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Targeting Epigenetics in Inflammatory Lung Diseases

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Epigenetics of Influenza: The Host-Virus Interaction. 10

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Abstract

With advancements in science and technology, an equivalent growth in diseases has also been observed. A disease that has remained prevalent for decades, showing an almost incomparable persistence and adaptability is influenza. With increasing research on DNA, we now know that external influences, like influenza, can successfully alter gene expression with lasting effects through epigenetics. In this chapter, the possible role that both influenza and its host play on an epigenetic level to alter each other's gene expression will be explored along with the possible effects these epigenetic changes have on virulence, the immune system, and other cellular mechanisms.

10.1 Introduction

While cells in a multicellular organism have the same genetic sequences, their phenotypes may differ greatly. The core of epi-(above)-genetics is this nongenetic cellular memory, which accumulates developmental and environmental signals [1]. The term "epigenetics" was coined to describe the poorly understood processes that led to the development of a fertilised zygote into a complex, mature organism. Due to the realization that all cells in an organism carry the same DNA and an improved understanding of gene expression mechanisms, the definition was revised to place more emphasis on the ways in which heritable traits can be connected to

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modification of DNA or the structural and regulatory proteins bound to it, rather than changes in nucleotide sequence. It may be beneficial to return to the definition of epigenetics as it originally existed, according to recent research into how these systems operate throughout embryonic development [2]. The network of functional linkages between the influenza virus and its hosts depends on epigenetic changes [2]. The influenza virus, of the Orthomyxoviridae family, is composed of influenza subtypes A, B, and C and has existed since ancient times, wreaking havoc through history, and killing millions [3, 4]. This spherical virus is encapsulated in a capsid and protected by a mix of surface proteins; neuraminidase (N), responsible for the destruction of infected cells to release the viral particles letting them infect more cells, and hemagglutinin (H), allows identification and aggregation of the viral fragments, and holds eight segments of single-stranded RNA (ssRNA) [5]. Eighteen hemagglutinin and nine neuraminidase proteins exist in influenza A, with H1/2/3 and N1/2 commonly known to impact human hosts [6]. This single-stranded RNA is what transfers itself into the host's nucleus through endocytosis, replicates using nuclear replicative machinery, and releases itself to infect neighbouring respiratory epithelial cells after an almost 6-h maturation period [7]. This exchange of nucleic acids offers an intimate point of contact, that many studies now confirm induces a change in gene regulation of both the host and the virus, engendering an amalgam of modifications [6, 8].

On the other hand, the chromatin structure of the eukaryotic genome is composed of a nucleosome, made up of an amalgamation of histones: H4, H3, H2B, and H2A [9]. Two of each of these histones come together to engender an octamer around which the 147 base pair (bp) DNA is wound, giving rise to a nucleosome [9]. Alongside the H1 histone, the nucleosome can coil to form a compact structure, which is then further altered through posttranslational changes to regulate cellular mechanisms [10].

10.1.1 An Introduction to Epigenetics

The DNA of an organism or an individual is pre-ordained at birth and remains consistent throughout their lifetime, or so we thought. Epigenetics is a new study that explores the various effects or alterations that may take place due to various factors like stress, diet, or exercise. These changes not only affect the way DNA/genes are expressed within the body but also may alter the genes of future offspring. These changes usually evolve because of modifications in histones (phosphorylation, methylation, ubiquitination, or acetylation), DNA methylation, or through non-coding microRNAs (miRNAs). Phosphorylation refers to the addition of phosphate molecules to activate (or deactivate) enzymes; methylation refers to the addition of methyl groups to alter gene expression; ubiquitination includes the addition of ubiquitin molecules which allows the degradation of specific protein molecules; and lastly, acetylation includes the addition of acetyl molecules to allow transcription [11]. These epigenetic changes may be positive or negative according to the change they induce and their long-term influence. For example, Colorectal

cancer patients who had experienced severe famine in the Dutch famine (1944–1945) were less likely to develop tumours labelled with a CpG island methylator phenotype (CIMP) [12]. In addition, increased B6 vitamin intake was proportional to methylation of MutL homolog 1's (MLH1), a gene involved in repairing DNA damage, promoter in men [13]. Additionally, even regular exercise has been reported to induce major changes in DNA methylation, affecting vulnerability to disease and metabolic phenotype [14].

Recently, research has shown that even external factors like diseases can lead to significant epigenetic changes. Viral particles hijack the cell's molecular mechanism and affect both the host's immune response to the virus, as well as the virus' pathogenicity. This same perspective can also be reversed to see the effect of the host on the virus' genome, histone modifications, and other structural changes.

