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Review:

Epigenetics recording varied environment and complex cell events represents the origin of cellular aging*

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Abstract: Although a relationship between epigenetics and aging phenotypic changes has been established, a theoretical explanation of the intrinsic connection between the epigenetics and aging is lacking. In this essay, we propose that epigenetic recording of varied cell environment and complex history could be an origin of cellular aging. Through epigenetic modifications, the environment and historical events can induce the chromatin template into an activated or repressive accessible structure, thereby shaping the DNA template into a spectrum of chromatin states. The inner nature of diversity and conflicts born by the cell environment and its historical events are hence recorded into the chromatin template. This could result in a dissipated spectrum of the chromatin state and chaos in overall gene expression. An unavoidable degradation of epigenome entropy, similar to Shannon entropy, would be consequently induced. The resultant disorder in epigenome, characterized by corrosion of epigenome entropy as reflected in chromatin template, can be stably memorized and propagated through cell division. Furthermore, the hysteretic nature of epigenetics responding to the emerging environment could exacerbate the degradation of epigenome entropy. As well as stochastic errors, we propose that outside entropy (or chaos) derived from the varied environment and complex cell history, gradually input and imprinted into the chromatin via epigenetic modifications, would lead inevitably to cellular aging, the extent of which could be aggravated by hysteresis of epigenetics without error erasing and correction.

Key words: Epigenetics; Environment; Cell event; Cellular aging; Epigenome entropy; DNA methylation
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1 Introduction

Aging is the process of life becoming older, characterized by debilitating losses of tissue or cellular function. It refers to an irreversible, progressive, and deleterious syndrome of changes occurring at molecular, cellular, tissue, and organismal levels (Johnson et al., 1999; Campisi, 2013). The causes of aging are usually assigned to all kinds of damage, which cause biological systems to fail. This damage may be induced by toxic and nontoxic garbage accumulation, such as protein cross-linking and aggregation, advanced glycation end products (AGEs), atherosclerotic and amyloid plaques, inflammatory cytokines, lipofuscin, cortisol, metals, dichlorodiphenyltrichloroethane (DDT), and polychlorinated biphenyls (PCBs) (Koschinsky et al., 1997). They are also derived from metabolic damage (i.e. free radicals and glycation), telomere shortening, declining and inadequate antioxidant defense, defective cell cycle control, declining efficiency of proteasomes, lysosomes, and heat shock proteins (Yan et al., 1997; Reiter et al., 2000).

Epigenetics refers to heritable changes in gene activity and expression without alterations in the

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DNA sequence (Allis et al., 2015). Today, stable and long-term but not necessarily heritable alterations in the transcriptional potential of a cell are also assigned to epigenetics (Calvanese et al., 2009). Indexing the genome and potentiate signals from the environment, the chromatin in eukaryotic organisms can be viewed as a dynamic polymer. This chromatin template is modified by a variety of covalent and non-covalent modifications. These modification processes include post-translational histone modifications, chromatin-remodeling steps mobilizing or altering nucleosome structures, the dynamic shuffling of histone variants, and the targeting role of small non-coding RNAs (ncRNAs). DNA itself can also be methylated usually at the cytosine residue of CpG dinucleotides (Allis et al., 2015). All these mechanisms provide a set of interrelated pathways regulating the accessibility of the chromatin template to the transcriptional machinery and ultimately determine which genes are expressed and which are not (Pirrotta, 2016). These different patterns of gene expression and silencing may be heritable through cell division and collectively contribute to the cellular phenotype (Allis et al., 2015).

Epigenetics mediates the relationship between the genome and the environment (Sutherland and Costa, 2003; Cooney, 2007; Steves et al., 2012; Toyokawa et al., 2012). In fact, the human being starts with a fertilized egg with a single genome. Accommodating a plethora of environmental signals and intrinsic and external stimuli, the genome is epigenetically programmed to hundreds of different types of cells with a remarkable multitude of distinct phenotypes (Aguilera et al., 2010; Allis et al., 2015). Epigenetics responds to and records all the cell environment and events, including all types of environmental signals and changes, and a wide variety of intrinsic and external stimuli (Sutherland and Costa, 2003; Baccarelli and Bollati, 2009; Barros and Offenbacher, 2009; Feil and Fraga, 2012). Here we present a theoretical essay on how epigenetics, which stands at the crossroads of genetics and environment, is essentially related to aging. With respect to the basic relationship between epigenetics and environment, we aim to explain why epigenetics will inevitably and ultimately cause aging, a long-standing mystery. We propose that outside entropy (or chaos) derived from the varied environment and complex cell history, gradually input and imprinted into the chromatin via epigenetic modifications, would lead inevitably to cellular aging, the extent of which could be aggravated by hysteresis of epigenetics without error erasing and correction.

