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# Development of aging changes: self-accelerating and inhomogeneous

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## Abstract

Aging changes including age spots and atherosclerotic plaques develop in a manner of inhomogeneous and accelerated. For understanding this phenomenon, development of aging changes is analyzed by Misrepair mechanism, which is introduced in Misrepair-accumulation theory. **I.** Misrepair is a strategy of repair for increasing the surviving chance of an organism in situations of severe injuries; however a Misrepair alters the structure of a tissue, a cell or a molecule, which are the sub-structures of an organism. **II.** Alteration of the structure of a sub-structure by Misrepair also alters the spatial relationship between local sub-structures, and this change will lead to increased damage-sensitivity and reduced repair-efficiency of these sub-structures. As a result, Misrepairs have a tendency to occur to the sub-structure and its neighbor sub-structures where an old Misrepair has taken place. In return, new Misrepairs will increase again the damage-sensitivity of these sub-structures and the surrounding sub-structures. The frequency of Misrepairs to these sub-structures is increased and the range of affected sub-structures is enlarged after each time of Misrepair in a vicious circle. Thus, accumulation of Misrepairs is focalized and self-accelerating. **III.** Focalized accumulation of Misrepairs leads to formation and growing of a “spot” or “plaque” in a tissue. Growing of a spot is self-accelerating, and old spots grow faster than new ones. New spots prefer to develop close to old ones, resulting in an in-homogenous distribution of spots. In conclusion, the inhomogeneous development of aging changes is a result of self-accelerating and focalized accumulation of Misrepairs; thus the process of aging is self-accelerating.

## Keywords

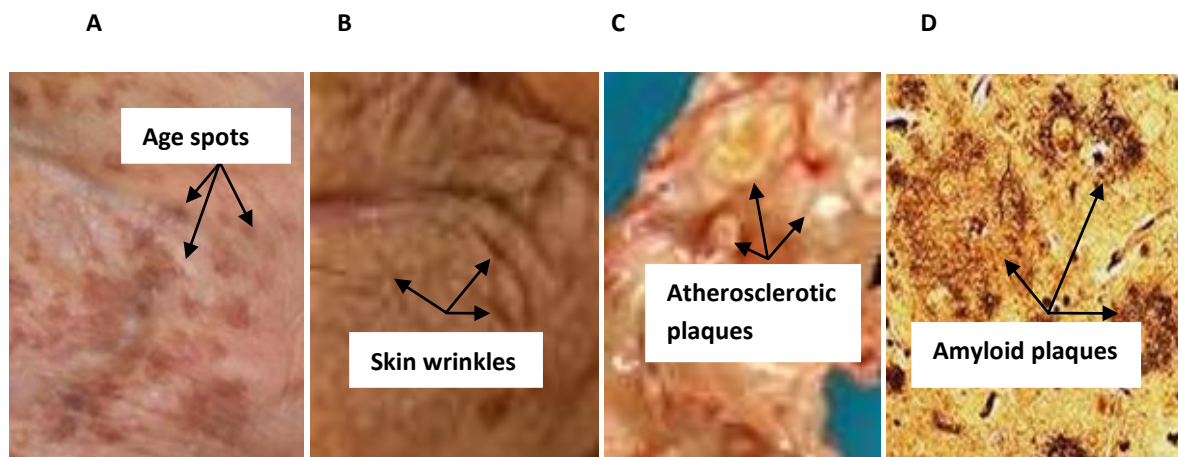
Aging, Aging science, age spots, atherosclerotic plaques, aged cells, in-homogeneous, Misrepair, Misrepair mechanism, sub-structure, neighbor sub-structures, increased damage-sensitivity, reduced repair-efficiency, vicious circle, accumulation of Misrepair, self-accelerating

