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## AGING AS A CONSEQUENCE OF MISREPAIR -- A NOVEL THEORY OF AGING

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### ABSTRACT

It is now increasingly realized that the underlying mechanisms which govern aging (ageing) are a complex interplay of genetic regulation and damage accumulation. Aging as a result of accumulation of 'faults' on cellular and molecular levels, has been proposed in the damage (fault)-accumulation theory by Kirkwood 2006. However, this theory fails to explain some aging phenotypes such as fibrosis and premature aging, since terms such as 'damage' and 'fault' are not specified. Therefore we introduce here a specification of the underlying mechanism of aging and arrive at a novel theory: *aging of the body is a result of the accumulation of Misrepair of tissue*. It emphasizes: a) it is Misrepair, not the original damage, that accumulates and leads to aging; and b) aging can occur at different levels, however aging of the body takes place at least on the tissue level, but not necessarily on cellular/molecular level. The novel concept of Misrepair introduced here unifies the understanding of the roles of environmental damage, repair, gene regulation, and multicellular structure in the aging process. The Misrepair-accumulation theory introduced in the present paper gives explanations for the aging phenotypes, premature aging, and the difference of longevity in different species, and is consistent with the point of view of physical theory of complex systems.

**KEY WORDS** aging (ageing), damage, Misrepair-accumulation, longevity

### INTRODUCTION

Many theories have been proposed to answer the question of why and how we age. These theories fall into two main groups: genetic regulation and damage-accumulation. The **gene-controlling theories** emphasize the genetic regulation on aging (ageing). Many genes have been found to be related to aging, and some have shown lifespan-extending effects on animal models by gene knock-out (or -in), however their associations with aging are debated and far from confirmed. The *Mutation-accumulation Theory* assumes that the weak selection by nature in late age allows a wide range of gene mutations to accumulate, with deleterious effects (1,2): one interesting point which remains unanswered is why genes mutate to be deleterious. The *Developmental Theory* suggests that

aging and development are coupled and regulated by the same mechanisms (3,4). It is theoretically interesting and reasonable; however this theory fails to explain how the development process influences the aging phenotypes. The **Damage-accumulation theories** imply that it is the extrinsic and intrinsic damage (or fault) accumulation on cellular or molecular level, that leads to aging: The causes can be free radicals, by-products, molecular cross-linking and so on (5,6). However, most of these theories actually mainly pointed out the phenotypes or causes but not the *underlying common mechanism* of aging.

It is now increasingly realised that genetic regulation and damage-accumulation actually interplay to account for aging, and it is predicted that: “aging is a result of accumulation of ‘faults’ at cellular and molecular level because of the limitation of maintenance and repair; the underlying driving force is damage. The genetic control of longevity comes through the regulation of the essential maintenance and repair processes that slow the build-up of faults”(7). However this recent damage (fault)-accumulation theory does not clarify the concepts of ‘damage’ and ‘fault’, and is weak in explaining some aging phenomena, such as fibrosis and premature aging. On the other hand, the slow process of aging in living beings must be complex, not simply explainable by the gradual accumulation of damage, as that in lifeless matter. Therefore we suggest here some crucial modifications of this theory and raise a novel theory of aging.

## **A NOVEL THEORY OF AGING**

### **Limitations of the current damage (fault)-accumulation theory**

In the above mentioned damage (fault)-accumulation theory (7), the terms of ‘damage’ and ‘fault’ are not clearly defined. The ‘damage’ may mean the primary damage before repair and/or the incomplete repair following damage. Incomplete repair may also include partial repair and incorrect repair. However it is necessary to distinguish between them. For example: burnt skin causes a scar. The burnt skin is the damage, and the scar is the incorrect repair. The ‘fault’ seems to mean the original damage which is either partially repaired or not at all repaired. However, if the damage is left unrepaired, it will develop life-threatening condition by destroying the integrity of structure, no matter whether the damage is on the molecular, cellular, or tissue level. Therefore, the original damage cannot remain unrepaired, and hence the concept of accumulation of ‘faults’ is misleading. Repair of any damage, and reconstruction of the structure, are essential to maintain the integrity of structure and the basic function for survival: even if sometimes it is imperfect. In most cases, repair is complete, so that the structure can be restored. However, incorrect repair can and even must occur in cases of serious or frequent injuries, where quick reparation is more important for the immediate survival than perfect reparation. Typical examples include the SOS Misrepair of DNA and the scar formation. The term ‘Misrepair’ appears applicable in a wider sense, not only to DNA, but also to other types of incorrect repair due to a similar mechanism.