2 Environment and cell events may shape the DNA template into a spectrum of chromatin states through epigenetic modifications

We first depict how environmental cues and cell (i.e. transcriptional) events induce an opening state of the chromatin template through epigenetic modifications. When an environmental signal (external or internal) causes a specific transcriptional event (Alberts et al., 2008), the initiated transcriptional event can concomitantly induce the underlying chromatin template from a native state to an active and open state (Struhl, 1998; Cavalli and Paro, 1999). Responding to environmental cues and transcriptional events, a number of dynamic and elaborate epigenetic mechanisms combine together and interact closely to bring about an opening state of chromatin. This process is accompanied by a series of activated epigenetic modifications, including histone modifications, nucleosome remodeling, and the replacement of core histones with histone variants (Allis et al., 2015). An example of activated modification is histone acetylation, which is proposed to neutralize the positive charges of highly basic histone tails and generate a localized expansion of the chromatin fiber, thereby enabling better access of the transcription machinery to the DNA double helix (Hong et al., 1993). Histone acetylation is closely associated with the polymerase II machinery, thereby providing a simple mechanism to account for the general correlation between transcriptional events and histone acetylation (Struhl, 1998). With the onset of transcription, RNA polymerase II may recruit specific lysine methyltransferases (KMTs; histone-modifying enzymes) to set some specific histone methylations, such as H3K4me3 around the transcriptional start site and H3K36me3 within the coding sequences (Sims et al., 2004; Smith and Shilatifard, 2013). Such histone modifications in place are often represented as transcriptionally active chromatin (Sims et al., 2007). They are also read by subunits of the nucleosome remodeling complex,

inducing the recruitment of nucleosome remodeling machines and resulting in looping, twisting, and sliding of nucleosomes (Wysocka et al., 2006). In concert with activated histone modifications, these nucleosome remodeling mechanisms are particularly important for chromatin opening. Finally, the replacement of specific core histones with histone variants may further facilitate the unraveling of the chromatin template upon transcriptional events (Weber and Henikoff, 2014).

We then consider how the cell environment and its historical events induce the underlying DNA sequence into a closed state. Repressive chromatin modification on a DNA sequence can be specifically targeted by transcription factors (TFs), such as de novo DNA methylation (Brenner et al., 2005). This mechanism appears to be directly determined by environmental stimulus (external or internal), which usually induces the on/off of TFs through a wide variety of molecular pathways. Alternatively, in the absence of or at low frequency of specific environmental signals and inductions, a related segment of DNA sequence would not be frequently visited by TFs and transcribed by RNA polymerase II. We propose that the DNA segment in this condition is inclined to be closely packaged by the nucleosomes, and gradually silenced by another series of combinational epigenetic modifications. This consumption, although at a molecular level, is similar to "use it or lose it" theory as put forward by Lamarck. Nevertheless, our hypothesis is reasonable since the major enzymatic systems catalyzing histone modifications and DNA methylation have their counterpart enzymatic systems reversing the modifications. In fact, much of evidence supporting such a hypothesis has come from work on the de novo DNA methylation. In the presence of TF and transcriptional events, de novo methylation of CpG sites is abolished (Brandeis et al., 1994; Macleod et al., 1994; Straussman et al., 2009; Gebhard et al., 2010; Lienert et al., 2011). When the binding sites to TF are mutated, CpG islands come to a methylated state (Brandeis et al., 1994; Macleod et al., 1994). Similarly, when TFs binding to specific gene promoters are down-regulated, the now-exposed CpG sites can be targeted for DNA methylation (Lienert et al., 2011). As well as the establishment of DNA methylation in CpG islands from gene promoters and body regions, silencing epigenetic pathways also involve histone tail deacetylation, methylation of specific histone lysine residues (particularly H3K9), and recruitment of heterochromatin-associated proteins (e.g. HP1).

3 Environment and cell history are imprinted and propagated on chromatin template through epigenetic modifications

As discussed above, cell environment and the history of a living cell (i.e. a series of transcriptional events) can induce a chromatin segment between the on and off states through epigenetic modifications, thereby shaping the DNA template into a spectrum of chromatin states. These epigenetic signatures as imprinted on chromatin template, in turn record a varied cell environment and its complex historical events. Epigenetic modifications offer a molecular explanation for the memorization and inheritance of acquired traits induced by the environment and the past. They actually mirror the historical cell events and environmental changes, significantly contributing to phenotypic variation. Epigenetic signatures in chromatin can be viewed as marks of the epigenome recording the cell environment and antecedent events, and in turn strongly determining the accessibility and expression potential of a chromatin region. When these marks are stably recorded onto the template, they can be memorized, propagated, and transmitted over many somatic cell divisions (Nakayama et al., 2001; Kaati et al., 2002; Margueron and Reinberg, 2011; Song et al., 2011; Allis et al., 2015). Some acquired traits could even be trans-generationally transmitted in the sense of Lamarckian evolution (Kaati et al., 2002).

