Premature aging as a consequence of Mis-construction of tissues and organs during development

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Abstract

Hutchinson–Gilford Progeria Syndrome, Werner syndrome, and Cockayne syndrome are three genetic disorders, in which the children have premature aging features. To understand the phenomena of premature aging, the similarity of aging features in the syndromes to that in normal aging is investigated. Although these syndromes have different genetic backgrounds, the patients all have abnormal structures in tissues/organs like that in normal aging. Therefore, the abnormality in tissue structure is the common point between premature aging and normal aging, and it links a defective development and a defective repair, the Misrepair. Defective development is a result of mis-construction of tissues/organs, as a consequence of genetic mutation; whereas aging is a result of mis-reconstructions, the Misrepairs, for maintaining the structure of tissues/organs. Construction-reconstruction of the structure of an organism is thus the coupling point between development and aging. Mis-construction and Mis-reconstruction (Misrepair) are the essential processes in the development of aging-like feathers.

Keywords

Hutchinson–Gilford Progeria Syndrome (HGPS), Werner syndrome (WS), Cockayne syndrome (CS), normal aging, premature aging, Misrepair, Mis-construction, Mis-reconstruction, and defective development
Premature aging, called also accelerated aging, is a group of genetic syndromes, in which the children have premature aging feathers. The three known premature aging syndromes on human being are Hutchinson–Gilford Progeria Syndrome (HGPS), Werner syndrome (WS), and Cockayne syndrome (CS). These syndromes have differences on genetic backgrounds, on ages of onset of abnormality, and on symptoms; however they are common on typical aging changes, including hair loss, tooth loss, thinness and hardness of skin, skin wrinkles, and senior spots. So far, none of traditional aging theory is able to interpret the phenomenon of premature aging. To understand aging, we have proposed a generalized concept of Misrepair in Misrepair-accumulation theory (Wang, 2009). The new concept of Misrepair is defined as incorrect reconstruction of an injured living structure such as a molecule, a cell and a tissue. In present paper, we will analyze the premature aging syndromes with a concept of mis-construction of a tissue/organ in development, which is similar to that of Misrepair in aging process. Our discussion tackles the following issues:

I. Symptoms of premature aging syndromes

II. A novel aging theory: Misrepair-accumulation theory

III. Premature aging as a consequence of Mis-construction of tissues/organs during development

   3.1 Mis-construction and Mis-reconstruction of a tissue/organ
   3.2 Premature aging in animal models with genetic modifications

IV. Analysis of the premature aging syndromes

   4.1 Hutchinson-Gilford Progeria syndrome
   4.2 Werner syndrome
   4.3 Cockayne syndrome

V. Conclusions

I. Symptoms of premature aging syndromes

Hutchinson–Gilford Progeria Syndrome (HGPS) is the first syndrome that is named as premature aging syndrome or Progeria. HGPS is a genetic condition with abnormal development and appearance of premature aging feathers from infancy (James, 2005). So far more than 100 cases of HGPS have been reported in the world (Hennekam, 2006). The Progeria children often look normal at birth; however they manifest the abnormal growth after birth. Growth abnormalities develop progressively with age, including growth failure, hair loss, hardening and thinness of skin, wrinkled skin, stiff joints, atherosclerosis, and loss of body fat and muscle. HGPS children all have a small body but big head with prominent eyes and narrow face, and they die mainly from heart attack or stroke in young ages. Differently from that in WS and CS, HGPS children have normal mental development, and they do not
develop cancer, cataract, and osteoarthritis. A gene mutation on lamin A \((LMNA\) gene), a protein for composing nuclear lamin, is identified in the HGPS patients (Eriksson, 2003).