The great variety of aging symptoms appears to be complex and hard to explain. An important issue in studying aging mechanism is to find out the common characteristics of different aging symptoms. We have observed that the age spots on skin and the atherosclerotic plaques in arterial walls develop in-homogeneously. The changing of age spots on number and on size seems to be somehow accelerated with time. It is interesting and important to know why these changes develop in this way and what the accelerating force is. To interpret aging, we have proposed a Misrepair mechanism in Misrepair-accumulation theory (Wang, 2009). In our view, Misrepair mechanism is a surviving mechanism for an organism and for a species; however accumulation of Misrepairs result in aging of the organism. In the present paper, we take age spots as an example to analyze the characteristics of development of aging changes with Misrepair mechanism. Our discussion is organized as follows:

- I. Development of aging changes: inhomogeneous and accelerated
- II. Aging as a result of accumulation of Misrepairs
- III. Effects of a Misrepair on a structure: increased damage-sensitivity and reduced repair-efficiency
- IV. Accumulation of Misrepairs: self-accelerating and focalized
- V. Conclusions

### **I. Development of aging changes: inhomogeneous and accelerated**

Age spots on the skin develop mainly on the face and on the back sides of two hands. Interestingly, age spots are always different to each other on size and on shape, and they distribute in-homogeneously. They have irregular shapes, and most of them are flat but some are protruding with deeper color. They are growing with time, and older ones are always bigger than younger ones. Smaller spots tend to develop in surrounding of a bigger one, which form a satellite-like distribution of them. Some spots in neighborhood can fuse together during growing (Figure 1A). Similarly, wrinkles on the face develop also in an inhomogeneous manner, and they have difference on lengths, depths, and directions. When new wrinkles appear successively, old wrinkles are growing in depth and in length (Figure 1B). Apart from age spots and wrinkles, the atherosclerotic plaques in arterial walls and the amyloid plaques in the brain have also inhomogeneous distributions respectively (Figure 1C and 1D). Additionally, age spots seem to develop in an accelerated rate. The acceleration manifests on two aspects: one is the enlargement of each spot, and the other is the increase of number of spots. We can have such an experience: a visible age spot on skin looks “unchanged” for many years, but once it starts to grow, it does rapidly! Larger spots are often old spots, growing faster than new ones. The number of spots increases faster and faster with time. For a person, the increase of number of spots during age of 60-70 years old is much more than that during age of 50-60 years old.



**Figure 1. In-homogeneous development of aging changes**

Aging changes, such as age spots **(A)**, skin wrinkles **(B)**, atherosclerosis plaques in arterial wall **(C)**, and amyloid plaques in brain **(D)**, are all inhomogeneous in distribution respectively. In each type of changes, the sizes and shapes of spots or plaques are different to each other permanently (Picture C from [Meddean.luc.edu](http://Meddean.luc.edu) and picture D from [hoplive.com](http://hoplive.com)).

The following questions will be asked on age spots: Why do they develop in-homogeneously? Why do they grow continuously? What is the accelerating force in the growing of spots? These questions are fundamental for understanding aging. Unfortunately neither damage (fault)-accumulation theory ([Kirkwood, 2005](#)) nor gene-controlling theory ([Longo, 2005](#)) can give satisfactory answer to them. On one hand, growing of an age spot cannot be a result of accumulation of random damage. If a spot is due to damage (injuries), accumulation of injuries should result in a homogenous distribution of spots. On the other hand, the in-homogeneity of age spots cannot be due to controlling of a gene. If a spot is a result of expression of certain genes, the spots should have similar sizes and in a homogeneous distribution, because these genes should work in the same way in the same types of cells. On interpreting the in-homogeneity of aging changes, these two theories are not tenable. In contrast, our novel theory, the Misrepair-accumulation theory, is exceptionally able to interpret this in-homogeneity and answer above questions.