Classical genetics considers that a panel of TFs is responsible for activation and initiation of gene expression. However, the availability and binding of TFs are transient and will be immediately lost. According to classical genetics, persistent gene expression requires persistent availability of TF. However, current epigenetics fully recognizes that the transcriptional state (repressive or active) is strongly determined by epigenetic modifications. The gene expression pattern is actually controlled epigenetically rather than genetically (Laurent et al., 2005; Calvanese et al., 2009). Epigenetics strongly impacts gene expression by regulating the accessibility of the

underlying DNA template to the transcriptional machinery. When a primary signal from the environment (external or internal) and a historical transcriptional event induce the opening of the underlying DNA sequence, this opening of local structure can be stably memorized through several cycles of cell divisions even when the initial signal and TFs are no longer present (Allis et al., 2015). The chromatin template recorded with historical events and cell environment thereby significantly impacts the pattern of gene expression and greatly determines the further response to the emerging environment.

4 Varied environment and complex cell events result in a dissipated spectrum of chromatin state and lead to the chaos of overall gene expression

Cells in either unicellular or multicellular organisms live in an unpredictable and variable environment. They are exposed to all kinds of environmental factors in the whole living history (Fig. 1a). These varied environmental factors/conditions can either be biotic or abiotic. Abiotic factors include temperature, pH, redox, ionic concentrations, nutrient availability, etc. Biotic factors can be physiological, including intracellular or extracellular signaling molecules, energy and metabolism homeostasis, chemotaxis, healthy and aging states, and so on. Biotic factors can also be pathological, including oxidative stress, toxic compounds, ultraviolet (UV) radiation, osmotic pressure, all types of wounding, inflammatory cytokines, pathogen infection, and so on (Sutherland and Costa, 2003; Baccarelli and Bollati, 2009; Barros and Offenbacher, 2009; Feil and Fraga, 2012; Yang et al., 2018). The history of a cell life is extremely complex and involves a variety of cellular events (Fig. 1b). They include information processing (i.e. transcription, translation, and replication) and cell signaling, growth and differentiation, metabolism, division, protein synthesis, and so on. Throughout their whole life, cells are doomed to undergo a variety of exogenous stresses and pathological attacks (Alberts et al., 2008; Feng et al., 2016).

Generally in a eukaryotic cell, each regulatory gene regulates the expression of a number of genes. Meanwhile the expression of this regulatory gene is usually regulated by many other regulated proteins. Tens of thousands of interactions between genes are organized into very complex networks that help to coordinate the cell's activity and relay signals into the cell from the cell's environment. Many a time, a regulated gene is involved in a multiple of cellular pathways. Through these molecular cell pathways, cells can respond and adapt to a wide variety of

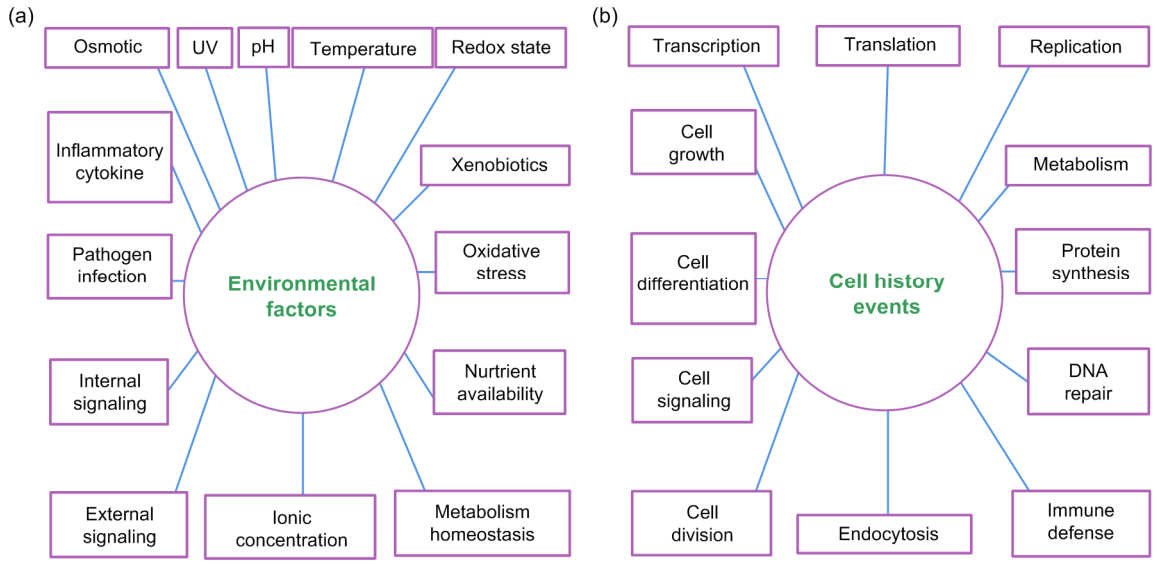

Fig. 1 Cells live in an unpredictable environment comprising many diversified environmental factors (a) and undergo a wide variety of cellular historical events (b)