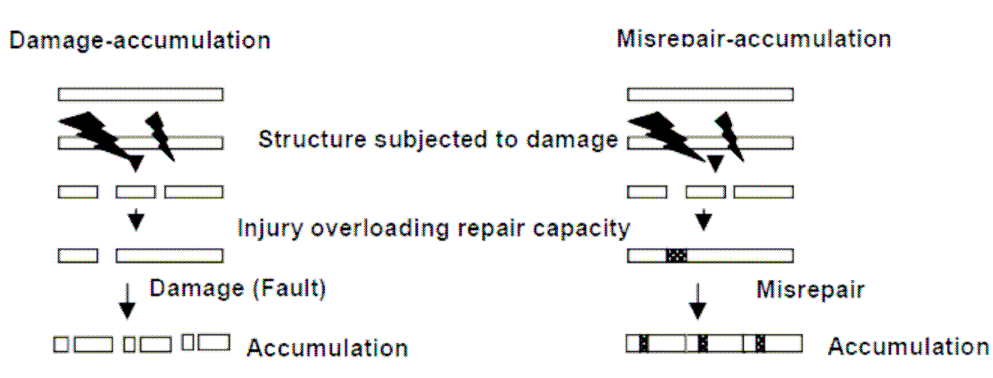
### **The concept of Misrepair**

We define the concept of Misrepair as *the incorrect reconstruction of a structure, after repairing the original damage*, which can lead to a change of tissue structure. The comparison between damage and Misrepair is shown in Table 1. We define the term “damage” as the structure change before any reparation has taken place, whereas “Misrepair” is the change of structure as a result of incomplete or defective reparation. Distinguishing these two concepts is necessary to understand the aging mechanism, in which damage is the cause and Misrepair is the effect. Misrepair is unavoidable when serious or frequent damage occurs no matter how powerful the gene-regulated repairing- and

maintenance system is, since repairing – many steps of biochemical reactions – needs time. A misrepaired structure cannot be ‘repaired’ any more (restored to the pre-damage state) and persists as a ‘scar’. So it is the Misrepair and not the original damage that accumulates. Therefore the term of *Misrepair-accumulation* is more appropriate than that of damage-accumulation (Figure 1). Damage drives the aging process by triggering Misrepair. Liver cirrhosis, for instance, is a result of accumulation of mis-reconstruction of tissue due to the quick death of hepatocytes. Misrepair is a result of the active repair processes beneficial for survival. Therefore the maintenance and repair system does NOT SLOW but even PROMOTES the occurrence of Misrepair if necessary, although a more powerful repairing system means lower rate of occurrence of Misrepair. Hence the appearance of Misrepair sacrifices long-term survival over the immediate survival of individual – which is more important for the survival of species. Therefore the Misrepair mechanism was selected by nature due to its evolutionary advantage. Aging is for survival, immediate survival and species survival. This is why evolution favors aging. Thus Misrepair might represent the mechanism by which *the body is not programmed to die but to survive* (8), and aging is just the price to be paid.

**Table 1. Comparison of damage and Misrepair**

Damage	Misrepair
Physical and chemical injury on cells/ECM	Imperfect reconstruction of tissue structure
Defect before repairing	Defect after repairing
Removable	Permanent
e.g. Cells/ECM injury and death	e.g. Change of the amounts of functional cells/ECM, and their locations or spatial relationships



**Figure 1. Comparison of Misrepair-accumulation and damage-accumulation**

**Damage-accumulation:** due to the limitation of maintenance and repair, some damage remains partially repaired or unrepaired. This remained damage (fault) will accumulate and lead to aging. **Misrepair-accumulation:** serious or too frequent damage triggers Misrepair in emergency to maintain the structural integrity and protect from immediate death. However the persistent Misrepair will accumulate and lead to aging.

### Aging of tissues

Aging can occur at different levels: molecular, cellular and tissue. However, an interesting point is whether the aging of tissue, which is directly related to organ function and body lifespan, should be always due to the aging of cells or molecules. The intact function of tissue not only depends on the intact functions of cells/ extracellular matrix (ECM), but also depends on the intact collaborations (spatial relationships) among them. If a defect occurs to the tissue structure, which affects the spatial relationships between cells/ECM, the defect could cause a decline in tissue function. If, however, the

defect occurs to the cells/ECM, there can be different outcomes depending upon the location. In tissue that can regenerate, the defect can be removed and replaced with new cells/ECM, and may not necessarily affect tissue function. In tissue that cannot regenerate, such as nerve tissue, the defective cells not only affect the cell-contributed tissue function, but also disturb the spatial relationships amongst other functional cells/ECM. Therefore, the residual non-functional cells/ECMs can be also regarded as a defect of tissue structure. All above together suggests that the aging of body takes place on tissue level at least and not necessarily on the cellular/molecular level. The common feature of body aging is the deleterious change of tissue structure, which includes the change of amounts, locations and the spatial relationships of functional cells/ECM. One reason why some aged cells can be found in old tissue is that, the aged cells cannot be replaced in time due to the reduced repair function of aged tissue. In this case, the aged cells are the effect of aging of tissue, but not the cause. In this aspect our view is the same as that in the *Multicellular Being Chaos Theory*, which suggests it is the failure of information transmission in multi-cellular beings between each part that leads to aging (9), however, this theory does not explain how the breakdown of information transmission occurs.