## **II. Aging as a result of accumulation of Misrepairs**

To explain aging changes, 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*. This concept is applicable to all living structures including molecules (DNAs), cells, tissues, and organs. For example, scar formation is a Misrepair of epidermal tissue. When a complete repair is impossible to achieve for a severe injury, Misrepair, a repair with altered material and in an altered remodeling, is a “SOS repair” that is essential for maintaining structural integrity for increasing the surviving chance of an organism. However, a Misrepair results in alteration of the structure and reduction of the functionality of a living structure. The structure-alterations caused by Misrepairs are irreversible and irremovable; therefore they accumulate and “deform”

gradually a living structure, appearing as aging of it. Thus, aging of an organism is a process of accumulation of Misrepairs. Misrepairs are essential for an organism to be able to survive till reproduction age; therefore Misrepair mechanism is essential for the survival of a species. Aging of individuals is a sacrifice for species' survival! Aging can take place on the levels of molecules, cells and tissue, respectively; however aging of an organism takes place essentially on tissue level. A change of the spatial relationship between cells/extracellular matrix (ECMs) in a tissue is *essential and sufficient* for causing a decline of tissue functionality and body functionality. Aging of our body does not essentially require aging of cells and molecules. Aging of a tissue is often the cause but not the effect of aging of cells.

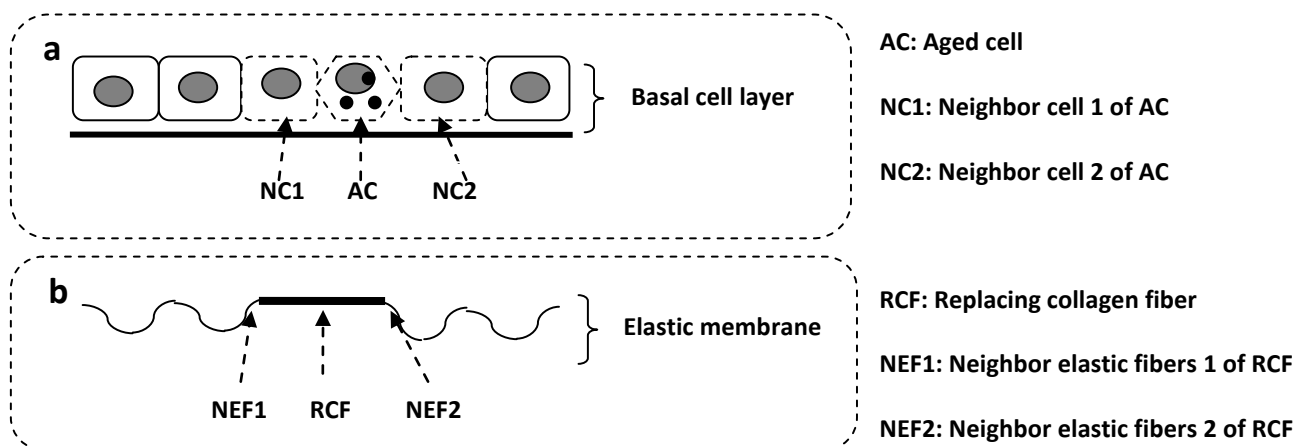
In our view, age spots, atherosclerotic plaques, and skin wrinkles are all results of accumulation of Misrepairs. **I.** Development of a flat age spot is a result of accumulation of aged basal cells, which contain lipofuscin bodies. Deposition of an aged cell is a Misrepair of a tissue, since a complete repair is to remove the aged cell and replace it with a new cell. **II.** Development of an atherosclerotic plaque is a result of altered remodeling or Misrepair of endothelium, since the infusion of lipids into sub-endothelium makes normal sealing of endothelium impossible to achieve. Accumulation of lipids and accumulation of Misrepairs of endothelium in local arterial wall result in formation of a plaque. **III.** Wrinkle formation is a result of repeated remodeling of skin derma with collagen fibers for replacing broken elastic fibers and other ECMs. When an elastic fiber is broken in an extended state, it will be replaced by a “long” collagen fiber. Accumulation of “long” collagen fibers makes the skin larger and stiffer. When a repairing collagen fiber in stiff skin is broken in a compressed state; it will be replaced by a shorter collagen fiber. The shorter collagen fibers will restrict the extension of the skin, and longer fibers have to rest permanently in a folding state, leading to formation of a permanent wrinkle. In these aging changes, Misrepairs tend to accumulate focally, resulting in formation of a spot or a plaque. What is the mechanism for this focalized accumulation of Misrepairs? This is the question that we will answer in the next parts.

