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# Aging as a process of accumulation of Misrepairs

Jicun Wang-Michelitsch<sup>1\*</sup>, Thomas M Michelitsch<sup>2</sup>

<sup>1</sup>CUH – Department of Medicine, Addenbrooke's Hospital, University Cambridge, UK  
(work address until 2007)

<sup>2</sup> Institut Jean le Rond d'Alembert (Paris 6), CNRS UMR 7190 Paris, France

## Abstract

We recently introduced Misrepair-accumulation theory as an interpretation on aging mechanism. For better understanding this theory, we discuss here in more details the new concept of Misrepair and the concept of accumulation of Misrepairs. **I.** Aging takes place uniquely on the systems that have a well-defined structure: an organization of its sub-structures. Aging of a non-living system is a result of accumulation of injuries (damage) of its structure. **II.** A generalized concept of Misrepair is important for reaching to a unified understanding of aging changes. In the situation of a severe injury, incorrect repair is a repair essential for maintaining structural integrity for increasing the surviving chance of an organism. With the same mechanism as that in “Misrepair of DNA”, the term of “Misrepair” can be used for describing all kinds of incorrect repairs on different types of living structures, including molecules, cells and tissues. A new concept of Misrepair is therefore proposed and defined as incorrect reconstruction of an injured living structure. Misrepair mechanism is beneficial for the survival of an organism, and it is essential for the survival of a species. **III.** Alteration of structure made by Misrepair is irreversible; therefore Misrepairs accumulate and disorganize gradually a structure, which appears as aging of it. Accumulation of Misrepairs takes place on molecular, cellular and tissue levels respectively: on tissue level, it appears as disorganization of cells and extracellular matrixes (ECMs); on cellular level, it appears as deformation of cytoskeleton and change of cell shape; and on DNA, it appears as accumulation of DNA mutations and alteration of DNA sequence. An essential change in aging of an organism is an irreversible change of the spatial relationship between cells/ECMs in a tissue. In conclusion, aging of an organism is a result of accumulation of Misrepairs on tissue level.

## Keywords

Aging, Aging science, Misrepair, accumulation of Misrepairs, injury, living structures, incorrect repair, structural integrity, survival, species' survival, alteration of structure, irreversible change, aging of a cell, aging of a molecule, aging of an organism, and tissue level

Aging is nowadays a popular topic. Some biological theories have been proposed for interpreting aging mechanism; however they are untenable for some aging phenomena. A key step for uncovering aging secret is actually to find out a change, which takes place often in an organism and which can remain permanently. Along this way, we found out that an incorrect repair like that in scar formation is such a change. Incorrect repair can take place when an injury on a cell or on a tissue is severe; and the alteration of structure by incorrect repair can remain permanently. On this basis, we proposed a generalized concept of Misrepair in our Misrepair-accumulation theory for describing all manners of incorrect repairs (Wang et al, 2009). Misrepair is a result of “SOS” repair for increasing the surviving chance of an organism by maintaining structural integrity. However, Misrepairs are irreversible and accumulating, leading to disorganization and aging of a cell and a tissue. For better understanding this theory, in the present paper, we will make a detailed discussion on the new concept of Misrepair and on the concept of accumulation of Misrepairs. Our discussion is organized in the following sequence:

- I. A generalized concept of Misrepair
  - 1.1 Incorrect repair as a strategy of repair
  - 1.2 A generalized concept of Misrepair
  - 1.3 Examples of Misrepairs
- II. Aging as a process of accumulation of Misrepairs
  - II.1 Accumulation of Misrepairs and deformation of a structure
  - II.2 Accumulation of Misrepairs on molecular level
  - II.3 Accumulation of Misrepairs on cellular level
  - II.4 Accumulation of Misrepairs on tissue level
  - II.5 Aging of an organism: on tissue level
- III. Conclusion: Misrepair-accumulation theory

## **I. A generalized concept of Misrepair**

Aging is a universal phenomenon in nature; however it takes place only on the systems that have a well-defined structure. A colony of bacteria has no aging, because the bacteria in a colony are not in a functional organization. Differently, an animal and a plant have a well-defined structure, namely, a special organization of its sub-structures, such as organs, tissues, cells and molecules. The properties of a structure are determined by its organization of its sub-structures; and a change on this organization will lead to a change of its properties and its functionality. Aging of an organism is in fact a gradual alteration of its structure accompanied with loss of functionality.

