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Immune Senescence, Epigenetics and Autoimmunity

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Abstract

Aging of the immune system in humans and animals is characterized by a decline in both adaptive and innate immune responses. Paradoxically, aging is also associated with a state of chronic inflammation ("inflammaging") and an increased likelihood of developing autoimmune diseases. Epigenetic changes in non-dividing and dividing cells, including immune cells, due to environmental factors contribute to the inflammation and autoimmunity that characterize both the state and diseases of aging. Here, we review the epigenetic mechanisms involved in the development of immune senescence and autoimmunity in old age.

Keywords

immune senescence; inflammation; autoimmunity; epigenetics

INTRODUCTION

The incidence and prevalence of many common autoimmune diseases are increased in the elderly despite the decline of immunologic response to antigenic stimulus with age. Unlike a person's genetic profile, the epigenome continues to change throughout life. This age-related "epigenetic drift" is associated with impaired maintenance of epigenetic marks and the loss of phenotypic plasticity. It is becoming increasingly apparent that environmental factors encountered over the lifespan strongly influence the epigenome and that these changes along with genetic susceptibility drive the development of inflammatory and autoimmune diseases. Epigenetic modifications include DNA methylation, histone modifications and chromatin remodeling which constitute multiple layers of control to modulate gene expression. Studies of genetically-identical twins (monozygotic) have illustrated the influence of non-genetic factors in autoimmune and inflammatory diseases by showing variable degrees of discordance depending on the phenotypic trait including susceptibility to these diseases. The autoimmune diseases rheumatoid arthritis and psoriasis have concordance rates of 12% [1] and 70% [2] in monozygotic twins, respectively. Monozygotic twin pairs have significant

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epigenetic variation [3, 4] which increases with age when the twins live in different environments [5]. These studies highlight the important contribution of environment on the epigenome and demonstrate how multiple phenotypes can originate from the same genotype.

Immune system decline in aging is characterized by a shift from a naïve to memory T cell phenotype, type 1 to a type 2 cytokine profile [6], defective humoral immunity [7], increased maturation rate of T cells [8], chronic low grade inflammation, and many other changes [9, 10]. Aberrant gene expression in immune system cells resulting from epigenetic changes may contribute to loss of immune tolerance, inflammation and autoimmunity. This review aims to discuss the role of epigenetics in the development of inflammation and autoimmunity that characterize several age-related diseases. Table 1 summarizes key relevant immune and inflammatory changes during aging and in autoimmunity.

AGE-RELATED CHANGES IN THE IMMUNE SYSTEM

Immunosenescence

Cellular senescence refers to the cessation of cell proliferation and terminal exit from the cell cycle [11]. While senescent cells accumulate in aging tissues, the role of cellular senescence in aging is still unclear. Cellular senescence has been associated with both tumor suppression and progression in several cancers [12, 13]. Senescent cells secrete inflammation-associated factors including IL-6 and IL-8, referred to as senescence-associated secretory phenotypes (SASP), which has been implicated in age-related diseases including rheumatoid arthritis and Alzheimer's disease [14]. Alterations of chromatin structure have been observed in senescent cells. Histone modifications such as trimethylated histone H3 at lysine9 (H3K9me3) and trimethylated histone H3 at lysine 27 (H3K27me3) have been noted in senescent cells as well as DNA methylation changes [15]. The role of cellular senescence may differ in various cell types and organs during aging.

The immune system 'ages' as a whole, but certain cell types, pathways and processes change more than others over one's lifetime. Aging affects both the adaptive and innate immunity systems [16, 17]. Neutrophils have a short lifespan and die by apoptosis if unstimulated, but pro-inflammatory stimuli such as lipopolysaccharide (LPS) can increase their lifespan [18, 19]. The number of neutrophils has been shown to be relatively high in the elderly with altered effector functions [20–22]. Changes in innate and adaptive immunity with age contribute to decreased efficiency of responses to new infections, poorer immunity to previously encountered pathogens and the development of chronic, low-grade inflammation and autoimmunity.

Monocytes and macrophages are critical regulators and effectors of inflammation and have also shown age-related changes. Though less studied in humans, many of the effector functions including cytotoxicity, intracellular killing, and antigen presentation are decreased with age [23, 24]. The inflammatory monocyte subpopulation CD14+CD16+ is increased with age and characterized by increased pro-inflammatory cytokine production during the quiescent state [25]. One particularly potent proinflammatory cytokine expressed in monocytes, interleukin-1b (IL-1b), is regulated by DNA methylation [26]. DNA methylation and post-translational histone modifications along with transcription factors of forkhead box

protein P3 (FOXP3), interferon regulatory factor (IRF), nuclear factor-κB (NF-κB), and signal transducer and activator of transcription (STAT) families regulate inflammatory genes in monocytes and T cells [27].