### **III. Effects of a Misrepair on a structure: increased damage-sensitivity and reduced repair-efficiency**

Misrepair is a strategy of repair that is essential for a long survival of an organism. However, Misrepair of a sub-structure (called **Z**) does not only alter the structure of **Z** but also alters the spatial relationship between **Z** and its neighbor sub-structures. Molecules, cells and tissues are all the sub-structures of an organism, whereas molecules are the sub-structures of a cell and cells are the sub-structures of a tissue. Substance-transportation and information-transmission can be disturbed by an alteration of spatial relationship of local sub-structures. As a result, the Misrepaired sub-structure **Z** and its neighbor sub-structures will have reduced efficiency on functions of adaptation and repair. When a load is increased, these sub-structures will not be able to make adaptive responses efficiently; thus they have increased damage-sensitivity. Because of increased damage-sensitivity and reduced repair-efficiency, these sub-structures will have increased risk for injuries and Misrepairs. Thus, Misrepairs have a tendency to occur to the sub-structure and its neighbor sub-structures where an old Misrepair has taken

place. For a tissue, under a constant damage, the location where the first Misrepair takes place can be random. However, the locations of the second Misrepair and the successive ones will not be any more random. New Misrepairs tend to take place next to or close to old ones. The locations of old Misrepairs are the centers of accumulation of new Misrepairs, since these areas are weak on functionality.

An age spot on the skin is pathologically a group of basal cells that contain lipofuscin inclusion bodies. Accumulation of lipofuscin bodies is a sign of aging of a cell. In a tissue, all cells need to communicate with their neighbor cells for functioning and for surviving. Remaining of aged cells in a tissue is a kind of Misrepair of tissue. When an aged cell remains in a tissue, with reduced functionality, this cell will affect the functionality of its neighbor cells. **Firstly**, the repair-efficiency of local tissue will be reduced, since this aged cell can interrupt local substance transportation. **Secondly**, neighbor cells cannot make efficient adaptive responses to changes of environment, and they become more sensitive to damage. Thus the neighbor cells of an aged cell will have increased risk for injuries and Misrepairs. In this way, deposition of an aged cell enhances the aging of its neighbor cells (Figure 2a). Similarly, increased damage-sensitivity can be also seen in Misrepaired arterial walls. When part of the elastic membrane of arterial wall is injured, collagen fibers are often used for replacing the broken elastic fibers. Being lack of elasticity, the replacing collagen fiber makes its neighbor elastic fibers have an increased risk to disrupt when they are being loaded (Figure 2b).



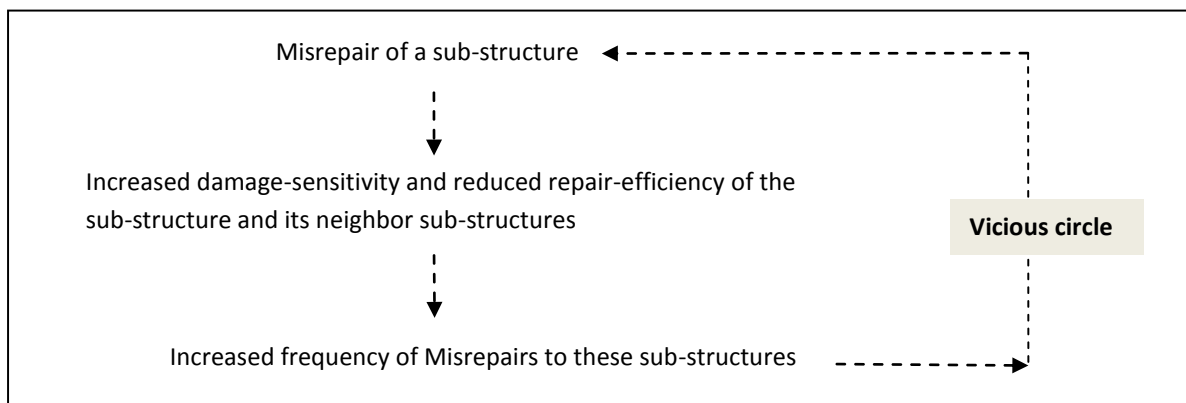
**Figure 2. Effects of a Misrepair on a structure: increased damage-sensitivity and reduced repair-efficiency**

