Epigenetics and aging

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Abstract

Aging is a multifaceted process characterized by genetic and epigenetic changes in the genome. However, epigenetic mechanisms have now emerged as key contributors to the alterations of genome structure and function that accompany aging. The epigenetic mark that has been most highly studied is DNA methylation. In this review, we focus on healthy human aging throughout lifetime and discuss dynamics of DNA methylation as well as how interactions between the genome, environment and the epigenome influence aging rates.

Keywords: Aging, Epigenetics, DNA, Methylation, Epigenetic Changes.

Introduction

Age

Why we age has been a question of heated debates for a very long time (Brunet & Berger, 2014). Age is the final destination in a human lifespan it is characterized by decline and an increase incidence of age- related degenerative diseases like diabetes, cancer, cardio vascular diseases and dementia. Now it is widely accepted that aging has multiple causes. LOPEZ, in a recent review (2013) proposed nine hallmark of aging in different organisms that represents common denominators these hallmarks are:

1. Genomic Instability
2. Telomere Attrition
3. Epigenetic Alterations
4. Loss of Proteostasis
5. Deregulated Nutrient Sensing
6. Mitochondrial Dysfunction
7. Cellular Senescence
8. Stem Cell Exhaustion
9. Altered Intercellular Communication

All these causes of aging are not independent, epigenetic systems control gene activity and thus directly and indirectly affect all other hallmark (Campisi, 2013). Scientific research has brought up many different theories trying to explain the aging problem, but none of them fully explain all of the aspects of aging process. The most known and studied is the free radical theory of aging by Denham Harman, which identifies the accumulation of free radicals produced by the energetic metabolism of the mitochondria that end up causing cellular toxicity (Harman & Maggert, 1956) and damage to the nuclear DNA (Bohr & Anson,1956), to cellular membrane structures , and to mitochondrial DNA (Balaban,2005). Several evidences support that aging is also associated with epigenetic changes (Lopez, 2013). Ground breaking studies performed in rat brain and heart showed a global loss of DNA methylation during aging (Vanyushinet,1973), which was later confirmed in different tissues from, rat, mouse, and cow (Romanov,1981), in primary fibroblasts from mice, hamsters, and humans grown in culture and in human lymphocytes and peripheral blood cells.

In summary, young healthy cells maintain an epigenetic state that promotes the formation of compact chromatin structure and precise regulation of all the biological processes. However, aging cells exhibit changes in all aspects of chromatin landscape, DNA accessibility and ncRNA production which finally leads the cells to succumb a permanent halt in progression through the life cycle.

This article aims to provide different concepts for understanding epigenetic effects on aging process and also provides understanding into epigenetic prevention and therapeutic strategies for age related human diseases.

Aging

It is manifested by gradual decline of normal physiological functions in the time- dependent manner. Organismal aging holds significant importance for human health, because it increases susceptibility to many diseases including, Cancer, Metabolic disorders, cardiovascular disorders and neurodegenerative diseases (Brunet & Berger, 2014).

On the other hand cellular senescence also called replicative senescence is a specialized process, considered to be a potential endogenous anticancer mechanism, during which there is an irreversible growth arrest in response to potentially oncogenic stimuli. Cellular senescence bears many similarities to the aging process but shows distinct features also (Holliday, 2006).

The epigenetic machinery

Holliday, in 1987, referred the term epigenetics as heritable changes in gene expression that are not due to alterations in the DNA sequence (Campisi, 2013). Therefore, these heritable changes, regulated by different systems include DNA methylation (DNAm), noncoding RNAs, histone modifications and variants.

Epigenetics and aging relation

The process of aging results in a host of change at the cellular and molecular levels, which includes senescence, telomere shortening and changes in gene expression.

Epigenetic pattern also changes over the life span, suggesting that the epigenetic changes may constitute an important component of aging process. Epigenetics not commonly defined as modifications to DNA and DNA packaging that do not involve changes to DNA sequence and that are potentially transmissible to daughter cells (Bird & Berger, 2007).