environmental factors. To answer a change of specific environmental factor (EF) such as EF I, we assume that a specific collection of gene variations is involved. This collection of gene assembly, through elaborating up-regulation or down-regulation of gene expression, collaborates and coordinates together to cope with the variation of a specific environmental parameter (Fig. 2a). However, actually, cells are exposed simultaneously to some other different environmental factors. The expression pattern of a specific gene that is up-regulated by one environmental factor, could be either down-regulated antagonistically or up-regulated synergistically by another environmental factor (Fig. 2b). These environmental factors are usually characterized by diversity and in conflict. In fact, unpredictable variation with diversity is an intrinsic aspect of different environmental factors. The assembly pattern of gene expression must answer all of these different environmental factors, and has managed to reconcile between those diverse, discordant, and conflicting factors (Fig. 2c). Imprinted by these varied environmental factors, a chaos of epigenetic states would be generated in the related regions of chromatin. An irreconcilable conflict between the ideal genetic regulation and the suboptimal epigenetic state would be conveyed to the chromatin template in answering each environmental factor (Fig. 2d). A perfect match between the actual epigenetic states and ideal genetic regulations in answering each specific environmental factor (here referring to EF I) actually does not exist (Fig. 2e). This awkward situation can even be generated by the overlay of environmental factors with temporal difference, considering the memorable (also hysteretic and irreversible) property of epigenetic modifications. An environmental factor changing in the opposite direction at different time can also produce such a discrepancy between the real epigenetic states and ideal genetic regulations.

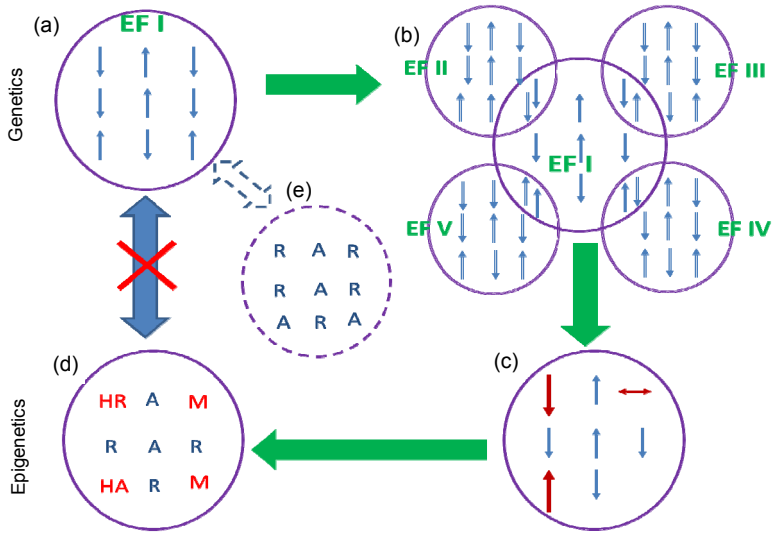

Fig. 2 Varied environmental factors producing irreconcilable conflict between the ideal genetic regulation and the suboptimal epigenetic state

(a) A specific collection of gene variations, up-regulated (↑) or down-regulated (↓), is involved to answer a specific environmental factor (EF I); (b) Actually, cells are exposed to and inevitably have managed to answer some other different environmental factors (i.e. EF II, EF III, EF IV, and EF V); (c) Both the synergistic (↑ or ↓ (red), vertical arrows) and antagonistic (↔, horizontal arrow) effects can be generated in the assembly pattern of gene expression in answer to all of these varied environmental factors; (d) Imprinted by these varied environmental factors, a spectrum of epigenetic states could be generated in the related regions of chromatin (A: activated epigenetic state; HA: highly activated epigenetic state; R: repressive epigenetic state; HR: highly repressive epigenetic state; M: medium epigenetic state). Consequently, the irreconcilable conflict between the ideal genetic regulation (a) and the suboptimal epigenetic state (d) would be conveyed in answering each environmental factor. (e) A perfect match between the ideal genetic regulations and actual epigenetic states in answering each specific environmental factor (here refers to EF I) actually does not exist (Note: for interpretation of the references to color in this figure legend, the reader is referred to the web version of this article)

Such conditions of dilemma as a result make cells always in suboptimal situations in response to the complex environment and become more sensitive to all aspects of damage sources and threatening factors. More importantly, when cells are exposed to a superposition of such varied environmental factors and complex cell events for a sustained period of time, all traits of their disorder would be recorded onto the chromatin template through various epigenetic mechanisms as depicted above. The irreconcilable conflict between the desired genetic regulation and the suboptimal epigenetic state would be conveyed to the chromatin template. When a wide diversity of environmental factors and the complex history of events are mapped together to the chromatin template by the combinational epigenetic modifications, a dissipated spectrum of chromatin state could unavoidably be produced. Mapping ultimately to the chromatin template, such chaos and disorder would inevitably lead to a gradual degradation of "epigenome entropy."

