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Review Article

The role of epigenetics in immunosuppression in patients with infectious diseases as a fascinating applied observation

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Abstract

The objective of the present study is to review infectious diseases during outbreaks and epidemics and to investigate how disease progression is affected and modified via the mechanism of epigenetics. The associated chronic refractory courses and the poor response to therapeutic interventions will also be considered. Specifically, two diseases will be reviewed and discussed in relation to epigenetics, namely tuberculosis, dermatophytosis, and viral infections, since many countries are currently running and experiencing epidemic states and outbreaks relating to these diseases.

Key words
Epigenetics, tuberculosis, dermatophytes, viral infections, immunosuppression, therapeutic resistance.

Infectious diseases

Infectious diseases are illnesses caused by pathogenic microorganisms such as bacteria, fungi, and viruses, or by their toxic by-products.[1] As one of the leading causes of global mortality and disproportionately affecting vulnerable populations, a thorough understanding of the factors determining disease severity, clinical presentation, transmission, and therapeutic resistance is vital for effective disease control.[1-2]

Epigenetic mechanism and Infectious diseases

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Epigenetics is the study of the reversible changes caused by environmental factors, such as infections during epidemics, that affect how genes work and function without changing the DNA sequence. Epigenetic changes affect gene expression and turn genes on and off using several mechanisms including DNA methylation, histone modification, or via non-coding RNA. Epigenetic changes can alter human health by several different routes, including infections, cancers, and nutrition, especially during pregnancy. In the present review, we will discuss how microbes can modify the epigenetics of individuals leading to a weakened immune system.

Epigenetic modifications facilitate rapid responses to stimuli and are integral to the maintenance of genome and cellular homeostasis, as well as in effectively coordinating and regulating disease-related processes such as cancers.[1,3-4] Epigenetic mechanisms allow for the control of gene expression and silencing within cells, and play a vital role in cell development and differentiation.[5] The three main epigenetic mechanisms that influence gene expression are DNA methylation, histone modification, and RNA-mediated gene silencing.[5]

DNA methylation involves the covalent addition of a methyl group to the C5 position of cytosine.[6] This typically occurs in CpG-rich regions, called CpG islands, within regulatory regions of DNA.[5] The methylation status of CpG islands influences gene expression, as increased methylation is associated with genome stability and decreased expression, whereas decreased methylation results in active transcription and increased gene expression.[5,7] To promote cell differentiation during development, DNA methylation can restrict the expression of some tissue-specific genes in non-expressing cells.[6-7] The use of histone modification for the epigenetic regulation of gene expression involves the use of post-translational modifications, such as acetylation, phosphorylation, methylation, or a combination of these.[7] Histone acetylation, for example, is the addition of an acetyl group to lysine residues on histone tails using histone transferases to stimulate transcription.[8-9] RNA-mediated gene silencing mainly utilises small non-coding RNAs such as microRNA (miRNA) to post-translationally regulate gene expression and mediate epigenetic DNA and histone modifications.[6] The use of non-coding RNA sequences plays a vital role in a range of processes including imprinting and X-chromosome inactivation.[10] RNA silencing by miRNA occurs via recruitment of remodelling complexes which promote histone modification. For instance, transcription can be suppressed by miRNA by recruiting RNA binding proteins which interfere with histone deacetylation.[6] Indeed, studies conducted by Kim *et al*., (2006) and Hawkins *et al*., (2009) suggest that synthetic siRNAs and endogenous miRNAs may direct gene silencing by recruiting proteins to form remodelling complexes.[11-12]

Epigenetic mechanisms often occur synergistically and can influence one another. For example, while miRNAs are thought to regulate 60% of protein-coding genes, they can also be regulated by histone modification, methylation in CpG islands, or both.[8] Similarly, histone modification and DNA methylation are often coupled to effectively alter chromatin structure and function, and regulate transcription status.[7] Further, histone deacetylation can be affiliated with methylation of CpG islands which is associated with an inactive chromatin state and repressed transcription.[6] Epigenetic modifications also play a significant role in the establishment and progression of many infectious diseases.[3]