## **I.1 Incorrect repair as a strategy of repair**

Injuries, as a consequence of steady damage-exposure, are unavoidable for a living organism. An injury (an original damage) is in fact a lesion of the structure of a molecule, a cell or a tissue. By destroying the structural integrity, an injury, if not repaired, will lead to failure of the structure and death of the whole organism. For example, if a wound on skin is not repaired, one can die from bleeding and infection. Repair of an injury is essential for maintaining the structural integrity and the functionality of a living structure for the survival of an organism. For repairing an injury of a tissue, a great deal of molecules and cells need to be produced and activated. A series of biochemical reactions need to take place successively and accurately, including expression of genes, production and secretion of proteins and small molecules, activation of enzymes, transportation of substance, and immigration of immune cells. It is time-consuming for an organism to accomplish all of these reactions successively; and repair of an injury needs time to be achieved.

Although the repairing process of an injury in a tissue and in a cell is complex, the result of repair is one of the followings: complete repair, failure of repair, and incorrect repair. When a lesion is small, full repair can be achieved and the injured structure can be completely restored. If a lesion is too large, complete repair will be impossible to achieve, and an organism can die from failure of repair. A strategy for increasing the surviving chance of an organism from a severe injury is incorrect repair, a repair with altered materials or in altered remodeling for closing the lesion quickly. Scar formation on the skin and in other organs tells us that such a compromising strategy of repair exists in living beings. Small but repeated injuries are also difficult to be completely repaired, since the repairing processes are disturbed by newly arrived injuries. Repeated constriction/dilatation of arterial walls, repeated smoking, repeated UV light-exposures, and chronic inflammations are the origins of repeated injuries of tissues and cells. For such injuries, incorrect repair is unavoidable. Likely, for an injury with un-degradable substance from dead cells, isolating the substance in a capsule is a way of repair for rebuilding structural integrity of a tissue. In these last three situations, quick but incorrect repairs, no matter in what a manner, have to be made to maintain structural integrity for increasing the surviving chance of an organism.

Different tissues have different potentials of repair, and some tissues are regenerable and some are un-regenerable. Regenerable tissues are the tissues, in which the cells can be reproduced and dead cells can be replaced by new cells. Epithelium, endothelium, hepatic tissue, and connective tissue are all regenerable tissues. In these tissues, small injuries can be fully repaired and restored; but severe injuries, repeated injuries, and the injuries with un-degradable substances have to be repaired incompletely. Differently, in un-regenerable tissues like nerve tissue and skeleton muscular tissue, an injury with death of cells, has to be repaired with other types of cells. For example, dead neuron cells will be replaced by glial cells, and dead muscular cells will be replaced by fibroblasts and collagen fibers (Table 1). On cellular level, although a cell can regenerate its sub-structures, complete repair of its structure could be only possibly achieved when an injury is not severe. For severe injuries and repeated injuries, incorrect repairs are the ways of repair for survival of the cells.

**Table 1. Results of repairs in tissues**

| Injuries                            | Results of repairs     |                           |
|-------------------------------------|------------------------|---------------------------|
|                                     | In regenerable tissues | In un-regenerable tissues |
| Small Injury with death of cells    | <u>Complete repair</u> | Incorrect repair          |
| Large Injury                        | Incorrect repair       | Incorrect repair          |
| Repeated injuries                   | Incorrect repair       | Incorrect repair          |
| Injury with un-degradable substance | Incorrect repair       | Incorrect repair          |

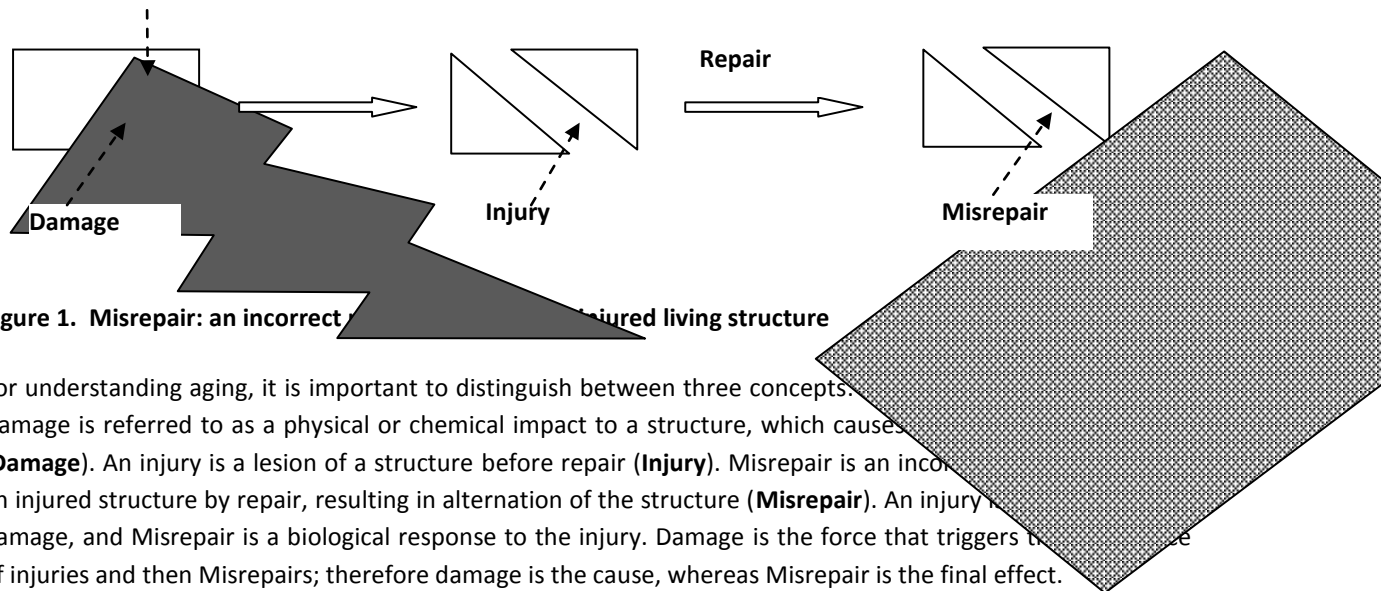
## I.2 A generalized concept of Misrepair

