce coding and non-coding RNA (ncRNA). Coding RNA is utilized to create proteins vital for various human processes. ncRNA aids in gene expression regulation by binding to target RNA and inducing cleavage, degradation, or inhibit translation. They may also recruit proteins to modify histones.

There are two types of ncRNA, categorized based on their size: small ncRNAs and long ncRNA (lncRNAs)[32]. In recent studies, it has been found that ncRNAs aid in epigenetic modification processes and can regulate expression at all biological levels to control cell differentiation.

Small ncRNAs can be further split into three categories: short interfering RNAs (siRNAs), microRNAs (miRNAs), and piwi-interacting RNAs (piRNAs). Each has their own unique functions, but they all ultimately help in the regulation of gene expression.

siRNAs are small ncRNAs derived from lncRNA, cut into RNA fragments[33]. It has also been observed that siRNA contributes to transcriptional gene silencing (TGS)[34]. For example, siRNA was found to be able to silence EZH2, a histone methyltransferase that can lead to CpG methylation, and ultimately, TGS[35]. siRNA has gained the most attention through its potential in therapeutic applications. Delivery systems of siRNA are being widely researched, and some have found that "carriers", or molecular complexes, will be utilized to deliver siRNA to target areas.

miRNA is thought to function as a negative regulator of target mRNA through silencing or translation inhibition. The main difference between siRNA and miRNA is that miRNA is the expression of biological genes, whereas siRNA is rooted in viral infection. However, it is hypothesized that they have similar mechanisms in terms of mediating transcriptional gene silencing. It is very rare for miRNA to completely match their target mRNA, and actually very little is known about its functional role in gene silencing. However, identification of miRNA complementary "seed regions" are showing more promising results in observation. This "seed region" plays an important role in the selection and binding of targets[36]. Approximately 50% of miRNA nucleotides are prone to structural changes due to their location on a chromosome[37].

piRNA mainly functions in embryonic development, specifically in the epigenetic regulation of sex determination[38]. They bind to Piwi proteins under physiological conditions, which then binds to polycomb group proteins and aids in silencing the homeobox gene[39]. This gene is critical in human and animal development as it ensures cell differentiation and the formation of anatomical features. Scientists have hypothesized that the piRNAs have played more significant roles in epigenetic regulation than currently thought[40]. Although the role of piRNA as regulators are still unclear, it is thought that they are associated with chromatin regulation, more specifically with the repression of RNA polymerase II transcription[41].

Finally, lncRNAs are generally found in the nucleus or cytoplasm and rarely encode proteins[42]. Studies have shown that lncRNA may hold multiple responsibilities such as X chromosome inactivation and genomic imprinting. Both processes require larger genomic regions to be altered, thus lncRNAs are believed to be the more efficient for the body to produce in aiding in more substantial mechanisms.

Link Between Epigenetics and Inflammatory Disease

The emergence of inflammatory diseases are hypothesized to be a product of two key stages: initiation and resolution of inflammation[43].

Initiation

Triggers of inflammation, as aforementioned, can be pathogens, trauma, pain, or tissue damage. The body recog-

nizes these triggers primarily through pattern recognition receptors (PRRs). PRRs main responsibility in the human body is to recognize and bind to pathogen-associated molecular patterns (PAMPS), molecules frequently found in pathogens. Multiple signaling pathways are catalyzed through the interactions between PRRs and inflammatory cytokines, often resulting in the activation of gene transcription[44]. The transcription complexes then begin to regulate the expression of inflammatory genes.

Resolution

The resolution phase of inflammation removes pathogens, cell debris, and inhibits cytokine production[44]. Resolution takes place towards the end of the inflammatory response, clearing the body from any harmful lingering molecules. Neutrophils undergo apoptosis and then are removed by phagocytic cells. Inflammatory macrophages will exit from the site of injury and switch to control inflammatory responses. Regulatory T cells, or Tregs, are recruited to restore tissue homeostasis. They primarily aid in the restructuring of tissue vasculature, architecture, and function. However, defects in resolution pathways may be the key to the emergence of various inflammatory diseases.

Epigenetic Factors

CRP Mediated DNA Methylation Exposure to risk factors such as excess adiposity or smoking can catalyze unwanted DNA methylation[45]. CpG methylation changes lead to alteration in gene expression patterns of human tissues. This can be inherited across generations, creating heritable traits that differ across ethnic boundaries[9].