Werner syndrome (WS), called also “adult progeria”, is a genetic disorder characterized by an early and progressive development of aging features (James, 2005). WS patients are mainly found in Japan. They have a normal development in childhood; however impaired growth begins after adolescence. The early features of aging are: loss of hair, changing of voice, and hardness of skin. With time typical WS symptoms appear and develop, including growth arrest, lens cataracts, skin ulcers, type II diabetes, loss of fertility, hardening of arterial wall, atherosclerosis, osteoporosis, rigidness of joint, and multiple and rare cancers. WS patients often die from cancer or atherosclerosis in their forties or fifties (Ozgene, 2005). A mutation on \(WRN\) gene was identified in the WS patients. Normal WRN protein is a kind of DNA helicase, and it assists DNA duplication and maintains the functionality of telomeres.

Cockayne syndrome (CS), called also “Weber-Cockayne syndrome” and “Neill-Dingwall syndrome”, is a rare genetic condition characterized by growth failure, impaired development of neural system, abnormal sensitivity to sunlight, and appearance of premature aging. Typical aging features in CS include thinness of skin, hair loss, sunken eyes, tooth decay and hearing loss. CS individuals have small figure with small head (bird head) but with long limbs, large hands and large feet. They often stand in a 'horse-riding stance' because of joint contractures in knees. In respecting to the severity of symptoms and the age of onset of symptoms, CS is classified into three subtypes. Type I, called classical type, is the most common subtype, in which the children have abnormal development at age of one year old. Type II is the severest subtype, and the babies are born with symptoms and die in childhood. Type III is the mildest subtype, in which the children have symptoms only in later childhood. Individuals of type I can survive till twenties, whereas those of type II die before age of 7 years old. Pulmonary infection is often the cause of death of CS patients (James, 2005). A gene mutation on a DNA repair enzyme was identified in the CS patients.

II. A novel aging theory: Misrepair-accumulation theory

Aging of an organism is characterized by the gradual disorganization of the structure and the reduction of the functionality of organs. We found out that incorrect repair is a common change in different types of aging symptoms, including fibrosis, atherosclerotic plaques, and wrinkles. Like that in Misrepair of DNA and that in scar formation, an incorrect repair will take place when a complete repair of an injury is impossible to achieve. On this basis, we proposed a generalized concept of Misrepair in our Misrepair-accumulation theory (Wang, 2009). The new concept of Misrepair is defined as **incorrect reconstruction of an injured living structure**, and it is applicable to all living structures including molecules (DNAs), cells, and tissues. When an injury is severe, Misrepair, a repair with altered materials and in altered remodeling, is essential for maintaining the structural integrity and for increasing the surviving chance of an organism. Without Misrepairs, an individual could not survive till the reproduction age. Misrepair mechanism is thus essential for the survival of a species. However, Misrepair results in a permanent change of a structure, which can accumulate. Thus accumulation of Misrepairs disorganize gradually the structure of a molecule, a cell or a tissue,
appearing as aging of it. Aging is a side-effect of the survival of an organism, and aging of an individual is a sacrifice for species’ survival.

The accumulation of Misrepairst in a part of tissue is not homogeneous rather focalized. Misrepairst have a tendency to accumulate to a local part of tissue where an old Misrepair has taken place, since this part of tissue has reduced efficiency on repair and increased sensitivity to damage. A Misrepair will promote more Misrepairst to occur locally by a viscous circle; and the accumulation of Misrepairst is self-accelerating. Thus the process of aging is self-accelerating. Aging takes place on each level of molecule, cell, and tissue, respectively; however aging of a multi-cellular organism takes place essentially on tissue level. An irreversible change on the spatial relationship between cells/ECMs in a tissue is essential and sufficient for causing a decline of organ functionality. Aging of an organism and aging of a tissue does not always require aging of cells and aging of DNAs. In conclusion, aging of an organism is a result of accumulation of Misrepairst on tissue level.

### III. Premature aging as a consequence of Mis-construction of tissues/organs during development

Why do the children with these syndromes have the symptoms, which are similar to that in normal aging? To answer this question, one needs to search for the common change underlying both of normal aging and premature aging. In our view, these children have aging features because they have abnormal structures on tissues/organs like that in normal aging. Thus, abnormality on tissue structure is the common point between premature aging and normal aging, and it links a defective development and a defective repair, the Misrepair.