The epigenetic mark which has been studied is DNA methylation, the process of methyl group at CPG Dinucleotide. These are often located near genes, promotes and associates with gene expression level**.**

How are epigenetics and aging related

The studies indicate that global levels of DNA, increases over first few years of life and then decreases with age. The concept of epigenetics is shown in developmental processes. The epigenetic patterns which exhibit during embryonic development are maintained throughout life in the somatic cells. These patterns are stable throughout life but certain changes occur in specific location due to environmental stimuli and recently with the advent of microarray and next generation sequencing technologies, increase in variability of DNA methylation with age have been observed and a number of site specific patterns have been identified. These observations point to existence of two phenomenon that both contribute to age related DNA methylation changes, epigenetic drift and epigenetic clock.[8] Epigenetic alterations represents one of the hallmarks of aging, by being an important mechanism behind the deteriorated cellular functions observed during aging. It is proposed that regulated epigenetic machinery slowly becomes deregulated leading to an altered epigenetic state with a process called epigenetic drift, and because of adaptation to environmental stimuli, this could render to increased risk of acquiring a number of age related changes. The information encoded within our epigenome includes DNA methylation, chromatin remodeling, post translational modifications of the histone proteins, structural and functional variants of histones, and transcription of noncoding RNAs. The combination of all of these different types of epigenetic information comprises the function and fate of cells and tissues.

Epigenetic Drift vs, the epigenetic clock: two phenomena underlying the relationship between DNA methylation and aging

Both epigenetic drift and the epigenetic clock contribute to age related DNA methylation changes, but in fundamentally different ways. While both are related to age, epigenetic drift represents the tendency for increasing discordance between epigenomes over time. Conversely, the epigenetic clock refers to specific sites that are consistently related to age across individuals.

We define, epigenetic drift as the collection of DNA methylation changes that are associated with age within an individual but are not common across individuals. The epigenetic clock, on the other hand, represents those sites that are associated with age

across individuals and can thus in some cases be used to predict chronological age.

Human diseases assosciated with age and epigenetic therapies

An aged epigenome is closely linked to reduced plasticity of stem cells, limited stem cell and malfunction of somatic cells in which alterations could result in pathologic changes. Most of the age related changes have an epigenetic component.

Numerous studies have shown a large spread variation in age related diseases like non communicable diseases such as cancer, diabetes and cardiovascular diseases. For example age related epigenetic component could induce long term alterations in metabolic regulations that causes Type 2 diabetes.

Genetic and epigenetic damage in aging is also related to cancer. Age related epigenetic risk may be the key factor to explain the rise of human cancer as human ages. Cancer susceptibility increases as cells accumulate epigenetic alterations and mutations during aging. Cancer is characterized by DNA hypo methylation and site specific promoter hyper methylation. Expression of miRNAs is altered during malignancy. Not only environmental stimuli like carcinogen induced genetic changes (e.g. Mutation) is a contributing factor to carcinogenesis, epigenetics adds up which might mediate link between genotype and environmental factors.

DNA methylation and allergic diseases

Allergic diseases are clinical conditions characterized by allergic hypersensitivity, the most prevailing diseases are Asthma, eczema, food allergy and anaphylaxis. Allergic diseases have been linked with genetic causes, environmental exposure. Family history is the most commonly associated risk factor and increased occurrence in monozygotic twins compared with dizygotic twins suggest that genetics play an important role. Several asthma and allergy susceptibility genes are epigenetically regulated for e.g. Transcription of STAT (6) and FOXP3 is regulated by DNA methylation. DNA methylation is deregulated in allergic diseases.

Aging skin

Skin is a vital organ that functions as a protective barrier against environmental factors. Skin aging is a complex biological process caused by intrinsic factors like structural, hormonal, and by extrinsic factors such as UV Radiations and chemicals. The regenerative ability of skin is maintained by the stem cells that are present in skin to provide for cellular turnover during repair upon injury. Multiple signaling pathways on genetics and epigenetic levels are important for regenerative properties of the skin stem cells. Data demonstrates widespread hypo methylation of the genome associated with sun exposure, the degree of hypo methylation is co-related with clinical measures of photo aging on skin.