Cutaneous diseases

The skin is an immunologically complex organ which constitutes a protective barrier against aggressive agents, and is the first line of defence against pathogens.[13-14] The skin is comprised of the epidermis, the outermost surface, the dermis, forming the layer below the epidermis, and the subcutaneous fat tissue.[15] To protect against pathogenic attack the skin acts as a physical barrier and employs various immune and non-immune cells, representing the skin-associated lymphoid tissue (SALT).[13-15]

Following skin surface damage, a series of complex immune signals and inflammatory responses are triggered which protect against pathogenic attack.[16] Skin-resident immune cells constantly survey the environment, ensuring foreign antigens are detected using pattern recognition receptors (PRRs). The innate immune response is precipitated by activation of

PRRs and the stimulation of inflammatory responses. Neutrophils and macrophages are recruited to phagocytose pathogens and amplify the inflammatory response.[15,17] Keratinocytes, the main epidermal cell type, are essential for the initiation and continuation of the cutaneous immune response. As well as expressing a range of innate pathogen-detecting receptors, keratinocytes also secrete anti-infection cytokines and chemokines, and antimicrobial peptides which locally modulate the immune response and provide additional protection against invading pathogens.[18-19] Langerhans cells (LCs) are epidermal macrophages which function as immune sentinels alongside keratinocytes, participate in the initiation of the innate immune response, and activate the slower, more specific adaptive immune response.[15,20-21]

The initial stages of the immune response are essential in eliminating pathogens and pathogenic toxins, as well as preventing further invasion.[15,17,22] As such, the skin provides an interface between the host and the environment, establishing an immune barrier and preventing systemic infection.[14-15,23] The skin is highly efficient at combating pathogenic threats, despite the many methods utilised by pathogens to infiltrate the system.

Infectious agents have developed a range of strategies to compromise defences, create an advantageous environment, and promote their survival within the body.[16] One such microbial protective strategy is the phenomenon of epigenetics.

Mycobacterium tuberculosis

Mycobacterial infections are a significant global health threat and a considerable contributor to mortality and morbidity worldwide. One of the most common types is Mycobacterium tuberculosis (M.tb), a deadly pathogen responsible for approximately 1.3–1.5 million deaths globally per year.[3,24-25] It is estimated that ~25% of the population is latently infected with M.tb, which poses a major risk to global health if activated.[3] Typically, infection begins following alveolar inhalation of aerosol droplets containing M.tb, and the subsequent infiltration of macrophages in the lung.[26] Macrophages usually play a role in the critical initial immune response, providing a first line of defence against pathogenic infections, and having a crucial role in the removal of pathogens and the overall outcome of infection.[27] However, M.tb has the ability to subvert this process, thus enabling its survival. Macrophages are the preferred habitat for M.tb and are therefore preferentially infected by bacteria, after which the macrophages may undergo apoptosis, destroying both the bacteria and the cell. However, if the macrophages undergo necrosis instead, the bacteria are released and disseminated, infecting more macrophages in the process. Survival of the macrophages enables M.tb to proliferate before the adaptive immune response can be activated.[27-29] M.tb may then invade the underlying epithelium, and cytokines are secreted to encourage other immune cells to migrate and invade nearby blood vessels. Granulomas, a hallmark of tuberculosis, are then formed in an attempt to limit and clear the infection.[3]

Cutaneous tuberculosis

Cutaneous tuberculosis (CTB) is a rarer example of mycobacterial infection and is predominantly caused by mycobacterium TB.[30] Endogenous invasion usually originates from pulmonary TB, whereas exogenous invasion occurs after direct inoculation of M.tb.[31] In a similar manner to pulmonary TB, a cutaneous immune response is activated, resulting in the formation of granulomas.[31] CTB is associated with a wide range of clinical presentations, which may be dependent on the route of infection, immunity of the host, and virulence.

