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Forum

Epigenetic networks driving T cell identity and plasticity during immunosenescence

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The aging process is associated with the accumulation of epigenetic alterations in immune cells, although the origin of these changes is not clear. Understanding this epigenetic drift in the immune system can provide essential information about the progression of the aging process and the immune history of each individual.

Immunosenescence is a complex process characterized by the progressive dysfunction of the immune system and associated low-grade inflammation. In recent years, increased transcriptional heterogeneity related to aging has been described in various tissues. This transcriptional noise could be associated with the presence of **somatic mutations** (see Glossary) in aged tissues [1], although it is not clear whether this is sufficient to explain all the observed alterations. It has been hypothesized that these changes may be the result of a type of stochastic **epigenetic drift,** intrinsic to stem cell populations and long-lived immune cell progenitors. From this perspective, the epigenome acts as an interface between gene function and the environment by integrating random changes during the aging process (Figure 1). Global levels of **histone marks** analyzed by mass cytometry in **monozygotic twin pairs**, such as H3K27me3, have demonstrated beyond doubt that the epigenetic profiles of aged T cells are more heterogeneous than those of younger cells [2]. However, the source of this epigenetic noise and its impact on immune function are not well understood. Genome-wide chromatin accessibility analysis of CD8+ T cells has shown that aged naïve and central **memory T cells** acquire an epigenetic landscape that partially resembles more differentiated effector memory cells. Therefore, these age-associated epigenetic changes appear to be cell specific and highly enriched in genes associated with immune functions, including chromatin alterations at binding sites of important transcription factors of T cell differentiation, such as BATF [3]. It could be argued that these results are not satisfactorily explained by a stochastic model in which most changes should be randomly distributed and not directly associated with T cell function. This raises questions about the sources of the age-associated epigenetic drift in immune cells. One possible explanation is that the phenotypic diversity within immune cell compartments is greatly underestimated. Single-cell transcriptomic analysis has demonstrated that many established immune cell compartments, such as innate lymphoid cells (ILCs) and T helper (Th) subsets, are anything but phenotypically homogeneous; by contrast, they are highly heterogeneous populations the transcriptional changes of which are associated with immunity [4]. This heterogeneity is well known, and several studies have factored in the phenomenon by restricting their analysis of aged cells to more defined cellular compartments or by applying deconvolution methods to infer cellular composition. However, the great diversity and plasticity of the immune system mean that these efforts are likely to be insufficient. Within this framework, single-cell epigenomics, although still challenging at the required scale, will be necessary to dissect the specific contributions of stochastic processes and immune cell plasticity to the observed epigenetic drift. This approach in quiescent muscle stem cells of mice has revealed a correlation between transcriptional and epigenetic noise in some promoter regions from aged cells [5]. Although these results neither provide a definitive explanation of the stochastic nature of the epigenetic drift nor demonstrate a causal link between epigenetic drift and cellular function, they nevertheless offer a necessary starting point for future studies in immune cells.

Clearly, if stochastic alterations alone cannot explain the age-associated epigenetic drift, many of the observed changes must be linked to the immunological history of each individual or the phenotypic adaptation of

Glossary

Epigenetic drift: epigenomic divergence due to the accumulation of stochastic changes during the aging process. These changes may affect cell functions in stem and long-lived cells, contributing to biological aging.
Histone marks: covalent post-translational modifications of histone proteins that may modulate chromatin functions, including gene transcription, heterochromatin formation, and DNA repair.
Inflammaging: chronic, low-grade inflammation that develops during the aging process.
Memory T cells: long-lived antigen-specific T cells that remain after antigen clearance. Upon antigen re-exposure, these cells initiate proliferation and acquire effector functions.
Monozygotic twin pairs: also known as identical twins, they are the result of a single fertilized egg. They share identical genomic DNA and, thus, can be studied to infer epigenetic influences on phenotypic variation.
Somatic mutation: a change in the DNA sequence that occurs after fertilization in any cell of the organism other than reproductive cells.
T cell exhaustion: progressive loss of effector function and proliferative capacity of T cells due to excessive and continuous stimulation. These cells are characterized by their sustained expression of inhibitory receptors and reduced production of effector cytokines.
T cell senescence: terminal T cell state induced by intrinsic cellular stresses, such as DNA damage, as a consequence of repetitive antigenic stimulation. Senescent T cells have lost the ability to divide but are able to produce large amounts of proinflammatory cytokines.
Virtual memory T cells: cells that express phenotypic memory markers without ever encountering their cognate antigen, and the expansion of which relies on cytokine stimulation.