Epigenetic alterations in premature aging

Premature aging syndromes have been instrumental in the characterization of molecular mechanisms that contribute to physiological aging. One of the most devastating syndromes of premature aging in humans is Hutchinson Gilford Progeria Syndrome (HGPS). HGPS is caused by mutation in the gene coding A - type Latin's, Latin's A and C, structural components of nuclear lamina and the inner nuclear matrix. The mutation in the LMNA gene associated with progeria leads to the expression of a truncated form of lamin A known as progeria, which is toxic to the cells. Interestingly, normal human fibroblasts from aged individuals also express progeria, linking alterations of A- type Lamins to physiological aging.

Enviornment, Nutrition and age related epigenetics

Several studies have determined the importance of environmental factors in regulation of aging and longevity, including diets, chemicals, lifestyles and radiation exposure. Physical activity can influence chromatin function, and promotes overall health and aging delay in humans.

Diet is the key environmental factor that shapes the activity of epigenome, both quantity and quality of diet may play crucial roles in the regulation of aging processes and chromatin structure.

Concluding remarks and future directions

A whole body of evidence indicates that alterations in the three major epigenetic mechanisms, DNA methylation, histone modifications, and ncRNAs, are hallmark for aging. These alterations can impact large chromosomal domains or specific genomic loci within the chromosome. Several epigenetic marks undergo changes during aging, this disorder of chromatin landmarks leads to age related diseases, which also affects the lifespan. The main cellular consequences of epigenetic deregulation are changes in the transcriptional activation and repression of many genes, an increase in genomic stability, and loss of phenotypic plasticity in aging and structural defects in heterochromatic domains which contributes to aging pathogenesis. The aging process is unquestionably complex. Genetic and environmental manipulations are unequivocally important to decipher the effect of any factor over the longevity process, it is becoming apparent mechanistically that many of those factors that do affect longevity act primarily through the modifications of epigenome. An understanding of age related epigenetic drift will allow us to manipulate the epigenome.

Various epigenetic modulators such as dietary components can be used to prevent or reverse epigenetic alteration during aging. Work on the effects of environmental stimuli on the rates of epigenetic aging would contribute on how or why specific environmental exposures result in increased mortality. Future research will be necessary to evaluate the optimal dosage and exposure for specific dietary components to get maximum epigenetic benefits against age and age related changes and further improve the quality of life. In summary knowing epigenome and being able to handle it hold promise for curing age related pathologies and extending the healthy lifespan.

The romance between nature and science is ever evolving. Man would keep unfolding the mysteries of nature and keep learning and growing. Research workers can come close to nature, may not be able to replace nature.

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Conflict of Interest

None.

References

1. Brunet A & Berger S.L. Epigenetics of aging and aging related disease. *J Gerontol Series Biol Sci Med Sci* 2014;69(1):517-20.
2. Bird A & Berger S.L. Perceptions of Epigenetics. *Nature* 2007;447(7143): 396-398.
3. Deans, C & Maggert, K.A. What Do You Mean, "Epigenetic"? *Genet* 2015;199(4):887-96.
4. Harman, D & Maggert, K.A. "Aging a theory based on free radical and radiation chemistry,". *J Gerontol* 1956;11(3):298-300.
5. Holliday, R. Aging is no longer an unsolved problem in biology. *Ann NY Acad Sci* 2006;1067:1-9.
6. Campisi J. Aging, cellular senescence and cancer. *Annu Rev Physiol* 2013;75:685-705.
7. Lopez-otin. The hallmarks of aging. *Cell* 2013;153(6):1194-1217.
8. Jones. DNA methylation and healthy human aging. *Aging Cell* 2015;14(6):924-932.
9. Holliday R. The inheritance of epigenetic defects. *Sci* 1987;238(4824):163-70.
10. Balaban. Mitochondria, oxidants, and aging. *Cell* 2005;120(4):483-95.
11. Romanov. Methylation of reiterated sequences in mammalian DNAs Effects of the tissue type, age, malignancy and hormonal induction. *Biochim et Biophys Acta* 1981;653(2):204-18.
12. Bohr V.A. & Anson R.M. DNA damage, mutation and fine structure. DNA repair in aging. *Mutation Res* 1995;338(1-6):25–34.
13. Vanyushin. The 5 methyl cytosine in DNA of rats. Tissue and age specificity and the changes induced by hydrocortisone and other agents. *Gerontologia* 1973;19(3):138-52.

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