Incorrect repair is one of the strategies of normal repair in cells and in tissues. Such “SOS” repair can save our life many times a day. Misrepair of DNA is an incorrect repair on molecular level, which is referred to as Mis-match repair of DNA. It has been realized that Misrepair of DNA is a survival strategy of a cell in situations of severe DNA injuries (Little et al, 2004). Misrepair of DNA is an important source of DNA mutations in somatic cells and in tumor development (Suh et al, 2006). Since Misrepair of DNA has the same mechanism as that of incorrect repair, we propose a generalized concept of Misrepair for describing all types of incorrect repairs. The new concept of Misrepair is therefore defined as: *incorrect reconstruction of an injured living structure*. This concept is applicable to all types of living structures including molecules, cells, tissues and organs. A generalized concept of Misrepair improves our understanding of life on three points: **A.** Misrepair mechanism exists in a living being; **B.** Misrepairs are a kind of compromises of an organism in struggling with destructive environment. **C.** Misrepair is a force in altering a living structure during repair. In this paper, the term of Misrepair is used not only for describing the process but also for describing the result of Misrepair as an alteration of a structure. Actually some scientists have hypothesized the existence of Misrepair mechanism on cellular level and on tissue level. Tobias has suggested a Repair-Misrepair mathematical model for analyzing the survival chance of cells under radiation (Tobias, 1985). Kondo has proposed a tissue-Misrepair hypothesis to explain the radiation carcinogenesis (Kondo, 1991). Unfortunately in their studies, the term of Misrepair was not clearly defined.

With a clear definition, a Misrepair is observable and detectable. Alteration of a structure made by Misrepair manifests in different ways: **A.** a change on the amount of its sub-structures, **B.** a change on the types of its sub-structures, and/or **C.** a change on the spatial relationship between its sub-structures. It is essential to distinguish the structure change in an injury from that in a Misrepair. Like that between a wound and a scar, an injury is a change of a structure before repair, which is caused by physical or chemical damage; whereas a Misrepair is an alteration of a structure as a result of repair. An injury appears as a lesion of a structure, whereas a Misrepair appears as a change on the organization of sub-structures (Figure 1). In scientific literatures, the term of injury and the term of damage have not been clearly defined, and this is one reason why we cannot understand aging mechanism. For

avoiding misunderstanding, in our theory, the term of damage is referred to as a physical or chemical impact to a structure, which causes an injury of the structure. An injury is a direct effect of damage, and Misrepair is a biological response to the injury. Damage is the force that triggers the occurrence of injuries and then Misrepairs; therefore damage is the cause, whereas Misrepair is the final effect.

**A living structure**



**Figure 1. Misrepair: an incorrect repair of an injured living structure**

For understanding aging, it is important to distinguish between three concepts. Damage is referred to as a physical or chemical impact to a structure, which causes an injury of the structure (**Damage**). An injury is a lesion of a structure before repair (**Injury**). Misrepair is an incorrect repair of an injured structure by repair, resulting in alternation of the structure (**Misrepair**). An injury is a direct effect of damage, and Misrepair is a biological response to the injury. Damage is the force that triggers the occurrence of injuries and then Misrepairs; therefore damage is the cause, whereas Misrepair is the final effect.