#### 3.1 Mis-construction and Mis-reconstruction of a tissue/organ

Development and repair are both a process of constructing of the structure of a tissue/organ. Any element that interrupts the constructing process, including the processes of cell division, cell organization, ECMs production, and ECMs modeling, will affect the result of development and repair. Abnormal and defective development is a result of mis-construction of the tissues/organs of an organism, leading to the low functionality of the tissues/organs. Similarly, aging is a result of accumulation of mis-reconstructions (Misrepairs) of tissues/organs. Thus, construction-reconstruction of the structure of an organism is the coupling point between development and aging. In this aspect, aging and development are regulated by the same mechanism like that proposed in developmental theory (Zwaan, 2003). Construction of an organism is genetically controlled, whereas reconstruction of an organism is promoted by an injury. Therefore, the concept of Misrepair does not only associate the process of development with that of aging, but also couple the genetic control and the environmental effect on aging. Figure 1 shows the relationship between premature aging and normal aging. In normal development of a tissue, correct construction makes a perfect organization of cells/ECMs, which has full functionality. In premature aging, mis-construction makes the organization of cells/ECMs different from that one in normal development, which has low functionality. In normal aging, Misrepair is promoted by death of cells/ECMs, and mis-reconstruction results in an altered reorganization of cells/ECMs, which has reduced functionality (Figure 1).

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Figure 1. Abnormality on tissue structure: the common point between normal aging and premature aging

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Differently from that of Misrepairs, which are local, only affecting the injured part of a tissue; the mis-construction caused by a genetic disorder is systemic, affecting all tissue/organs. The organs that develop defectively in these syndromes have low potential of functionality and will go to failure earlier and faster. A Misrepair is not a “real mistake” but a compromise of an organism necessary for surviving; whereas the mis-construction in development is a “real mistake”, and it will lead to a failure of development. For the individuals with premature aging syndromes, especially for those, who have survived over childhood, Misrepairs also contribute to their aging feathers. The phenomenon of premature aging is a powerful evidence to disprove some traditional aging theories. The premature aging features in these syndromes: A. are not caused by damage (Damage-accumulation theory (Kirkwood, 2005)); B. are not caused by free radicals (Free-radical theory (Harman, 1956)); C. are not controlled by a common gene (Gene-controlling theory (Bell, 2012)); and D. are not due to cell senescence (Cell senescence/telomere theory, (Hayflick, 1965; Blackburn, 2000)).

3.2 Premature aging in animal models with genetic modifications

Premature aging features have been also observed in animal models, which have been genetically modified and have abnormal developments. Fibulin-5 is an extracellular protein
and is important in assembling and modeling of elastic fibers in extracellular matrixes. A mutation on gene *FBLN 5* in human beings results in the production of non-functional fibulin 5 proteins and is the cause of cutis laxa, a disease that is characterized by weakened connective tissue and wrinkled skin. A study with an animal model showed that the mice that have Fibulin-5-/- modification undergo defective development of connective tissue and they manifest aging symptoms including loose and wrinkled skin, vascular abnormalities, and emphysema (Hirai, 2007). Klotho protein is a kind of trans-membrane protein with the activity of beta-glucuronidase, and it is important in regulating cell calcium homeostasis. Klotho-deficient mice have multiple accelerated aging changes including extensive and accelerated arteriosclerosis (Kuro-o, 1997). It is found that impaired development of blood vessels is the cause for the dysfunction of vasodilatation and angiogenesis in Klotho-deficient mice (Lanske, 2007). Studies on different animal models with different genetic modifications demonstrated that a defective development can result in premature aging features (Sun, 2004; Razague, 2006; Trifunovic, 2004; de Boer, 2002; Espada, 2008).

### IV. Analysis of the premature aging syndromes

Although the gene mutations in these syndromes have been identified, the concrete association of each mutation with the symptoms of each syndrome is not yet clear. An interesting question is, why these children with defective developments could be born and even survive for some years. It is possible that in these children the development of embryo in early stage is normal, but abnormal development is triggered by an internal process. Finding out the promoting process is important for understanding the tragedy of premature aging. For example, in WS the promoting affair might be failure of cell division in some cells when the telomeres in these cells are too short. In CS, a promoting affair might be death of some key cells from DNA injuries. In this part, we will analyze these syndromes to find out how a gene mutation exhibits effects on tissue-development in each syndrome.