We now consider building a model of epigenome entropy. The epigenome is a semiosis system with many similarities with languages and computer systems. Thereby, the information (or Shannon) entropy can be used as reference for the definition of epigenome entropy. Since Shannon entropy is negatively related to thermodynamic entropy, cells at age of zero are assumed to have the maximum value of epigenome entropy. The resultant disorder in the chromatin template with age growth actually reduces epigenome entropy. For a specific epigenetic mechanism such as DNA methylation, the reduced epigenome entropy in a single cell is proposed to be represented as Eq. (1):

$$\Delta\text{Entropy}_{\text{DNA methylation, single cell}} = -\sum_{i=1}^{n} W_i \times \frac{1}{2}\log_2\left(\frac{1}{2}\right) = \frac{1}{2}\sum_{i=1}^{n} W_i, \quad (1)$$

where i refers to the sequence number of CpG sites where the status of DNA methylation, demethylation or methylation, has changed in response to changing environment and cellular events. Because the gene regulation impact of each change in DNA methylation at different chromatin sites is different, we introduce a weighting coefficient W_i to the model. For the sake of computability, the values of W_i can be assigned to a few fixed values based on the genome regions of CpG sites (i.e. gene promoter, gene body, and inter-genetic region). The reduced epigenome entropy derived from DNA methylation for a cell assembly with J cells can be represented as Eq. (2):

$$\Delta\text{Entropy}_{\text{DNA methylation, cell assembly}} = \frac{1}{2}\sum_{i_1=1}^{n_1} W_{i_1} + \frac{1}{2}\sum_{i_2=1}^{n_2} W_{i_2} + \ldots + \frac{1}{2}\sum_{i_j=1}^{n_j} W_{i_j}. \quad (2)$$

For a homogenous cell assembly, Eq. (2) can be simplified to Eq. (3):

$$\Delta\text{Entropy}_{\text{DNA methylation, cell assembly}} = \frac{1}{2}J \times \sum_{i=1}^{n} W_i \times \sqrt{(D_{i,t} - D_{i,0})^2}. \quad (3)$$

$D_{i,t}$ is the percent of DNA methylation for site i at time point t, and $D_{i,0}$ is the percent of DNA methylation for site i at original time. J refers to the cell number of the cell assembly.

The quantification of reduced epigenome entropy from some other epigenetic modifications, i.e. all forms of histone modifications, can be obtained using a similar discipline to that above. The "epigenome entropy" should be inevitably decreased. The resultant chaos would gradually accumulate in a living cell, or even pass to its offspring cells, since the epigenetic modifications can be memorized, propagated, and transmitted over many somatic cell divisions. Note that the environmental factors and history events here refer to those lasting for a time period and occurring at a certain intensity, which can produce distinct chromatin alternations.

5 Irreversibility and hysteresis of epigenetics in response to the emerging environment and new events may induce the increased loss of epigenome entropy

One defining characteristic of epigenetics is its relative irreversibility and hysteresis (Laurent et al., 2005; Nagaraj et al., 2014). Many epigenetic marks may persist through several rounds of cell division, and a few could even be inherited as germ line modifications. A typical example is shown in the reprogramming field. In recent years, one of the most

influential discoveries is that somatic cells can be induced to become pluripotent stem cells in tissue culture (Takahashi and Yamanaka, 2006). However, the efficiency of reprogramming was actually very low (<0.1%). Certain somatic epigenetic modifications, such as repressive H3K9me3 and DNA methylation, are the major obstacles, which are very difficult in reprogramming. These epigenetic modifications are stably transmitted through somatic cell divisions and some even resist reprogramming in the oocyte.

In fact, hysteresis occurs ubiquitously in biology in different spatiotemporal scales. Epigenetics has many characteristics of a non-linear bi-stable system, exhibiting distinct hysteresis effects and an associated bifurcation diagram (Noori, 2014). Darlington (1937) discussed hysteresis in his classic works on genetics, as something that occurs as a failure of the external form of the chromosomes to respond immediately to the internal stresses of the chromosomes. In cells with distinct epigenetic modifications, gene expression is actually controlled by the combinational functions of both epigenetics (external form) and genetics (internal stresses). The epigenome carries the chromatin signatures as a memory of historical environment and events, and subsequently affects the expression pattern of genes responding to a new environment and emerging events. The hysteretic nature of epigenetics makes the current state of underlying chromatin, which has been recording the historical environment and events of a cell, a key determinant of the gene expression pattern. Recorded with the past environment and cell history, cells modify the chromatin template to accommodate the new environment and emerging events. It means that epigenetic modifications are not entirely responsive to the present environmental stress, but it seems to make compromised epigenetic modifications between the existing epigenetic records and genetic stresses derived from the emerging environment. This is similar to two component forces (epigenetic records and genetic stresses) producing a resultant force (emerging epigenetic modifications) (Fig. 3a). As shown in Fig. 3b, epigenetic hysteresis may potentially result in a range of epigenetic states when confronted with a specific genetic stress, dependent on historical cell events and environmental changes. Hysteresis thereby results in significant epigenetic drift for different cells, where the possible pattern of epigenetic states at different gene locations varies greatly for different cells corresponding to environment change (Fig. 3c). To answer one changing environment, the epigenetic state for the collection of genes involved would be modified, but with different hysteretic paces. As shown in Fig. 3d, the epigenetic state of cells at each gene location is first at their beginning position. After a series of round-trip changes in cellular events or environmental parameters, dissipated patterns of epigenetic states could be generated due to a different hysteretic degree of epigenetic modifications at different gene locations. Although epigenetic hysteresis makes gene expression more resistant to noise, it inevitably leads to a dissipated spectrum of the chromatin state with degradation of epigenome entropy as an inevitable side-effect.