Misrepair is neither a fault nor a mistake of an organism due to the limitation of repair/maintenance; however it is a result of active repair, which is essential for the survival of a living being. An organism with normal repair/ maintenance system DOES NOT SLOW but even PROMOTES Misrepairs when it is necessary. Without Misrepairs, an individual was not able to survive till reproduction age; therefore Misrepair mechanism is essential for the survival of a species. Species' survival is simply a result of the survivals of its individuals till reproduction age.

### **1.3 Examples of Misrepairs**

A Misrepair is actually a tiny scar; however it can appear differently in different structures and in different situations. Although we have techniques for high-resolution imaging such as electron micro-graphing and con-focal imaging, most Misrepairs in molecules, cells, and tissues, are too small to detect. A visible pathological change in an organ is often a result of multiple times of Misrepairs. Here we give some examples of Misrepairs: **A. on tissue level:** scar formation, altered remodeling of cells and/or extracellular matrixes (ECMs), esophagus intestinal Metaplasia, and formation of Langhans giant cells; **B. on cellular level:** altered remodeling of cytoskeleton; and **C. on molecular level:** Misrepair of DNA ([Table 2](#)).

**Table 2. Examples of Misrepairs**

| Tissue level                      | Cellular level                     | Molecular level  |
|-----------------------------------|------------------------------------|------------------|
| Scar formation                    | Altered remodeling of cytoskeleton | Misrepair of DNA |
| Altered remodeling of cells/ECMs  |                                    |                  |
| Esophagus intestinal Metaplasia   |                                    |                  |
| Formation of Langhans giant cells |                                    |                  |

Scar formation on the skin is a result of reparation of epidermis and derma by connective tissue. Basement membrane in epidermis has low potential of regeneration; and a lesion of basement membrane in a deep wound has to be closed by at first fibroblasts and later collagen fibers. Scarring is a repair for sealing, and it is a powerful evidence for the existence of Misrepair mechanism. Scarring takes place often in skin and in connective tissues; however a process of scarring can be too small to be detected. Apart from scar formation, altered remodeling of cells/ECMs has been observed in other manners. For example, a defective remodeling of ECMs, appearing as a dense and poor organization of ECMs, is observed in myocardial tissue of patients with Chagas' disease, a disease that is caused by infection of protozoan parasite *Trypanosoma cruzi* (Spinale, 2007; Rossi, 2001). An extensive dendritic remodeling between retina cells was observed during normal aging of human retina (Eliasieh et al, 2007). An altered interaction of cells through neurite sprouting and abnormal axonal projections of cone photoreceptors was seen in age-related macular degeneration (AMD) of human retina (Pow et al, 2007).

Esophagus intestinal metaplasia is also a result of Misrepair, and the injured esophagus mucosa is repaired with intestinal epithelium. Metaplasia is an adaptive change, since the intestinal epithelium makes local esophagus mucosa more robust to damage (Stein et al, 1993). Langhans giant cells are huge cells that develop from fusion of multiple [macrophages](#). Such giant cells can be observed in granulomatous diseases such as lung transbronchial and lymph node [sarcoidosis](#). A characteristic of a Langhans [giant](#) cell is the horseshoe-shaped distribution of multi-[nuclei](#) in cell periphery and the deposition of necrotic tissue (Caseous necrosis) in cell centre (Lay et al, 2007). Fusion of macrophages is a result of repair, in which un-degradable substance of dead cells are isolated in fused [macrophages](#). Deposition of a Langhans [giant](#) cell has altered the local structure of a tissue, and it is a Misrepair of the tissue.

Altered remodeling of cytoskeleton is an example of Misrepair on cellular level. Cytoskeleton is the architect structure of a cell, which is composed of three types of filaments: microfilament, microtubule, and intermediate filaments. The structure of cytoskeleton is important for maintaining cell shape, nuclear shape and for maintaining a functional organization of organelles. Cytoskeleton filaments compose also the pathways for substance transportation in cytoplasm or via filament cables. The organization of cytoskeleton filaments are in a dynamic dismodeling-remodeling state for adapting cell functions. An

altered and irreversible remodeling of cytoskeleton can take place when part of cytoskeleton structure is severely injured. For example, altered expression and altered remodeling of cytoskeleton proteins including Tintin protein, desmin filaments, and microtubules, are found to contribute to the lengthening and malfunction of myocytes in chronic pressure overload and congestive heart failure (Wang et al, 1999). On molecular level, Misrepair of DNA is the example. Invention of DNA sequencing technique is a miracle in science history, and it makes us able to detect a change on molecular level: a single DNA mutation! In somatic cells, Misrepair of DNA is the main origin of DNA mutations (Suh et al, 2006).