Types of CTB

Lupus vulgaris is a chronic, endogenous variant of CTB that typically results from the contagious expansion of M.tb residing in underlying tissues; however exogenous infections have been observed previously.[32-33] Clinically, lupus vulgaris in adults presents as erythematous patches, consisting of papules and nodules, and are most commonly located on the lower half of the body.[32-34] The plaques grow by peripheral enlargement with serpiginous borders accompanied by central discolouration and atrophy.[32-34] Scrofuloderma, another form of CTB, is most prevalent in children and young adults. The initial M.tb infection develops in lymph nodes, bones, and joints, and commonly coexists with pulmonary TB. Initially, firm nodules are observed, which progressively increase in size prior to softening and rupturing, resulting in fistulas and ulceration, following which spontaneous healing may occur resulting in scarring, retractions, and atrophic sequelae.[31,32,35]

Mycobacterium tuberculosis and epigenetic modifications

Mycobacterium tuberculosis is thought to manipulate the host immune response via epigenetic mechanisms to avoid destruction.[3] Modifications to the host epigenome, including histone modifications, alterations to miRNA expression patterns, and DNA methylation facilitate immunomodulation of the host. Additionally, M.tb can further establish infection by secreting products which regulate the host transcriptional machinery.[3] Such modifications can manipulate the clearance capacity of the host to prevent its destruction, disrupt essential macrophage responses such as immune cell activation, and downregulate key cytokines and chemokines. Further, a study conducted by Bai *et al*., (2013) described a region-specific strain of TB with the ability to cause drug resistance via DNA methylation. Collectively, these strategies subvert the antibacterial strategies of the host, enabling M.tb survival, and resulting in effective immunosuppression of the host.[3]

Viral infections

Pathogens that modulate epigenetic mechanisms to survive host immune responses are not exclusively attributed to mycobacteria, and whilst most viruses are incapable of utilising host genome sequences, they can challenge immunity by hijacking the epigenetic machinery to advance viral replication.[36-37] A study conducted by Marazzi *et al*., (2015) demonstrated that pathogenic H3N2 influenza A virus inhibited host innate immune system initiation by interfering with the epigenetic control of gene expression.[38] Moreover, Schafer and Baric indicated that viruses such as HIV-1 have developed antagonistic mechanisms to directly target innate immune responses or prevent key immune signalling responses.[39] In addition, they suggested that newer viruses, including those of the coronavirus family, may employ comparable strategies. These findings were verified by other studies which implied that severe acute respiratory syndrome (SARS)-CoV may employ epigenetic modifications to delay pathogen recognition or alter the expression of pro-inflammatory cytokines.[4,39-41] Utilising antagonistic functions targeted at regulatory machinery in the host epigenome creates a permissive environment for viral replication and expansion.[4,42]

Viral infections and epigenetic modifications

Epigenetic alterations by SARS-CoV may also determine the severity of the disease and the route of entry into host cells.[43] DNA methylation has been identified as one of the main mechanisms that impacts disease progression in SARS-CoV-2, a severe viral infection that resulted in the recent COVID-19 pandemic.[4,43,44] Typically, modifications such as DNA methylation are involved in altered cell development and ageing processes, and play a key role in maintaining genome stability. Therefore, this may aid in understanding the increased incidence of hospitalisation, higher mortality and morbidity, and elevated disease severity observed with increasing age in COVID-19 patients.[43,45] Furthermore, RNA-seq studies conducted using patients diagnosed with SARS-CoV-2 demonstrated alterations in interferon-stimulated antigen presentation, and proinflammatory genes.[46-47] Interferons are key mediators of antipathogenic actions and initiators of pathogen-driven immune responses which are heavily regulated by epigenetic marks,[44] and thus alterations in associated genes may have a considerable impact on essential immune functions.[43-44] These findings were further substantiated by Corley *et al*., (2021), who demonstrated that epigenetic alterations varied depending on cell type, and reported that abnormal DNA methylation was observed at specific regulatory regions related to cell type in patients with severe COVID-19.[48]