6 Epigenetic modifications on single copy chromatin lack the mechanisms of error-epigenetic checking and erasing

To maintain a homeostatic and healthy state, life has a myriad of checkpoints, error-correcting mechanisms and immunities to defend against all kinds of damage (Johnson et al., 1999; Alberts et al., 2008). Combating metabolic damage such as free radicals and glycation, life can create fewer free radicals by more efficient mitochondria. They may use less energy to live, and have more effective antioxidant defenses, better DNA protection and DNA repair. Stem and germ cells contain telomerase to prevent telomere shortening. Animals can have a better immune system and detoxify more effectively in the liver tissue. To avoid garbage accumulation, damaged and misfolded proteins are eliminated by the enzymatic and proteolytic proteasomes. Lysosomes are responsible for the degradation of aging mitochondria.

Unlike the error-correcting mechanisms combating all aspects of damages as listed above, so far there is no evidence for mechanisms of error checking for epigenetic modifications. Epigenetic modification is a dynamic process and is not sustained over an indefinite period. Most characteristic epigenetic marks can be reset during the course of differentiation (Kohli and Zhang, 2013). The modification or reprograming of the epigenome of a cell is strongly influenced by its

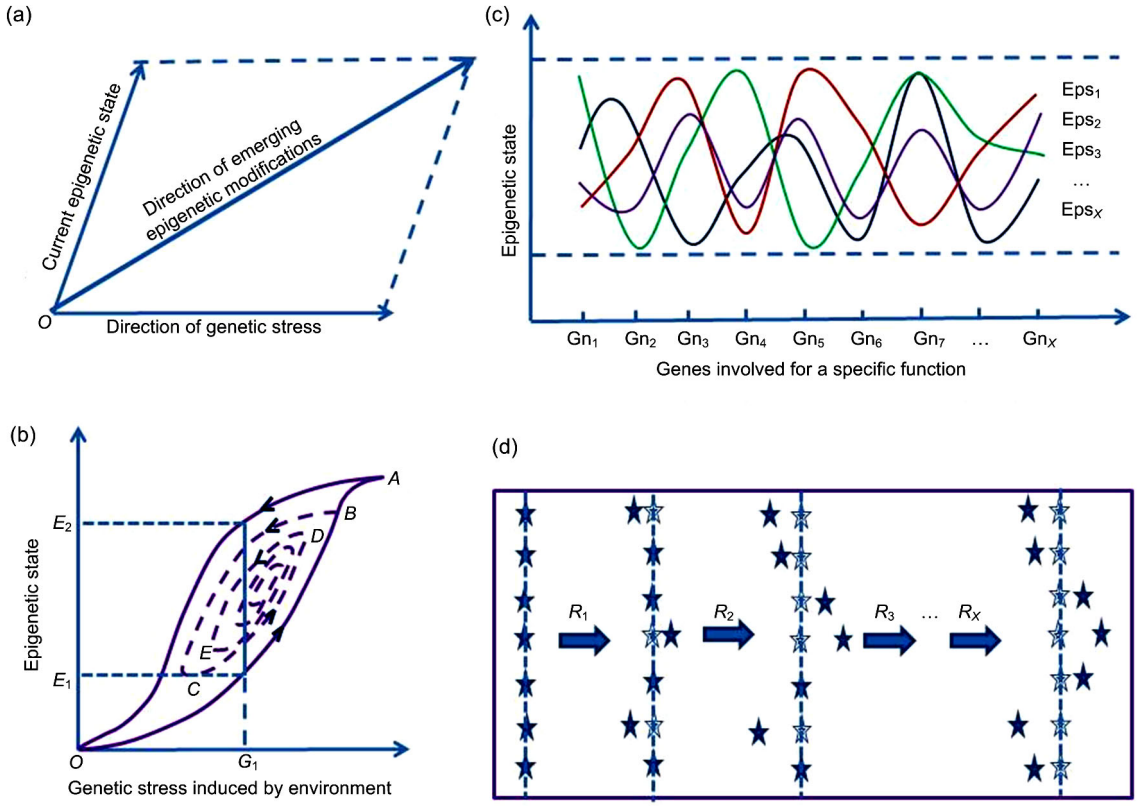

Fig. 3 Irreversibility and hysteresis of epigenetic modifications in response to new environment and emerging events, which would inevitably lead to a dissipated spectrum of chromatin state with increasing loss of epigenome entropy
(a) Cells make compromised epigenetic modifications between the epigenetic records and stresses derived from environment. (b) Epigenetic hysteresis may produce a range of epigenetic states (from E_1 to E_2) when confronted with a specific genetic stress (G_1). A, B, C, D, and E refer to the possible states when a cell responds to the varied environment. (c) Hysteresis thereby results in epigenetic drift, where the epigenetic states (Eps_1, Eps_2, Eps_3, …, Eps_X) of different cells at each gene location (Gn_1, Gn_2, Gn_3, …, Gn_X) vary greatly in a specific environment; (d) The epigenetic state at each gene location (symbol of five-point stars) is first at their beginning position. After a series of round-trip changes (R_1, R_2, R_3, …, R_X) in specific cellular events or environmental parameters, dissipated patterns of epigenetic states are generated due to the different degrees of hysteresis for different gene locations