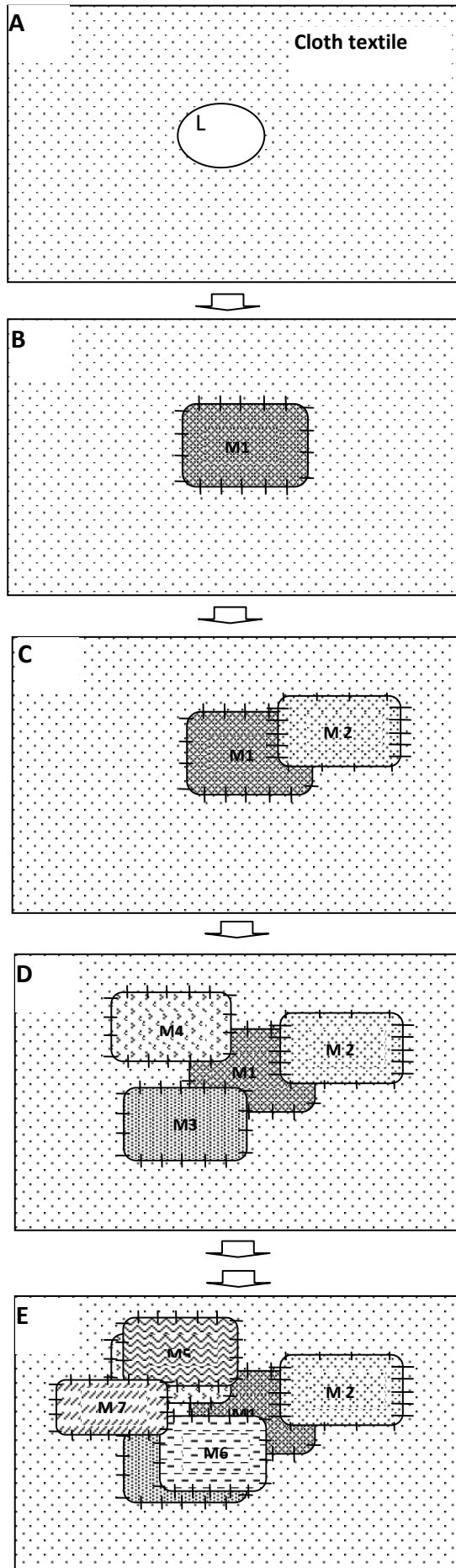
## **II. Aging as a process of accumulation of Misrepairs**

Misrepairs make us survive each day; however they alter the structures of our cells and tissues and reduce their functionality. Like that in scar formation, a Misrepair is an irreversible change of a cell/tissue as a final result of repair. Being unavoidable and irreversible, Misrepairs will remain and accumulate. Accumulation of Misrepairs will gradually deform the structure of a molecule, a cell and a tissue, appearing as aging of them.

### **II.1 Accumulation of Misrepairs and deformation of a structure**

As discussed above, distinguishing a Misrepair from an injury (original damage) is a key step for understanding aging mechanism. Damage (faults)-accumulation theory suggests that because of the limitation of maintenance and repair, some faults can take place and accumulate, and they are the origin of aging (Kirkwood, 2005). However, a fault is in fact an intrinsic damage, and it makes a lesion of the structure of a cell or a tissue; thus it could not remain if not unrepaired. For example, when a cell produces un-functional proteins by a fault and when the proteins are not removed or isolated in the cell, they will remain as a lesion of the structure of the cell. By interrupting intracellular substance-transportation and information-transmission, they will cause death of the cell. Therefore “unrepaired” or “untreated” faults cannot remain and accumulate in a living organism. Differently, Misrepairs are the results of repair and they can accumulate. Accumulation of alteration of a structure after each time of Misrepair will gradual disorganize the structure, which appears as aging of it. For example, accumulation of scars on skin is a part of aging of the skin. The process of gradual deformation of a living structure by accumulation of Misrepairs is similar to the gradual alteration of a cloth textile, which has been repaired many times with different textile material (Figure 2). Repair of a lesion of a cloth textile with an altered type of textile is a kind of Misrepair. When several times of such Misrepairs are made in a local part of textile, the repairing materials gradually overlap each other and deform this part of textile.





## Figure 2. Schematic representation of structure-deformation by accumulation of Misrepairs

The process of gradual deformation of a living structure by accumulation of Misrepairs is similar to the gradual change of a cloth textile, which has been repaired many times with different textile material. Repair of a lesion of a cloth textile with altered type of textile is a kind of Misrepair. For example, a textile (A) is firstly repaired for closing a lesion (L) by Misrepair 1 (M1 in B), then by Misrepair 2 (M2 in C), and then by M3 (M3 in D). When several times of such Misrepairs are made in a part of textile, the repairing materials of M1, M2, M3, M4, M5, M6, and M7 overlap each other: M1 + M2 + M3 + M4 + M5 + M6 + M7, and deform gradually this part of textile.