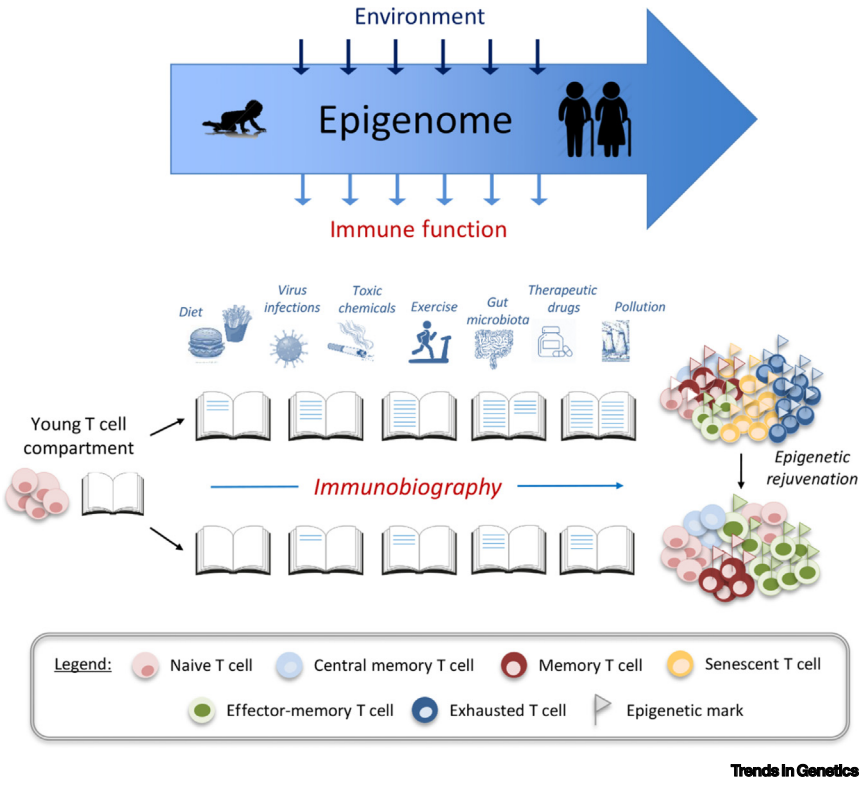

Figure 1. Contribution of the epigenome to the immunobiography during the life course. (Top) The epigenome integrates environmental changes into the phenotype and function of immune cells. Throughout life, this process could happen either randomly and independently of the immune cell type or in a deterministic manner, governed by the immune history of each individual (Bottom). The high plasticity of the immune cells makes young T cells (unwritten book) respond differently to a range of stimuli (diet, persistent viral infections, cigarette smoke, exercise, gut microbiota-derived metabolites, drugs or pollution, among others), creating a range of functional states (memory, effector-memory, senescent, and exhausted T cells). Thus, the decline of immune system functionality associated with age (immunosenescence) could be a consequence of the quality and strength of the initial stimuli that immune cells receive (immunobiography) and integrate throughout the epigenome. From this perspective, the loss of immunological fitness during the aging process could be restored by epigenetic rewiring.

immune cells in aged tissues. Consequently, two critical questions need to be addressed: how do epigenetic mechanisms contribute to the plasticity of immune cells, and how do they help establish the limits to cell identity and function during the aging process? The precise epigenetic mechanisms driving immunosenescence are yet to be disentangled, although we know that immunosenescence is a multifactorial process that is highly reliant on the environment and the many and varied antigenic challenges a human faces throughout their life (Figure 1). Epigenetic alterations appear not to be trivial; thus, the answer lies in determining which of these mechanisms are 'adaptive' and which are 'maladaptive', and how we could distinguish the two of them. The T cell compartment, in particular, is strongly molded with age, because it is constantly replenishing its cellular constituents and defending the organism against endogenous and exogenous threats. Continuous antigenic stimulation, driven by pathogens that produce latent and persistent infections, such as cytomegalovirus (CMV), herpes simplex virus (HSV)-1, HIV, and hepatitis B virus (HBV), or recurrent seasonal viruses, such as influenza, together with other sources of age-associated damage, including reactive oxygen species (ROS), metabolic stress (Box 1) and other environmental stresses, provoke chronic T cell stimulation. Such stimulation contributes to the **inflammaging** phenotype and the accumulation of dysfunctional subpopulations, such as the **senescent and exhausted T cells** observed especially often in older humans. However, although T cells are one of the main drivers of inflammaging [6], the causal relation between this process and age-associated epigenetic drift is not clear. In this sense, longitudinal studies to track the epigenetic behavior of T cells from the same individual during the aging process would be a very useful approach with which to address this matter.