Natural killer (NK) cells function in the killing of virus-infected and cancerous cells. Changes are seen in the two distinct NK populations with age: the CD56 bright subpopulation decreases and the CD56 dim subpopulation increases [16, 28]. Additionally, numbers of NK cells increase with age though they have reduced cytotoxic activity.

These changes in the innate immune system point to a basal activation state with aging that is characterized by increased pro-inflammatory mediators and decreased receptor signaling and effector function [29–31]. It is unclear why these changes are occurring, however chronic low-level stimulation by infectious agents has been proposed. Barriers of the gastrointestinal tract are more permeable in the elderly due to the presence of low-grade inflammation, and gut microbiota-related substances have been found in the circulation and tissues [32, 33]. Growing evidence has shown that the microbiota and their metabolites can modulate immune cells and cytokines through epigenetic modifications [34]. One particular metabolite that has been associated with immune system function are the short-chain fatty acids (SCFAs), produced mainly by the gut microbiome from undigested complex carbohydrates in the host colon. SCFAs have been shown to modulate inflammation [35–39]. Additionally, microbial components such as polysaccharide A (PSA) also have immunomodulatory function [40, 41]. The microbiota can affect the epigenome via the activity of epigenetic enzymes, through providing substrates such as folate and choline for epigenetic modifications, and by translocation of microbiome ncRNAs or epigenetic enzymes into host cells [34]. Several other antigens are also chronically generated including cellular debris, oxidatively modified proteins, modified DNA, and cancer-related antigens, which generate and sustain the basal activation of innate immune cells and form the basis for the inflammaging concept [42] (*vide infra*).

The adaptive immune system undergoes marked changes with age. Naïve T cell populations decrease and memory populations increase resulting in loss of diversity of the TCR repertoire. This leads to decreased response to vaccines and increased susceptibility to new infections, and reduced memory to previously encountered pathogens. Additionally, an expansion of senescent $CD28^-$ T cells is seen in normal aging and several autoimmune diseases including rheumatoid arthritis (RA), multiple sclerosis, and diabetes mellitus [43]. Chronic antigenic stimulation from internal altered tissue and molecular debris or micro-organismal material is postulated as the cause of the increase in senescent T cells [44]. Functional changes also occur in T cells with age. CD4+ T cell subpopulations shift with an increase in the number of T-helper type 2 cells (Th2) and regulatory T cells (Tregs) resulting in inadequate adaptive immune response towards new antigens and altered memory response. Age-associated differences in signaling are present in T cells including changes in surface receptor signaling such as the TCR/CD3 complex, cytokine, and co-stimulatory receptors, resulting in altered activation.[44–46].

The human body’s constant exposure to foreign antigens throughout life requires a balance between protective and pathogenic immune responses. Tregs, characterized by expression of

CD25 and the transcription factor FOXP3, are central to the maintenance of self-tolerance and homeostasis. Importantly, defective Tregs function plays a critical role in the pathogenesis of autoimmune diseases [47]. The number and function of naturally occurring Tregs increase with age and are linked to the hypomethylation of FOXP3 regulatory elements [48, 49]. These changes are also associated with the downregulation of dendritic cell co-stimulatory molecules [50]. The increase in Tregs number in old age has been correlatively linked to a number of cancers [51–53] and impaired vaccination responses [54, 55]. At present, it is unclear if the alterations in Tregs function in aging contribute to the high incidence of autoimmunity in older adults.

Inflammaging

The term ‘inflammaging’ was coined in 2000 by Franceschi et al. to refer to a progressive increase in the blood level of inflammatory cytokines and proteins accompanied by a loss of protective immunity in aging [42, 56]. The beneficial inflammation working to eliminate harmful pathogens early in life becomes detrimental in later life. Inflammaging is characterized by a gradual increase in proinflammatory mediators, including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and IL-1, which presumably develops through continuous antigenic stimulation with age [44, 57]. Various sources can provide this antigenic stimulation including pathogens such as CMV and herpes simplex virus-1, cellular and molecular debris from reactive oxygen species (ROS) transformations, nitrosylation, and cancer cells. The proinflammatory mediators produced under chronic inflammatory conditions have been implicated in the development of several diseases of aging such as autoimmune disorders, chronic obstructive pulmonary diseases, neurodegenerative diseases, and cancer. TNF-α, IL-1, and IL-6 also regulate insulin-like growth factor-1 (IGF-1) [58], induce insulin resistance [59], inhibit erythropoiesis [60], and promote vascular dysfunction [61] and muscle wasting [62]. These changes may directly or indirectly contribute to autoimmunity in old age and exacerbate the associated pleiotropic comorbid cardiovascular disease, sarcopenia, metabolic syndromes/diabetes, anemia, and physical functional impairment.