surrounding cells via the intercellular junctions. The epigenetic deflection of this cell might be partly rectified from the extracellular microenvironment. However, all mechanisms of epigenetic modifications including those putting chromatin marks in place, maintaining and responding to them, are first based on the existing chromatin states, which have been imprinted with past events and environment. It is the past environment and cellular events superposed with ongoing genetic stresses that determine the new assembly pattern of epigenetic modifications. Except for germ cells, most somatic cells lack the molecular mechanisms of checking and erasing epigenetic modifications. There are no cellular pathways to recover lost epigenome entropy with age growth. Although the DNA double helix provides potential mechanisms for DNA replication and repair, and for the maintenance and propagation of DNA methylation (Song et al., 2011), it does not provide mechanisms for error-checking or erasing of epigenetic modifications in either histone or DNA sequence level. Epigenetic disorders are eliminated only in the germ cells. The renewing of epigenetic modifications is carried out in embryos of new life, but not in any adult animal cells.

Through deposition of various epigenetic modifications, the DNA double helix records the cell history and responds to the changing environment. As illustrated above, epigenetic modifications are regulated

by an array of delicate molecular machines, including DNA-binding interactions, histone modifications, histone variants, nucleosome remodeling, DNA methylation, and ncRNAs (Allis et al., 2015). On the one hand, this highly organized and dynamic polymer can be viewed as a single molecule because for each specific DNA sequence only one copy exists in the cell nucleus. On the other hand, the process of epigenetic modification is extremely elaborate and intricate, requiring the assembly of very many multi-protein complexes. It is the low-affinity associations of hundreds of multi-proteins along a DNA sequence. Thereby, one would expect that stochastic factors should play a substantial role in depositing epigenome disorder and chaos onto the chromatin. The stochastic errors and imperfect fidelity in maintenance of epigenetic marks are generally thought to be the main mechanism of epigenetic drift, a gradual change away from baseline, and aging (Martin, 2005; Teschendorff et al., 2013; Issa, 2014). As well as stochastic errors, in this essay we propose that epigenetic disorder and chaos imprinted by varied environment and complex cell events play an essential role in epigenetic drift and the resultant cellular aging.

7 Cellular aging as a result and its implications on organismal aging and cell life expectancy

Mechanisms behind cell aging are extensively addressed, which include telomere shorting, genomic and epigenomic damages, oxidative stress, unbalanced mitogenic signals, and so on (Johnson et al., 1999; Campisi, 2013). Epigenetics has emerged as an important subject area in aging biology (Calvanese et al., 2009; Horvath, 2013; Huidobro et al., 2013; Brunet and Berger, 2014; Lardenoije et al., 2015). The relationship phenomenon between epigenetic drift, a gradual change away from baseline, and age was proposed many years ago (Martin, 2005; Teschendorff et al., 2013; Issa, 2014). The direct relationship between epigenetic modification and cellular aging is generally ascribed to epigenetic drift, which is described as stochastic errors and imperfect fidelity in maintenance of epigenetic marks. It is proposed that the fidelity of transmission of epigenetic patterns is variable across the genome (Issa, 2014). Epigenetic drift is related to many of the aging phenotypic changes. For example, genomic global DNA methylation decreases with age (Berdyshev et al., 1967), whereas a number of specfic loci become hyper-methylated during aging (Oakes et al., 2003). Other important epigenetic factors, such as histone modification, also change during aging (Narita et al., 2003). Although the relationship between epigenetic drift and aging phenotypic changes is established, the intrinsic nature of epigenetics causing cellular aging and ultimately the organism aging is not yet fully elucidated. An intrinsic connection between epigenetics and aging still needs to be theoretically illuminated.

Aging can be considered as an irreversible, progressive, and deleterious syndrome with gradual increase of disorder, chaos, and entropy occurring in a living system as changes at molecular, cellular, tissue, and organismal levels. We depict the inner nature of epigenetics recording complex historical events of a living cell and the associated outside environment changes. We then propose that outside entropy (or chaos) derived from the varied environment and complex cell history, gradually input and imprinted into the chromatin via epigenetic modifications, would lead inevitably to cellular aging, the extent of which could be aggravated by hysteresis of epigenetics without error erasing and correction (Fig. 4). An inevitable dissipated spectrum of chromatin state with degraded epigenome entropy as imprinted by complex history of a living cell and variable environmental factors will ultimately cause cellular aging. From this point of view, we propose that cellular aging is inherently rooted in epigenetics, not requiring any specific hormonal signaling and transcriptional programming, although we recognize that specific mitogens and proliferation-associated genes are involved.