#### 4.1 Hutchinson-Gilford Progeria syndrome

A characteristic pathological change in HGPS is the blebbing of cell nucleus (Lans, 2006). The abnormal structure of nuclear lamina, caused by a gene mutation on lamin A (*LMNA* gene), is thought to be associated with the development of HGPS (Eriksson, 2003). Nuclear lamina is a part of nuclear skeleton located beneath the nuclear membrane, and it is composed of lamin A and lamin B. Nuclear lamina is important in maintaining the nuclear shape and maintaining the functional organization of chromosomes in nuclei. During normal modeling of nuclear lamina, Lamin A, in form of prelamin A, is transported from cytoplasm and localized to the inner nuclear membrane by its farnesyl group at carboxyl-terminus. After localization, the farnesyl group will be cut off, and lamin A becomes free and mature for integrating into nuclear lamina. In HGPS, a point mutation on *LMNA* gene results in the production of a shorter form of prelamin A. By missing the 50 amino acids at carboxyl-terminus, the mutant lamin A, called progerin, lost the cleaving site for removing the farnesyl group. As a consequence, the mutant lamin A cannot be released from nuclear membrane for integrating into nuclear lamina. Lacking of lamin A, the structure of nuclear lamina is defective and fragile, and the shape of nucleus is altered. In addition, the un-functional
progerins accumulate beneath the nuclear membrane. Defective structure of nuclear lamina and deposition of progerin can both contribute to the blebbing change of the nucleus (Dechat, 2007). Distribution of chromosomes, DNA duplication, cell mitosis, RNA transcription, and substance transportation can all be affected by the defects of nuclear lamina.

So far, the mechanism how the defect of nuclear lamina is associated with the abnormal development in HGPS is not known. Apart from HGPS, some diseases are also related to gene mutations on lamin-A/C, including Emery-Dreifuss muscular dystrophy (EDMD), dilated cardiomyopathy (DCM), and limb-girdle muscular dystrophy. Deformation of nuclear membrane is also seen in these dystrophies; however most of the patients with these diseases can survive over middle age. A main defect in adult patients is the fragility of the muscular cells in skeleton and in the heart. These patients have muscular dystrophy from death of muscular cells. The fragile nuclear lamina caused by mutations on lamin A/C might be the pathological basis for the death of muscular cells caused by cell deformations. HGPS children could have also fragility on muscular cells and other cells; and this can be a reason why HGPS children die often from heart failure. The fragility of nuclear lamin in HGPS might be severer than that in above diseases; and the cell death caused by cell deformations does not only take place on muscular cells, but also on epithelial cells, fibroblasts, and endothelium cells. Exceptionally, the neuron cells in the brain need not deform for functioning; and this might be the reason why the development of neural system is not severely affected in HGPS.

4.2 Werner's syndrome

WRN protein is a kind of DNA helicase, and it assists DNA duplication and maintains the functionality of telomeres. WRN is a gene that is inherited in autosomal recessive pattern, and the individuals with one copy of the mutated gene do not have abnormality on development. The WRN mutant in WS is an altered and shorter variant of WRN protein, which lost the ability of interacting with DNA and protecting telomeres (Gray, 1997). Rapid shortening of telomeres and the subsequent genomic instability are thought to be associated with the disorders of WS. Failure of DNA duplication, adoption of DNA mutations, failure of separation of chromosomes during cell division, and failure of gene expression can all be the consequences of the instability of chromosomes. The destination of a cell with instable chromosomes one of the followings: A. cell death as a result of failure of gene expression, B. failure of cell division as a result of failure of DNA duplication or failure of separation of chromosomes, and C. cell transformation as a result of accumulation of adopted DNA mutations.