A Misrepair will alter the structure of a cell (or a molecule) and its spatial relationship with neighbor cells (or molecules). As a result, these cells (or molecules) will have increased damage-sensitivity and reduced repair-efficiency. For example, when an aged cell remains in a tissue, with reduced functionality this cell will affect the functionality of its neighbor cells on repair and on adaptation. The neighbor cells will have an increased risk for injuries and Misrepairs. Thus deposition of an aged cell (**AC**) enhances the aging of its neighbor cells (**NC1** and **NC2**) (a). In arterial walls, when elastic membrane is injured, collagen fibers are often used for replacing broken

elastic fibers. Being lack of elasticity, a replacing collagen fiber (**RCF**) will make its neighbor elastic fibers (**NEF1** and **NEF2**) have increased risk to disrupt when they are being loaded (**b**).

#### IV. Accumulation of Misrepairs: self-accelerating and focalized

A Misrepair increases the risk of a sub-structure and its neighbor sub-structures for Misrepairs. New Misrepairs in these sub-structures will in return increase again the damage-sensitivity and the repair-efficiency of local sub-structures in a larger range. The frequency of Misrepairs to these sub-structures will be increased and the range of affected sub-structures will be enlarged after each time of Misrepair in a vicious circle (Figure 3). A Misrepair has a cascade amplifying effect, and an old Misrepair will promote new Misrepairs to take place in an increased frequency to local sub-structures. Thus accumulation of Misrepairs is self-accelerating. For example, an aged cell in a tissue will enhance the aging of itself and the aging of its neighbor cells. In this way, more and more neighbor cells become aging and the group of aged cells is enlarged gradually. In arterial walls, once an elastic fiber is replaced by a collagen fiber, this replacement will promote more replacements of neighbor elastic fibers by collagen fibers, and the remodeling area of elastic membrane is enlarged gradually.