10.1.2 Epigenetics and Viruses

The influence of virus on epigenetics is a serious concern as it may lead to increased vulnerability of the host, or additional pathogenicity of the virus. Many diseases like cancer, influenza, hepatitis, tuberculosis, etc. have been reported to play their part in influencing the genome through epigenetics. For example, in the human immunodeficiency virus (HIV) significant changes in gene promoter regions were observed that resulted in alterations in H3K9ac and H3K4me3 signalling consequently playing a role in HIV latency. Moreover, for instance an increase in methyl groups in the Class II major histocompatibility complex transactivator (CIITA) gene promoter's CpG islands results in a more persistent case of hepatitis B virus [15]. As another example, tuberculosis (TB) methylation profiles showed a distinct difference in macrophage methylation between active and latent TB [16]. Similarly, here we will highlight the epigenetic changes enforced by and on to the influenza virus by the host.

10.2 Influenza and its Epigenetic Changes on the Host

The influenza virus is an RNA-based virus with no histones of its own. However, its interactions with its host leave an imprint, some of which are epigenetic. Here we will explore the epigenetic changes that the influenza virus inflicts on its host. These effects may range from changes to the host's immune system and cellular mechanism, to changes that help the virus' infection into the host and pathogenicity. The influenza virus infects the respiratory tract, causing a robust pro-inflammatory response but also compromising response of host immune system, increasing vulnerability to secondary infections [17, 18]. Opportunistic bacterial infections following the primary influenza virus are a common complication that accounts for a majority of deaths during pandemics [18]. Research has shown that there may be a higher risk of a secondary bacterial infection even after viral clearance. These illnesses often manifest themselves within a week after contracting the influenza virus [19]. Influenza virus infection, especially H5N1 and pathogenic H1N1, acute

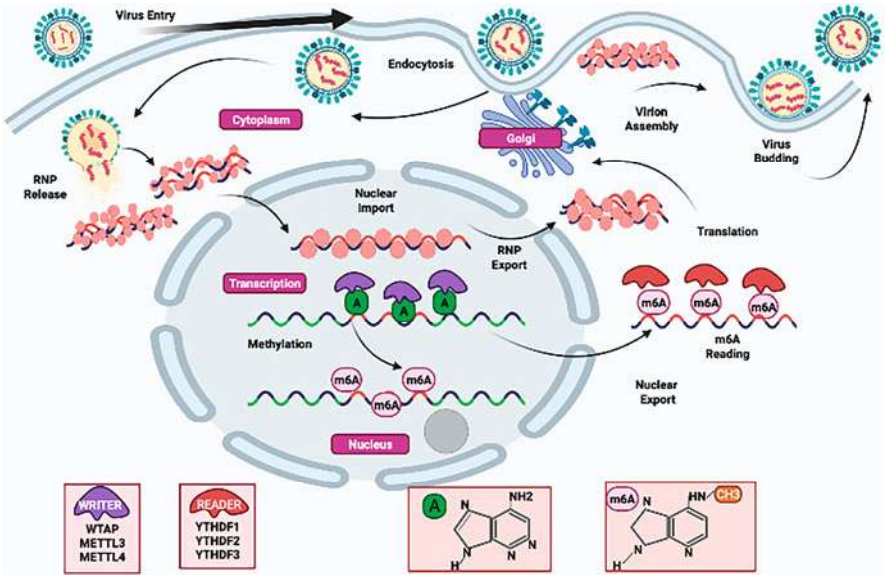

Fig. 10.1 Mechanisms of immunity's epigenetic remodelling during influenza virus contamination [8]

inflammation brought on by increased cytokine release has been seen. It has been demonstrated that increased cytokine release during infection of influenza virus caused by inflammatory gene promoter DNA by change in methylation. Additionally, the pathogenicity of the influenza virus strain and its variation has a significant impact on the change in methylation level. With highly pathogenic H5N1 influenza viruses, studies have seen the most substantial alterations in the DNA methylation of inflammatory genes [20]. Fig. 10.1 shows the epigenetic modifications of the immunity that occur due to influenza virus A.

10.2.1 Influenza's Effects on the Body's Inbuilt Immune System

The body's immune system is at the forefront of any battle that takes place against intruders. Therefore, it is expected that an intruder would be most likely to affect it in some way. A study reported in 2018 had concluded that although they found little epigenetic alterations in the DNA methylation, they did find a decrease in acetylation of histones, which meant that the host's transcriptional system was impaired [11]. Moreover, they found a unique player—lysine 79 of histone 3 (H3K79)—which plays a role in regulating the cell cycle and repairing damaged DNA. H3K79 when methylated by disruptor of telomeric silencing 1-like (Dot1L), a histone methyltransferase enzyme, instigated interferon signals, leading to metabolic changes, that worked towards counteracting the viral infection [21]. Therefore,