Interestingly, some symptoms that develop in WS do not develop in HGPS and in CS. The symptoms specific in WS include the retardation of development of symptoms, the development of multiple and rare cancers, and the development of lens cataract. I. The retardation of development of symptoms might be a result of the delayed effect of WNR mutation. In the cells that have mutant WRN protein, the telomeres is shorter and shorter after each time of cell division; and the disorders in development could only appear when the telomeres are too short and lost of their functionality in some cells. II. Development of multiple and rare cancers might be a result of accumulation of adopted DNA mutations.

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Genetic instability makes the new generations of cells adopt new DNA mutations in high frequency. Differently from the DNA mutations in somatic cells, which take place only in the injured cells, adopted DNA mutations can occur to any one of the cells of the patients with WS. Rapid accumulation of adopted DNA mutations results in the development of multiple tumors and rare tumors. III. Development of lens cataract might be a result of failure of cell division caused by the decay of telomeres. Transparency of the lens relies on the regular arrangement of lens fibers, and the lens fibers are differentiated from the epithelial cells in lens capsule. The epithelial cells in capsule must continue dividing for producing new cells for maintaining the regular arrangement of lens fibers. Thus, failure of cell division will lead to failure of the maintenance of the transparency of the lens.

4.3 Cockayne's syndrome

A gene mutation on a DNA repair enzyme was found to be associated with the development of CS. This enzyme is coded by ERCC6 gene (also known as gene CSB) and gene ERCC8 (also known as gene CSA). The mutation on ERCC6 gene results in a defective form of ERCC6 protein, which loses its ability of repairing certain types of DNA injuries (Hoeijmakers, 2009). These genes are inherited in autosomal recessive pattern, and the CS patients all have two copies of mutated gene (Bertola, 2006). Variety of injuries can occur to DNA, and in a cell different groups of enzymes are responsible for repairing different types of DNA injuries. ERCC6 protein is an essential enzyme in the pathway of transcription-coupled nucleotide excision repair (TC-NER). Defect of ERCC6-related DNA repair makes all somatic cells in danger of death from DNA injuries. Thus, death of cells from DNA injuries in early stage of development is probably associated with the symptoms of CS.

Firstly, death of cells in early stage of development will affect severely the development. DNA injuries can take place during DNA duplications, and they will lead to cell death in early stage of development in CS. Most of embryonic cells have the potential of proliferation and differentiation; and death of some cells can severely impair the further development. Different individuals of CS have great difference on the severity of symptoms, and in our view, the severity is related to the age of onset of cell death. The earlier cell death takes place, the severer it will affect the development. Secondly, CS children have severe impaired development of nerve system. A normal baby has the same number of neurons at birth as that in an adult; and a child of three years old has the same weight of the brain as that of an adult. Thus, cell death in early stage of development can severely impair mental development. Thirdly, CS children have abnormal sensitivity to sunlight. In nature, DNA injuries are mainly caused by UV radiation, and failure of DNA repair is the main reason for the hyper-sensitivity of cells to sunlight in CS.

Another interesting phenomenon in CS is the patients do not develop cancer. In our view, cell transformation is a result of accumulation of DNA mutations through many generations of cells. Two preconditions for the accumulation of DNA mutations are: A. survival of the cells with DNA mutations, and B. potential of cell proliferation. DNA mutation in somatic cells is a result of Misrepair of DNA; however Misrepair of DNA can only take place when the cells have a normal functionality on DNA repair. In CS the cells have defect on DNA repair;
therefore they have no ability to make complete repair and Misrepair! The chance of accumulation of DNA mutations in CS is too low!

V. Conclusions

Premature aging syndromes are a group of genetic diseases in which the children develop aging feathers. The premature aging in these disorders is not a result of aging rather a result of defective development. The abnormality on tissue structure is the common point between normal aging and premature aging. The defective development in these syndromes results from mis-construction, whereas normal aging results from Misrepairs (mis-reconstructions). Construction-reconstruction of the structure of an organism is thus the coupling point between development and aging. Mis-construction and Mis-reconstruction (Misrepair) are the essential processes in the development of aging-like feathers.

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