Loss of the naïve T cell repertoire due to thymic involution, along with the accumulation of exhausted and senescent T cells, are key features seen in aged individuals. However, T cell exhaustion and senescence, while concomitant, are not equivalent at the epigenetic level. For instance, exhausted T cells depend on a TOX-induced epigenetic program and display specific enhancer maps [7,8], whereas senescent T cells rely on other epigenetic mechanisms that are more often shared with other senescent non-immune cell types. Importantly, mapping the epigenetic signatures of exhausted T cells after viral infection showed that anti PD-1 pathway blockade was not sufficient to reinvigorate these cells in a durable way as long as the antigen persisted [9]. This highlights the possibility that epigenetic modifiers have the last word in ensuring the long-lasting rescue of T cell functionality. Thus, persistent antigenic stimulation that occurs in older humans may act as a brake on T cell-efficient epigenetic rewiring. Remarkably, disease-specific epigenetic features have been identified within the exhausted T cell population [10], and it could be interesting to monitor these in the particular setting of age-associated diseases, with a view to

Box 1. Crosstalk between metabolic and epigenetic networks in immunosenescence

In recent years, it has become clearly established that metabolic and epigenetic mechanisms are functionally linked in immune cells. T cell activation involves genome-wide epigenetic remodeling accompanied by changes in glycolysis, and fatty acid and mitochondrial metabolism. This metabolic shift is, to a great extent, regulated at the transcriptional and epigenetic levels. However, metabolic changes can also act as drivers of epigenetic remodeling. For instance, T cell activation is associated with a glycolytic metabolic shift that involves the activation of lactate dehydrogenase A (LDHA), which increases acetyl-CoA levels [13]. This process enhances the deposition of H3K9Ac at the IFNγ promoter, inducing its expression. Therefore, metabolic and epigenetic networks do not act independently but interconnect, modulating each other in the immune cells.

By contrast, the immune system is also highly sensitive to systemic metabolic alterations. Metabolic disorders, such as obesity and type 2 diabetes mellitus, and cardiovascular diseases are associated with chronic low-grade inflammation and the acceleration of T cell senescence and exhaustion [14,15]. Consequently, dysmetabolic conditions are, in a sense, linked to immunosenescence. In this context, it could be hypothesized that the metabolic milieu is one of the primary drivers of the epigenetic drift observed in the aged immune system. In any case, it is likely that metabolic alteration associated with chronic diseases, or that is due to the normal deterioration of physiological functions during the aging process, may have an essential role in shaping our immune system.

Finally, metabolic alterations are also associated with age-related dysbiosis and low-grade inflammation. During aging, the composition and function of the gut microbiome changes, leading to a loss of bacterial diversity and a global decrease in beneficial metabolites, such as short-chain fatty acids (SCFAs). These metabolites are essential for the proper function and differentiation of immune cells via epigenomic modifications. Propionate and butyrate, two of the main SCFAs, act as histone deacetylase (HDAC) inhibitors, modulating the regulatory T cell (Treg)/Th17 balance, the CD8+ T cell effector function, and the inflammatory response [16]. Therefore, it is possible that age-associated epigenetic editing in immune cells is partially linked to the alteration of these metabolites.

designing immunomodulatory strategies. The drivers of senescence and exhaustion epigenetic signatures observed in older humans are yet to be dissected, although recent studies claim that signals coming from the old environment (geronic factors) are key to the shaping of different cellular identities and to the control of cellular plasticity [11,12]. For instance, the aged environment is fundamental in determining the expansion of **virtual memory T cells** [12], which may be achieved through epigenetic alterations that are stably maintained. It appears that, once the aged environment-derived molecules have shaped the epigenetic signature of the T cells, stable and largely irreversible changes are established. Thus, the full recovery of T cell functionality in the aged may need to be tackled not only by hindering tissue aging, but also by targeting the molecular pathways within the T cells *per se.* Further studies are needed to identify these cell-extrinsic age-related factors.

It is increasingly clear that there is an immunological adaptation to recurrent infections and chronic inflammation in aging that is tightly regulated at the epigenetic level, rather than being the result of an accumulation of stochastic genetic and epigenetic errors (Figure 1). We know that the quality and strength of T cell responses drop with increasing age, as part of the immunosenescence process, which leads to an ineffective response to novel antigens and vaccines and may result in an increase in the likelihood of occurrence of age-associated diseases, such as tumorigenesis, autoimmunity, chronic inflammation, and defective pathogen clearance. A recent example has arisen in the context of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which has disproportionately affected older people. Importantly, the use of epigenetics to discriminate between age-associated failures and useful adaptations of the T cell compartment encourages the design of interventions tailored to tackle specific age-associated diseases and to favor those states that are more advantageous to the individual.

Concluding remarks

A growing body of evidence suggests that chromatin acts as an integration node at which various aging mechanisms converge. Stimulation and polarization of immune cells leave persistent epigenetic traits, such that the epigenetic landscape is a true reflection of their immune history. On this basis, single-cell epigenomics could be used to reconstruct activation or differentiation trajectories associated with chronological age and pathological processes. In the future, this strategy should allow us to generate predictive signatures related to human disease and to track the loss of immunological fitness during the aging process.

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Declaration of interest

The authors declare that they have no competing interests.

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