through decreased methylation of H3K79, the antiviral response is subdued and viral replication increases [11]. Moreover, the influenza virus is known to quell antigen presentation in host by epigenetically downregulating antigen presentation genes [22]. This downregulation was found to possibly vary according to the type of virus: Middle East respiratory syndrome coronavirus (MERS-CoV), relies on DNA methylation, while the H5N1 influenza infection relies on a mix of epigenetic mechanisms to affect antigen presentation [22]. The influenza virus has long-term repercussions too as it damages neutrophil's—a common white blood cell involved in fighting infections—performance and decreases the host's defence against secondary bacterial infections after the virus' exposure [23]. Its immunosuppressive condition is achieved through the activation of IFN-B (beta interferon) and chemokine's transcriptional regulation [23]. As part of the innate immunity, the Interferon Regulatory Factor 7, 3, and transcription factors NF-kB of activated B cells are triggered when host pathogen recognition receptors detect influenza A virus (IAV) infection intracellularly. The pattern recognition receptors (PRRs) comprise melanoma differentiation-associated gene 5, retinoic acid-inducible gene-I protein, and Toll-like receptors (TLRs). The type I and type III IFNs expression is then induced by these active transcription factors. The interaction between IFNs released by infected cells and their receptors activates the JAK-STAT signalling pathway, which controls the production of numerous genes that stimulate IFN as shown in Fig. 10.2 [8, 24].

10.2.2 Influenza's Effect on Host's Cellular Mechanism

Upon infection, influenza carries out a series of events that damage and initiate chaos in the cell's routine. One of these instigated changes includes a disruption of the host's mRNA splicing function [25]. Studies have shown that following an infection, hundreds of genes in the host reveal changed alternative splicing [25]. A possible reason behind this may be its manipulation of the splicing machinery of the host, or perhaps that the non-structural protein 1 (NS1) protein of the influenza virus shows a tendency to bind to intronic regions, contributing to a higher intron retention and altered splicing [26]. In addition, it has also been shown that defective termination of the transcription process takes place post-infection [27–29]. Influenza's unwanted interactions with its host do not stop there. The virus goes on to interfere with the host's long non-coding RNAs, specifically upregulating PSMB8-AS1 in infected cells [30]. This increase is in direct proportion to the increase in viral genes—NS1 and NP—and protein expression—NS1, PB1(polymerase basic protein 1), and NP (nucleoprotein) [30]. Overall, it has been reported in an experiment that 1913 long noncoding RNAs were altered in A549 cells after they were inoculated with the influenza A virus [30].

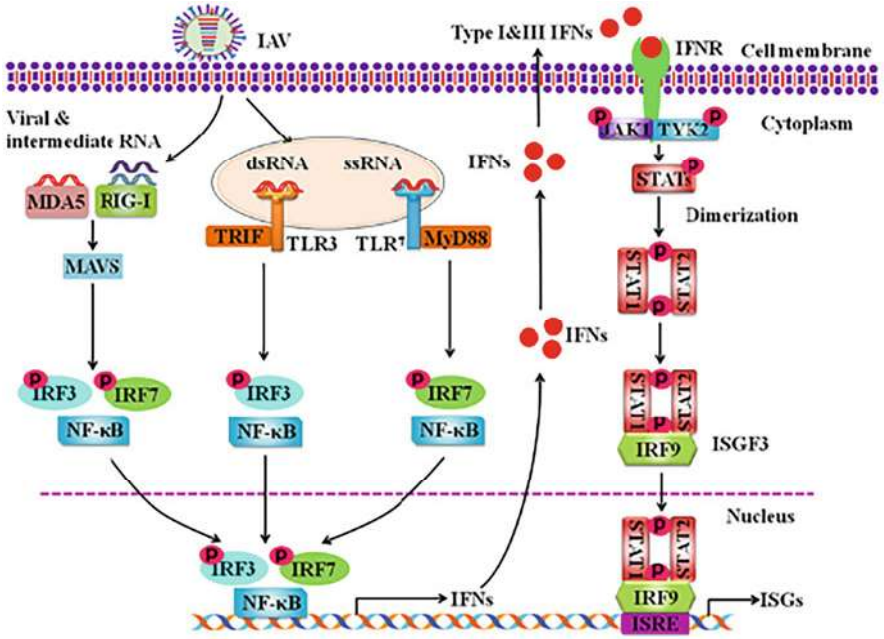

Fig. 10.2 Diagram of the innate immune system's defence against infection by the influenza A virus (IAV) [24]

10.2.3 Epigenetics Effect on Pathogenesis and Progression

Influenza, without a doubt induces epigenetic changes into the host. Some of these changes inevitably result in favour of the infectivity of virus. In a study observing mouse lung cells infected with influenza, they uncovered that by deleting the histone methylation gene it is possible to affect replication and pathology of the virus [31]. Additionally, the study highlights that the influenza virus interferes with the gene silencing mechanism, regulated by histone methyltransferase, to activate controlled genes [31]. These genes are unique because once activated they allow viral replication to occur [31]. Additionally, the influenza virus, specifically H3N2 subtype, contains a special non-structural protein 1 (NS1) protein which works as a histone mimic, similar to H3 histone tail of host, hampering the cell's antiviral response [32]. NS1 does this by binding to human PAF1 transcription elongation complex (hPAF1C), responsible for decreasing the force of influenza infection, and suppressing its expression leading to increased susceptibility and reduced antiviral response [32].