Epigenetic mechanisms modulate the expression of several proinflammatory mediators and consequently may mediate the development of chronic inflammation. TNF-α is involved in early inflammatory responses and is secreted by a variety of cells at the site of injury upon promoter hypomethylation of Toll-like receptors by lipopolysaccharide [63] or activation by lipid mediators and cytokines [64–67]. When dysregulated, TNF-α can promote the development of several diseases including cancer [68]. DNA methylation and histone acetylation are both involved in modifying the TNF-α locus during development and in response to acute stimulation [69]. DNA methylation actively regulates the expression of TNF-α, and lower methylation at two specific CpG sites in human macrophages correlated with high production of TNF-α mRNA, possibly explaining the variation in inflammatory response between individuals [70]. TNF-α is overexpressed in several inflammatory diseases including rheumatoid arthritis, Crohn’s disease, ulcerative colitis, and asthma.

The transcription factor NF-κB in its activated state binds to specific DNA sequences in target genes to regulate numerous genes involved in inflammation and immunoregulation

[71]. Various stimuli can activate NF-κB including proinflammatory cytokines, T and B cell mitogens, bacteria, viruses, and double-stranded RNA [72]. NF-κB mediates chronic inflammation and is regulated by acetylation, lysine methylation and arginine methylation [27]. Acetylation of histone H3 is observed with NF-κB driven inflammatory gene expression [73]. Reversible acetylation of NF-κB plays a major role in modulating inflammatory gene expression.

Aging-Associated Epigenetic changes and Autoimmunity

The incidence of many common autoimmune diseases rises with age [74–79]. Increased levels of autoantibodies have been documented in the elderly population as well as in systemic autoimmune diseases. Healthy adults over 70 years of age have higher levels of antinuclear antibodies compared to healthy younger individuals [80]. While chronic inflammation increases with age, it is unclear whether it contributes to the increase in autoimmunity seen in the elderly.

Many human diseases and conditions have been linked to epigenetic alterations. The aging process has been conceptualized as the interconnection between genetics and environmental exposures [81] with intrinsic and extrinsic exposures or stochastic errors accumulating over the course of a lifetime causing changes to the methylome resulting in ‘epigenetic drift’ [82]. The epigenome is therefore an attractive link connecting environmental ‘stressors’ to the development of autoimmunity with age. While epigenetic changes in aging result in largely unpredictable changes in gene expression, some of these likely represent unidirectional adaptive changes that contribute to the basic biological underpinning of aging [83, 84]. Recent studies focusing on transcriptomic approaches have confirmed that age-associated methylation changes vary depending on the specific leukocyte populations and T cell subsets [85, 86]. Amongst the various immune cell populations, the T cell compartment may be most affected by the aging process [86, 87]. A recent human study reported age-related hypermethylated sites primarily located at CpG islands of silent genes and enriched for repressive histone marks of CD8 cells from older individuals [86]. However, the investigators also observed strong correlation between methylation changes and gene expression of interferon gamma, CCL5, CCL7, CD27, and other T cell function genes. There are also regions of aging-associated DNA hypermethylation at bivalent chromatin domain promoters of CD4 T cells that are believed to be involved in tumor pathogenesis [88]. However, the overall functional consequences and the implication for aging and aging-associated autoimmune diseases of these reported changes are unclear.

Histone methylation and acetylation changes have been linked to aging and longevity in animal models [89–91]. A histone demethylase specific for lysine 27 of histone H3 (H3K27me3) is associated with repressed chromatin and has been shown to regulate worm lifespan [92]. Interestingly, Toll-like receptor 4 (TLR4) of macrophages has distinct histone and nucleosome marks that may determine their immune responses [63]. There is an overall decreased level of core histone proteins in aged cells that may in turn allow inappropriate access to genetic sequences. Others have shown that the age-associated loss of heterochromatin leads to expression of otherwise silent retrotransposon elements [83].