Accumulation of Misrepairs leads to gradual disorder of a living structure and gradual reduction of its functionality. Aging of a structure is not essentially a reduction of number of its sub-structures, not essentially a change of types of its sub-structures, and not essentially a deposition of “waste”, but essentially and sufficiently an accumulation of alterations of the structure by Misrepairs. Aging of an organism is a result of accumulation of Misrepairs of its structure. For non-living structures that cannot be repaired, such as architecting materials, damage can remain and accumulate. Therefore “aging of a material” is a result of accumulation of damage. In fact, there are also non-living structures in an organism. Hairs, nails, the lens, and intervertebral discs are tissues that have lost biological functionality and they are dead structures. Aging of these tissues are not due to Misrepairs.

Animals and plants are multi-cellular beings, and a multi-cellular being is composed of five levels of sub-structures: molecules, organelles, cells, tissues, and organs. Molecules and cells are the units of repairing materials, and from the aspect of repair, these sub-structures are on three levels: molecular, cellular and tissue. DNAs are on molecular level, and they are repaired by small molecules such as nuclide base pairs. Organelles and cells are on cellular level, and they are repaired by small molecules and big molecules such as proteins. Tissues, organs and the whole organism are on tissue level, and they are repaired by cells and ECMs. Misrepairs and accumulation of Misrepairs take place on each level of these structures respectively.

### II.2 Accumulation of Misrepairs on molecular level

Accumulation of Misrepairs of DNA is on molecular level. In somatic cells, changes on genome DNAs can take place by different mechanisms. A big change on a genome DNA such as loss or gain of a fragment of chromosome can cause cell death. However, a point mutation of DNA, which does not essentially alter cell phenotype, can survive and accumulate. Therefore, point mutations are the main type of mutations that can accumulate in DNAs and in cells. Misrepair is the main source of point mutations in somatic cells. Since the surviving rate of a cell through Misrepair of DNA is low, accumulation of DNA mutations can take place only possibly in the cells that can proliferate. Accumulation of DNA mutations needs to proceed in many generations of somatic cells, and it is a slow process. Accumulation of DNA mutations alters gradually DNA sequence, DNA structure and the functionality of DNAs in a cell, which can be understood as aging of the genome DNA of a cell. Cell transformation and tumor development is one of the consequences of aging of genome DNAs. In malignant

tumor cells, aging of genome DNAs are accelerated by the deficiency of DNA repair and the rapid cell proliferation.

### 2.3 Accumulation of Misrepairs on cellular level

In a cell a Misrepair takes place mainly on the structure of cytoskeleton, and it appears as an alteration of the organization of some filaments after repair of an injury. When the alterations are irreversible, they accumulate and gradually deform the cytoskeleton of the cell. Deformation of cytoskeleton will lead to a change of the distribution of organelles and a change of the shapes of cell and nucleus. This is the reason why aged cells have shrunk cell/nuclear membranes and agglomerated euchromatins. Cytoskeleton filaments also compose the pathways of substance transportation in a cell: via filament cables or via cytoplasm. Disorganization of filaments will affect intracellular substance transportation and information transmission, and result in reduction of efficiency of the cell on metabolism and on adaptation. An aged cell has one of the four destinations: **A.** die and be replaced by a reproduced cell, **B.** die and be replaced by other types of cells/ECMs such as fibroblasts and collagen fibers, **C.** continue aging with accumulation of lipofuscin bodies, and **D.** die and be isolated by connective tissue when dead substance is un-degradable. Neurofibrillary tangle is an aging change of neuron cells, in which neurofibrils are in an abnormal organization (Lee, 2005). In our view, Neurofibrillary tangle is a part of disorganization of cytoskeleton filaments, and it is a result of accumulation of Misrepairs of Neurofibrillary.

### 2.4 Accumulation of Misrepairs on tissue level

A Misrepair in a tissue can appear as a change on the type, the amount, and/or the distribution of cells/ECMs. Accumulation of Misrepairs in a tissue will distort gradually the organization of cells/ECMs. Liver cirrhosis is a rapid process of aging of a tissue as a consequence of chronic inflammations of the liver such as hepatitis type B. A normal liver has a regular organization of hepatocytes, which are grouped into hepatic lobules. However, after repeated attacks by viral B, repeated deaths of cells, repeated reproductions and reorganizations of new cells/ECMs, the beautiful organization of lobules is gradually deformed. During hepatitis, many dead hepatocytes have to be replaced by fibroblasts and collagen fibers in repair, and accumulation of collagen fibers, which are in an irregular organization, makes liver tissue stiff. Other aging changes in tissues such as tissue degenerations and irreversible hyperplasia are also results of accumulation of Misrepairs of tissues.