Cellular senescence/aging is thought to play an essential role contributing to tissue and organismal aging (Ben-Porath and Weinberg, 2005; Tchkonia et al., 2013). Senescent cells with degraded epigenome entropy could ultimately induce tissue and organismal aging. We believe that it is epigenetic recording of unpredictable environment and complex cell events that determines the inevitable aging of cells. In this epigenetic point of view, one could predict that life expectancy of a living cell in animals is strongly impacted by the stability of its living experience and

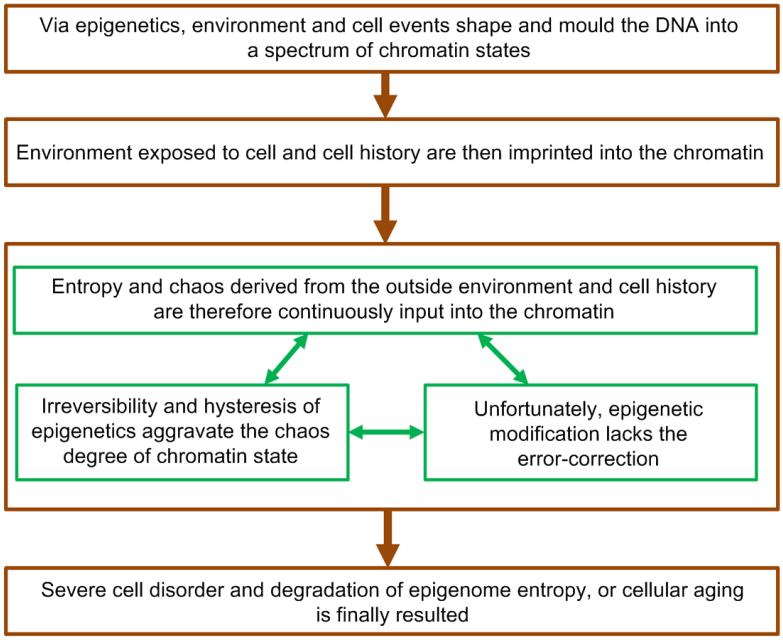

Fig. 4 Outside entropy (or chaos) derived from the varied environment and complex cell history, gradually input and imprinted into the chromatin via epigenetic modifications, would lead inevitably to cellular aging, the extent of which could be aggravated by hysteresis of epigenetics without error erasing and correction

surrounding environment, the plasticity of its epigenetic mechanisms, and the complexity of its physiological function. A living cell in animals is expected to have relatively long life expectancy if its living experience and surrounding environment are stable, if its epigenetic modification is more plastic, and if its physiological functions are relatively simple and narrow.

As an example, the environment of the living niche for a stem cell is very stable. Its epigenetic state is quite plastic (Hemberger et al., 2009). The physiological function of a stem cell is mainly division and renewal, which is supposed to be relatively simple and specific. Thereby, the stem cell usually has a longer life expectancy. Similarly, neurons in the human brain have a long life expectancy likely due to their highly stable living environment and highly specified function as processing and transmitting electrical and chemical signals. However, the hepatocyte lives in an unpredictable environment with all types of variable stresses. The hepatocyte in the human body is responsible for a very comprehensive function, including protein synthesis, detoxification, and carbohydrate and lipid metabolism (Klaassen, 2008). Epigenome entropy in the hepatocyte is likely to degrade more rapidly, as imprinted by its multi-physiological processes and variable environment stresses. Therefore, hepatocytes in animals often have a relatively short life expectancy.

Contributors

Xue-jun GUO was responsible for the presentation and derivation of the viewpoints of this review, and the writing of this paper. Dong YANG and Xiang-yuan ZHANG helped the revision of this work. All authors read and approved the final manuscript.

Compliance with ethics guidelines

Xue-jun GUO, Dong YANG, and Xiang-yuan ZHANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：多变环境和复杂事件的表观遗传记录是细胞的衰老之源

概　要：虽然表观遗传和衰老的关联性已经被广泛接受，但是两者之间内在的因果关系需要深度的理论阐述和分析。本文通过分析环境与表观遗传相互作用及其过程的本质特征，证明表观遗传记录多变的细胞环境和复杂的细胞事件是细胞的衰老之源。细胞周围环境以及所经历事件可通过表观修饰激活或抑制染色体上各个基因的表达，从而对染色体模板以及基因表达模式进行塑造。外在环境和细胞历史的多变性以及内在冲突性由此被逐渐记录在染色体模板上，整体上导致染色体模板以及基因表达模式的混乱和耗散。这将导致细胞表观熵（类似于 Shannon 信息熵）不可避免地逐渐衰减，其混乱度可通过细胞分裂而进一步被稳定积累、记忆和扩增。另外，表观修饰应对外在环境的变化存在滞后性和一定的不可逆性，加剧了表观熵的衰退。

关键词：表观遗传；环境；细胞事件；细胞衰老；表观熵；DNA 甲基化