Dermatophyte infections

Keratinocytes are the first epidermal cells encountered during infection, forming a physical barrier against invasions and offering an early defence mechanism by triggering a skin-specific immune response.[49] During fungal invasions, host cells secrete extracellular molecules which specifically detect fungi using PRRs, resulting in the initiation of signals promoting fungal phagocytosis.[50] If this essential physical barrier is removed or compromised, host immunity is suppressed, and the severity of infection is increased.[14,22,49]

Skin mycoses are superficial fungal infections which can infect the keratinous, epithelial, and dermal layers and may cause severe disease, depending on the specific fungus involved.[23] Dermatophytes are an example of skin mycoses and are the most common agents of superficial fungal infections.[50] Dermatophytosis, or tinea infection, is caused by adaptive filamentous parasitic fungi in the keratinised tissue of mammals.[50] Microsporum, Epidermophyton, and Trichophyton are the most common species of fungi involved in such skin infections.[51-52] Whilst anthrophilic dermatophytes, which are responsible for most fungal skin infections, are transmitted between humans, geophilic dermatophytes are disseminated from soil, and zoophilic dermatophytes circulate from animal hosts.[52]

Upon entry into the epidermis, dermatophytes germinate and invade the superficial skin layers and keratinocytes, and virulent hydrolytic enzymes which degrade keratin are secreted.[50-51] Concurrently, immunosuppressive proteins may be released to prevent dermatophyte degradation and further establish the infection.[53] Since dermatophyte invasions are predominantly restricted to keratinised tissues, widespread chronic and invasive systemic infections can occur in patients with cell-mediated immunodeficiencies or keratinised disorders.[50]

Traditionally, the diagnosis of dermatophyte infections is relatively simple and does not require extensive laboratory investigations. Typical clinical presentations include an itchy rash on exposed skin surfaces such as the neck, circular or ovoid lesions, inflammation, and the presence of plaques.[54] However, superficial fungal infections are known to imitate other dermatoses. For example, one study conducted by Sharquie *et al*., (2021) showed that tinea can mimic other cutaneous diseases by presenting clinically atypically, thus increasing the difficulty of accurate diagnosis and treatment planning following immunosuppression via epigenetic mechanisms.[51]

Fungal pathogens have also been observed to circumvent innate immune mechanisms and modulate the activation of disease-causing cells in the skin. The complement system is a vital component of the innate immune response. A metalloprotease produced by A. fumigatus conidia facilitates the cleavage of proteins associated with the complement system, thereby disrupting the host immune response.[55] The fungal pathogen Candida albicans has been shown to secrete proteases that promote inflammation, damage the epithelial membrane, and trigger danger response signalling pathways, and it has been suggested that a similar process may occur with dermatophytes.[50,56]

The early eradication of pathogens is essential in establishing a protective anti-pathogenic state within hosts, and to limit systemic metastasis.[44] To achieve this, the skin has developed multi-layered, complex defences to ensure that a wide range of pathogenic invaders can be rapidly managed and eliminated. Despite this, the pathogens causing some of the deadliest infectious diseases have evolved elaborate counter strategies to evade or utilise those efficient immune responses to aid in their survival. Epigenetic changes to host machinery are one of many strategies employed, however, owing to their reversible and responsive nature they may be an ideal therapeutic target. Thus, a deeper understanding of infectious disease pathogenesis, clinical presentation, and immune evasion strategies may improve the likelihood of eliminating infections.[51] Therefore, early intervention and rapid clearance of infectious agents may help to prevent the suppressive immunological changes associated with epigenetic roles, thus minimising the chronicity of infectious diseases.

Conclusion

Chronic infectious diseases such as skin tuberculosis, dermatophytosis and viral infections may utilise epigenetics to influence the host immunological response. The resulting genetic alterations may have an immunosuppressive effect which promotes the progression of diseases such as TB and dermatophytes, with the consequence of running chronic refractory courses and exhibiting poor therapeutic responses.

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