It has often been demonstrated that H1N1 influenza patients who experience a catastrophic illness outcome have CRP (C-reactive protein) levels that are noticeably higher. The findings of this study indicate that serum CRP, together with other biomarkers, may be used to predict the complications of H1N1 influenza [33]. A baseline rise in numerous biomarkers related to inflammation, coagulation, or

immunological function in individuals with infection of H1N1 pdm09 virus of different severity clearly predicted a higher risk of illness development. Interventions intended to lower these baseline increases could potentially have an impact on how a disease develops [34]. A novel technique for diagnosis of early influenza has been made possible by the findings of miRNA and its distinct flu sufferers' expression profiles. Additionally, we showed a correlation between throat swab miRNA indicators and influenza virus infection. miR-449b-5p, miR-205-5p, miR-181a-5p, miR-34c-3p, miR-34b-5p, miR-30c-5p, and miR-29a-3p are some examples of these biomarkers. They could be utilised to distinguish patients having infA and infB from unaffected healthy individuals. Additionally, they can be used to diagnose H1N1 and H3N2 infections. We anticipate that in the near future, this non-invasive method employing the miRNAs from throat swabs will be a reliable method for diagnosing influenza [35]. Infection with the influenza virus usually has more severe side effects in people over 65 (the elderly). Immunosenescence makes people more susceptible to viral infections and reduces the effectiveness of immunization. Designing preventative and immunomodulatory techniques to lower mortality and morbidity in the old age requires a thorough understanding of age-related immune system variations [36].

10.3 Epigenetic Changes Induced by Host on Influenza Virus

The influenza virus is significantly dependent on post-translational modifications, ubiquitination, acetylation, phosphorylation, and SUMOylation (attachment of SUMO proteins to lysine residues in proteins), to maintain normal viral protein structure and function [37]. Like the long list of changes that the influenza virus imparts onto the host, the host too plays a role in impacting the infecting virus. The host holds special enzymes called acetyl transferases which shift an acetyl group from an acetyl-CoA to a histone's lysine amino acids to relax and open coiled chromatin structure and allow transcription. The host body uses PCAF (P300/CBP-associated factor) and GCN5 (general control non-derepressible 5), two special acetyltransferases, to attach acetyl groups on the virus' Lys-90 and Lys-31 on the nucleoprotein (NP) which then impacts the polymerase activity of the virus [38]. Interestingly, the study mentioned that by silencing PCAF, viral polymerase became more active but with the silencing of GCN5, the viral polymerase activity decreased; showing that acetylation of both lysine residues has an opposite effect on the virus' replication [38]. In another study, they found that H3K4 (histone 3, lysine) methylation decreases playing a possible role in body's defence against virus. Moreover, they found that seasonal viral flu caused fewer changes in DNA methylation as compared to the virus in hens or A549 cells [39].

The host's fight against influenza can also instigate antiviral response but also stifle the virus' normal mechanism. For instance, on viral entry, demethylation of the IL-6 promoter leads to increased IL-6 expression resulting in cytokine secretion and the launch of an immune response [40]. Additionally, an influenza infection instigates the expression of miRNA-29 through epigenetic changes, resulting in an

increase in DNA methyltransferase (DNMT) expression that induces cyclooxygenase-2 (COX-2) expression and an accumulation of COX2-derived prostaglandin E2 (PGE2) [41]. This then promotes an inflammatory cascade, playing a role in the body's antiviral programme [41]. Moreover, in an influenza infection study on mice, eosinophils, blood defence white blood cells, show a decreased activity alongside a viral recognition protein transcription and T-box transcription factor (Tbx21) promoter's CpG methylation [42]. In an example of a more direct impact of the host on the virus, epigenetic modifications in the Interleukin 32 (IL32) promoter increase its transcription, effectively hampering viral replication [43]. This is done when the influenza virus instigates the CpG demethylation at the CREB, cAMP-response element binding protein binding point, increasing the binding of IL32 promoter and CREB, and increasing IL32 transcription [43]. Therefore, the host succeeds in not only launching its own immune response but also hinders the viral virulence.

10.4 Summary

Due to the constraints of space, the emphasis of this review was on the impact that histone changes have on the expression of viral genes and the replication of viruses—Interactions Between Hosts and Viruses: Looking at Things Through the Lens of Epigenetics.

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