It has been well established that environmental factors contribute to the development of autoimmunity in genetically susceptible individuals. Several case reports have linked autoimmune disease onset with preceding bacterial or viral infections. Some retroviruses such as the Epstein-Barr virus are regulated by DNA methylation and can promote epigenetic changes in host B cells, supporting the connection between epigenetics, infection, and autoimmunity [93]. Drug-induced lupus is another well-documented example of an environmental factor triggering autoimmune disease. Procainamide and hydralazine are the two drugs that are most commonly associated with the development of drug-induced lupus and have been shown to inhibit DNA methylation in CD4+ T cells leading to autoreactivity [94].

A clear gender bias exists in many autoimmune diseases with women being afflicted more often than men [95]. Women are two to three times more likely to be affected by rheumatoid arthritis and multiple sclerosis than men, and nine times more like to have systemic lupus erythematosus or Sjogren's syndrome. While endocrinological factors contribute to these differences, epigenetic mechanisms are an attractive explanation since DNA methylation regulates imprinting and X chromosome inactivation in females. DNA methylation silences most of the genes on one of the two X chromosomes, referred to as X-chromosome inactivation. Reactivation of silenced genes on the inactive X-chromosome in female lupus patients has suggested that there is a 'genedose' effect from the X-chromosome. Additionally, males with Klinefelter's syndrome (XXY) who have an extra X-chromosome have a 14 times higher incidence of SLE compared to normal males (XY) [96].

Epigenetic changes in the pathogenesis of individual autoimmune diseases has been discussed recently [97] and will not be reviewed here. However, it is important to note the role of epigenetics as a mechanistic link between immunosenescence and autoimmunity. A recent study by Dozmorov et al. reports the age-associated DNA methylation changes in naïve CD4+ T cells from healthy individuals [98]. The authors identified 11,431 age-associated CpG sites, over half of which were hypermethylated with age. Of note, the study observed several age-related methylation changes that support findings previously observed in T cells from lupus patients. CD40LG and CD11a (encoded by *ITGAL*) were hypomethylated with age in the study and have been previously shown to be overexpressed in lupus CD4+ T cells and normal CD4+ T cells treated with DNA methylation inhibitors [99, 100]. MAPK signaling pathway was hypermethylated with age signifying silencing at the epigenetic level in aging naïve CD4+ T cells, and has previously been shown to be defective in lupus T cells [101]. mTOR activation which is characteristic of lupus T cells and contributes to a proinflammatory phenotype and T cell autoreactivity [102] was progressively poised for activation with age in naïve CD4+ T cells. Finally, apoptosis-related pathways were hypomethylated with age in naïve CD4+ T cells from healthy individuals and increased apoptosis in T cells from lupus patients has been hypothesized to contribute to T cell autoreactivity by providing the source of autoantigens [103]. The findings from this study strongly support a role for age-related epigenetic changes in T cells as a contributor to the increase of autoimmune disease in aging.

CONCLUSIONS

Aging is a complex biological process involving the interplay of genetic and environmental factors leading to cellular damage. Immunosenescence, or aging of the immune system, results from genetic and epigenetic events accumulating throughout the lifespan. An important feature of immunosenescence is the development of low-grade inflammation called inflammaging that contributes to the development of most age-related chronic diseases. The etiology of inflammaging is unknown, but immune changes with age along with epigenetic alterations contribute. Autoimmunity is another feature seen in the aging immune system. Autoimmune disease develops in individuals with an appropriate genetic background. Age-related epigenetic changes in immune cells likely contribute to the development of autoimmune disease in those who are susceptible. Further studies in characterizing age-related epigenetic alterations will allow for the development of epigenetic therapeutic targets in inflammatory and autoimmune diseases.

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Table 1

The aging immune system and autoimmunity-selected changes relevant to epigenetics and inflammation.

	Aging	Autoimmunity
Influence of age and sex	DNA methylation/epigenetic drift and global T cell hypomethylation	X-chromosome inactivation and reactivation; T cell hypomethylation
Inflammation	Chronic low grade inflammation	Acute and chronic inflammation
T cells	Thymic involution; decreased T cell receptor diversity; memory T cell expansion; increased regularity T cell function; accumulation of CD28-T cells	Thymic sclf-reactivc T cells avoiding self-selection: shift in Th1/2 cytokines; selected clonal expansion; impaired regulatory T cell function; accumulation of CD28-T cells
B cells	Impaired humoral responses; non-specific autoantibodies	B cell activation; disease and organ specific autoantibodies
Dendritic cells	Impaired function	Role In induction of autoimmunity
Telomere length	Shortening in cellular senescence	Premature shortening
Chronic inflammatory conditions	Increased risk, of obesity, heart disease, cancers	Increased risk of obesity, heart disease, cancers
Microbiota	Role in age-related obesity and systemic inflammation	Promotes mucosal inflammation and autoimmunity

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