**Tissue degenerations:** Atherosclerotic plaques and hyaline degeneration are two typical aging-related degeneration changes. A common change in tissue degenerations is the deposition of abnormal substance in a tissue or in a cell. The deposited substance can have two sources: one is un-degradable substance, and the other is the products of cells for repair. To un-degradable substances, an adaptive response of a tissue is to isolate them *in situ* in a fibrotic capsule for rebuilding structural integrity; and this is a Misrepair. For example, development of an atherosclerotic plaque in a part of arterial wall is a result of Misrepairs of endothelium, since the infusion of lipids makes a complete repair of endothelium impossible.

Another source of substance for deposition is the products of cells for repair. Like that in metabolisms in cells and that in immunoreactions in tissues, all active molecules will be removed immediately after functioning, and this is essential for maintaining the stability of intracellular and extracellular environment. Exceptionally, the products for repair are used for reconstructing a structure, and finally they are integrated into the remodeled structure. When a repair is accomplished by altered materials and in an altered remodeling, the repair is a Misrepair. For example, the hyaline degeneration in scars and arterial walls is a result of accumulation of collagen proteins, which are used for replacing the injured elastic fibers, myofibers and other ECMs.

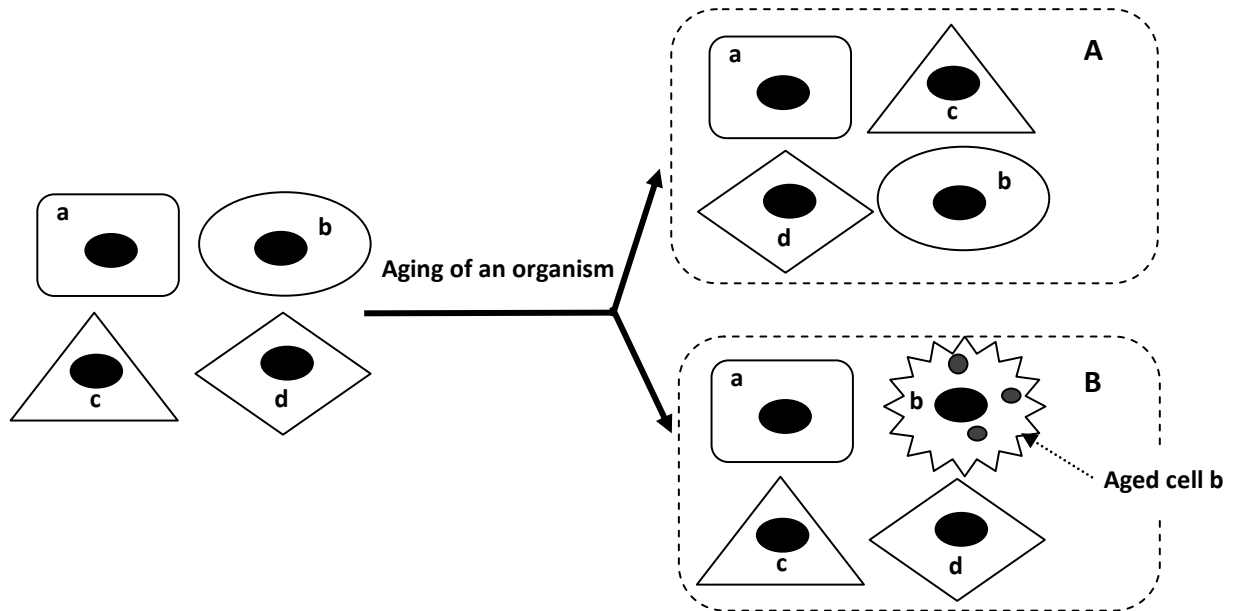
**Hyperplasia:** Hyperplasia is a phenomenon that a tissue has excessive cells by cell proliferation. There are three types of hyperplasia: physiologic hyperplasia, pathological hyperplasia, and neoplasia (tumor). Physiologic hyperplasia is a temporary tissue response to environment change, in which proliferation of cells will stop and cell number will be reduced to normal when the stimulator is withdrawn. The breast hyperplasia during breeding is a type of physiologic hyperplasia. Differently, pathological hyperplasia is irreversible. For example, the synovial hyperplasia in osteoarthritis is a result of repeated repairs of synovial tissue. The over-proliferation of synovial cells is triggered by repeated injuries of cartilage. In an organism that has no genetic disorder, a permanent proliferation of normal cells can only be a result of repair. These cells are normal genetically; however they are in a reorganization that is different from that one in a normal tissue. Therefore pathological hyperplasia is a result of Misrepairs of a tissue. In neoplasia, cell proliferation is uncontrollable and the cells are abnormal genetically. Neoplasia is a result of accumulation of DNA mutations in somatic cells. Pathologic hyperplasia and neoplasia are both results of accumulation of Misrepairs; however the former is on tissue level, whereas the latter is on DNA level.