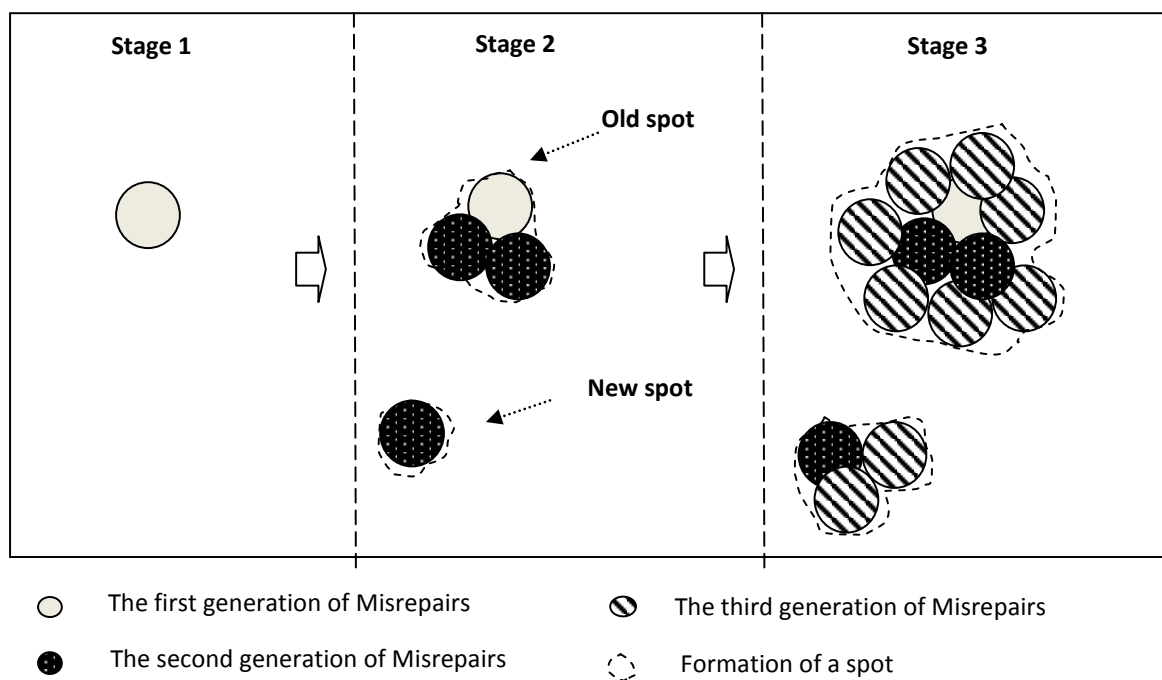


**Figure 3. Accumulation of Misrepairs: a self-accelerating process**

A Misrepair makes a sub-structure and its neighbor sub-structures have increased damage-sensitivity and reduced repair-efficiency. Thus Misrepairs have a tendency to occur to the sub-structure and its neighbor sub-structures where an old Misrepair has taken place. In return, New Misrepairs will further increase the damage-sensitivity and reduce the repair-efficiency of these sub-structures and the surrounding sub-structures in a larger range. The frequency of Misrepairs to these sub-structures will be increased and the range of affected sub-structures will be enlarged after each time of Misrepair in a vicious circle (**Vicious circle**). Therefore, aging, the process of accumulation of Misrepairs, is self-accelerating.

The tendency of new Misrepairs to occur to the locations of old Misrepairs also makes the accumulation of Misrepairs focalized and inhomogeneous. In a tissue, focalized accumulation of Misrepairs makes a Misrepaired area larger and larger, forming a visible “spot”. As shown in Figure 4, in early stage (Stage 1), the earliest generation of Misrepairs (No. 1) takes place

randomly. In stage 2, the No. 1 generation of Misrepairs promotes the occurrence of No. 2 generation of Misrepairs (No. 2), which accumulate to the locations of No. 1. In stage 3, the No. 2 generation of Misrepairs promotes the occurrence of No. 3 generation of Misrepairs (No. 3), which accumulate to the locations of No. 2. Aggregation of Misrepairs from different generations in a neighborhood results in formation of a “spot”. The location of a spot in a tissue is determined by the location of the first Misrepair in this area. Further Misrepairs accumulate next to each other resulting in the “growing” of a spot with irregular shape. The new Misrepairs that take place far away from old ones will become centers of new spots. By the same mechanism, new spots prefer to develop close to old ones, resulting in an in-homogenous distribution of spots. Bigger spots are always the older ones, because they have longer time of accumulation of Misrepairs.



**Figure 4. Development of a spot: due to focalized accumulation of Misrepairs**

Development of a spot in a tissue is a result of focalized accumulation of Misrepairs of the tissue. Firstly, an earliest generation of Misrepairs (**No. 1**) takes place randomly (**Stage 1**). Secondly, **No. 1** generation of Misrepairs promotes the occurrence of **No. 2** generation of Misrepairs (**No. 2**), which accumulate to the locations of No. 1 (**Stage 2**). Thirdly, **No. 2** generation of Misrepairs promotes the occurrence of **No. 3** generation of Misrepairs (**No. 3**), which accumulate to the locations of No. 2 (**Stage 3**). Aggregation of Misrepairs from different generations in a neighborhood results in formation of a “spot”. A spot developed in this way is irregular in shape and “grows” with time.

## V. Conclusions

Development of an aging change is a consequence of Misrepairs, and growing of the change is a result of focalized accumulation of Misrepairs. In development of age spots, deposition of an aged cell is a Misrepair of the tissue, and the aged cell can enhance the aging of its neighbor cells. Development of an age spot is a result of accumulation of aged cells.



Enlargement of the range of aging cells in a neighborhood makes an age spot “grow”. The force for accelerating the growth of an aging spot is the Misrepair of the tissue. In summary, the in-homogeneous distribution of aging changes is a result of centralized accumulation of Misrepairs; and aging is a process of self-accelerating. Misrepair mechanism makes us understand why aging-associated diseases are all progressive with time.

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