It is hypothesized that the risk factors are the underlying component in DNA methylation as a result of C-reactive protein, or CRP. CRP has been observed to be a proxy for low-grade chronic inflammation. A recent study observed that within CpGs associated with BMI and smoking (typical risk factors), a large proportion of DNA methylation was mediated by CRP. The low-grade inflammation associated with CRP often leads to the development of a wider range of inflammatory diseases such as rheumatoid arthritis. These behaviors may be a driving force in CpG methylation and subsequently the emergence of inflammatory diseases. It is important to take note of unhealthy human behaviors and habits, as they may contribute to alteration of essential biological processes.

Histone Acetylation When assisted by HATs, histone acetylation can activate inflammatory genes. In contrast, increased levels of histone deacetylase (HDAC) can result in inflammatory gene repression. HDACs regulate transcription of pro- and anti-inflammatory cytokines. Airway biopsies from patients afflicted with chronic obstructive pulmonary disease found that macrophages increased histone acetylation, commonly associated with decreased HDAC activity[46]. However, the recruitment of HDACs leads to histone deacetylation and gene repression, creating a positive feedback loop. It can be observed that repression of inflammatory responses is hindered in areas where histone modification occurs.

Taking a look back at psoriasis, it is commonly thought that factors including genetic susceptibility, environmental factors, and immune responses contribute to the high complexity at which this disease performs. When analyzing blood samples from psoriasis patients before and after treatment, it was found that levels of acetylated H3 and H4 were reduced while the level of methylated H3K4 was increased[47]. A trimethylation mediator, EZH2, was also found to have increased levels in the epidermis of lesional skin. This has been found to directly cause abnormal proliferation of keratinocytes. Ultimately, EZH2 could be a target in reducing excess skin cells that create the scaly patches associated with psoriasis.

Pro-inflammatory Non-coding RNA Defects in the transcription, maturation, and function of ncRNAs may play a role in numerous pathologies. Most ncRNAs function as silencers or mediators of nuclear organization, RNA processing, transposon suppression, and other transcriptional processes[48]. There are two major categories of ncRNA involved in the human body's inflammatory response: miRNAs and long non-coding RNAs (lncRNAs).

Each miRNA can target hundreds of mRNAs and is thought to act as negative regulators of inflammatory processes at the posttranscriptional level[49]. miR-146, miR-155, and miR-223 have been identified as inflammatory response miRNAs. This means that they either silence the expression of positive signaling proteins or act as inhibitors of the same pathway. Either way they play a role in the regulation and maintenance of the inflammatory response. However, proinflammatory miRNAs are expressed at higher levels to engage in anti-inflammatory processes[49]. Therefore, a defect in these pathways can lead to autoimmunity, where inflammation is a continuous loop without any feedback to return the body to homeostasis.

Future Directions

Inflammatory diseases have one of the highest mortality rates globally, without a viable cure at present. While significant strides in the identification of biomarkers and epigenetic factors that ultimately contribute to the inflammatory process are being made, the data is still limited by technological sensitivity and driven by hypothetical understanding of these interactions in immune cells. Current science has not advanced enough for us to know if there are defects in non-coding RNA, DNA methylation, or histone modification that lead to increased cytokine production, and it's these gaps that limit ef-

fective treatment options. Inflammatory diseases also have a broad impact on the body from the skin to the brain. Each of these various inflammatory conditions has a multitude of differing processes that drive inflammation. However, the one factor they share is that inflammation occurs, a possible common ground for observation that can lead to multiple innovations. By engaging in further research focused on the identified epigenetic factors, millions of patients will see an increase in more targeted, specified, effective, and long-term treatment options.

An increased use of bioinformatics within this research would help parse through dense data at a fraction of the time, comparing various independent groups to identify specific biomarkers/parameters. By improving sequencing strategies to identify disease-specific signatures, it will allow scientists to act with more efficacy and efficiency when targeting and delivering treatments to pinpoint locations. In junction, creating predictive models based on disease mechanisms/characteristics will be essential in possible early detection, flagging for risk factors in patients. This will require large data acquisition in the form of common biological traits shared by affected individuals. Shifting research and medical interventions from a response to a preventative method of treatment.

Conclusion

The studies of epigenetics and immunology are intertwined as epigenetics impacts cellular biology, including immune cell function and regulation. While there is a shift in the medical field to approach clinical care with a global view of the patient, the emergence of our understanding regarding epigenetic's impact on cellular functions may provide vital in narrowing the search for sustainable treatments and cures for inflammatory disease. From existing studies, it is highlighted that the emergence of inflammatory diseases may be multifaceted. Each major branch of epigenetics– DNA methylation, histone modification, non-coding RNA– shows evidence of playing a role in altering biological processes leading to a sustained inflammatory response. Therefore, the role of epigenetics in chronic inflammation is prevalent and must be further explored to fully understand the underlying processes that drive inflammatory diseases.

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