## **2.5 Aging of a multi-cellular organism: on tissue level**

The aging of DNAs, cells and tissues can be independent, but a critical question is whether or not aging of an organism is a result of aging of cells and aging of molecules. In fact, in some aging symptoms, such as synovial hyperplasia and atherosclerotic plaques, there is no change on cells and molecules themselves. A common and consistent change in most aging symptoms is an irreversible change on the organization of cells/ECMs, which is actually on tissue level. In our view, aging of an organism, which is disease-related, takes place essentially and sufficiently on tissue level.

Full functionality of a tissue/organ depends not only on a full functionality of each cell and each ECM, but also on a perfect collaboration (spatial relationship) of them. An altered reorganization of normal cells/ECMs is sufficient for causing a decline of tissue functionality and body functionality; and this change is neither on cellular level nor on molecular level but on tissue level. When dead cells and injured ECMs are replaced by new cells/ECMs of the same types however in an altered reorganization, tissue functionality will be reduced (Figure 3A). When an aged cell remains in a tissue, it alters also the spatial relationship of local cells/ECMs and affects tissue functionality (Figure 3B). Therefore an essential change in aging of an organism, by which we can develop diseases, is an irreversible change of the

spatial relationship between cells/ECMs in a tissue. Aging of an organism does not essentially require aging of cells and aging of molecules but requires aging of tissues. Interestingly, in regenerable tissues, deposition of aged cells is an effect rather than a cause of aging of a tissue. On one hand, aging of a tissue can accelerate aging of cells, since the efficiency of substance transportation and cell communication is reduced in an aged tissue. On the other hand, aged cells cannot be efficiently removed, since the repair-efficiency of an aged tissue is also reduced.



**Figure 3. An essential change in aging of an organism: a change of spatial relationship between cells/ECMs**

An altered reorganization of normal cells/ECMs is sufficient for causing a decline of tissue functionality and body functionality; and this change is neither on cellular level nor on molecular level but on tissue level. When dead cells and injured ECMs are replaced by new cells/ECMs of the same types however in an altered organization (a, b, c, and d), tissue functionality will be reduced (A). When an aged cell remains in a tissue (aged cell b, in B), it alters also the spatial relationship of local cells/ECMs and affects tissue functionality (B). Therefore an essential change in aging of an organism is a change of spatial relationship between cells/ECMs in a tissue. Aging of an organism does not essentially require aging of cells and aging of molecules but requires aging of tissues.

### III. Conclusion: Misrepair-accumulation theory

With a generalized concept of Misrepair, we have explained the roles of a structure, damage, an injury, and repair/maintenance function in a process of aging. By causing injuries, damage promotes the occurrence of Misrepairs, in which damage is the causing factor whereas Misrepair is the final effect. Misrepair is a strategy of repair, which increases the chance of survival of an organism from severe injuries and repeated injuries. Misrepair mechanism tells us that an organism is programmed to make all efforts to survive in destructive environment. Since Misrepairs are unavoidable and they alter a structure permanently, they accumulate with time. Accumulation of Misrepairs alters gradually the structure and the functionality of a molecule, a cell or a tissue, appearing as aging of them. Misrepairs are the common changes under all aging symptoms. Misrepair mechanism is essential for the survival of a species, and

aging of individuals is the price to be paid. Aging can take place on levels of molecule, cell and tissue, respectively; however aging of an organism takes place essentially and sufficiently on tissue level. We summarize our idea by our Misrepair-accumulation theory: aging of an organism is a result of accumulation of Misrepairs on tissue level.

With this theory, we can understand why we age and how we age. We age because we have to make Misrepairs for survive when we suffer injuries. We cannot avoid aging, because without Misrepairs we could not survive till mature age to have children, and the species of human being could die out. "Aging of a non-living structure" is a result of accumulation of injuries (damage) but not of Misrepairs. Misrepair mechanism is a mechanism showing why organisms are not programmed to die but to survive, as long as possible (Kirkwood, 2005).

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