### **The Novel theory and its consistence with the physical view of aging**

*We propose that aging is a result of accumulation of Misrepair of tissue.* Likewise, we also hypothesize that the aging of a cell is a result of accumulation of Misrepair of intracellular structure. The distinguishing between damage and Misrepair clarifies what is the cause (damage) and what is the effect (Misrepair) in the aging process. Misrepair as an imperfect repairing result links the functions of gene-controlling and damage-exposure in aging. The concept of tissue-Misrepair couples aging and development, which obey a similar mechanism: tissue-(re)construction. Therefore this theory unifies the multi-factors in aging mechanism. Actually, any kind of structured body with maintenance function, e.g. a city, a road, or a building, has also the aging problems from the same mechanism.

Our interpretation is consistent with the physical view of aging. In terms of the Second Law of Thermodynamics, cyclic processes of metabolism increase the entropy in a living system. Entropy actually characterizes the degree of disorganization. Living beings continuously need to release entropy to protect them from running into thermodynamic equilibrium (death) (10-12). However the entropy increases unavoidably due to the un-removable Misrepair. Therefore it is the Misrepair that account for the permanent increase of entropy. In addition, in the spirit of the physical theory of complex systems (11,12), living beings must be conceived as complex self-organised systems. The characteristics of complex systems are their 'emergent' properties and functions, which are qualitatively different from those of their subsystems. Hence some properties of living beings such as longevity and aging cannot be reduced to the properties of their subsystems such as cells and molecules (13).

## **INTERPRETATION OF AGING PHENOTYPES AND LONGEVITY IN THE LIGHT OF THE NOVEL THEORY**

### **Aging-related disorders**

**Fibrosis** is a typical phenotype of aging, unexplained by the damage-accumulation theory. However, in our view, fibrosis is the result of accumulation of over-produced ECM for repairing, essential for survival by limiting damage, isolating the undegradable cells or by-products and reconstructing the structures. **Atherosclerosis** is an aging-related chronic inflammation disease, and the formation of

plaques is the result of the over-proliferation and accumulation of macrophages for clearing the lipid in the wall of blood vessel when the endothelium is frequently damaged. This can be one underlying mechanism showing the effect of the caloric restriction on retarding aging (14). **Aging-related tumours** are the results of mutations due to the accumulation of Misrepair of DNA, which leads finally to tissue disorganization. The lack of cancer in simpler organisms(15) may be because their lifespans are too short to accumulate sufficient Misrepair of DNA.

### **Premature aging**

Development and repair are both tissue/body constructing processes. Any element that interrupts the construction process will affect the development/repair and lead to *mis-construction/mis-reconstruction* (imperfect construction) of tissue/body. On this point, the aging and the development procedures are regulated by a similar genetic mechanism (3,4). This *mis-construction* might be the mechanism of premature aging. For example, the **Hutchinson-Gilford Progeria** is caused by a gene mutation in the nuclear envelope protein Lamin A (16). The change of lamin A results in nuclear blebbing, which interrupts DNA/RNA synthesis and affects cell division.

### **Genes restrict the maximum lifespan by shaping the body**

It is unavoidable that tissue structure goes finally to breakdown due to damage and Misrepair; therefore, the potential of tissue is the key point for longevity. Death often happens from a failure of a key tissue/organ, e.g. the blockage of blood vessel in brain and heart due to Atherosclerosis. The maximum potential lies in the complexity and maintenance of the tissue structure. Genes predetermine this potential by controlling the development. Therefore gene configuration restricts the maximum lifespan by shaping the body. Longer living species' often have a longer development time for their more complex functionality and need longer time for accumulating sufficient Misrepair. This may be the mechanism explaining why different species' have different maximum lifespans. An exception is the big difference in the lifespan between the queen and the worker ants: in spite of their similar gene configurations. However, the queen and the workers undergo different development, which leads to different body structures. In *C. elegans*, an alternative (*duater*) developmental pathway results in a significant longer lifespan (17). These examples indicate that it is the difference of body structure that finally and directly determines the difference of maximum longevity.

It is possible that nature develops longer-living species by increasing the body complexity; however, if the lifespan is too long, individuals would die before the reproduction age which would lead to the extinction of the species. The survival of species is the result of limited longevity and it is the best evidence of the essentiality of limited longevity.

Although gene configuration determines the maximum longevity of a species, the individual lifespan is more related to the environmental damage-exposure, and it can only be extended to a certain limit. Our theory suggests that for extending lifespan all efforts need to focus on the reduction of Misrepair. This can be achieved by avoiding damage exposure as far as possible. This includes improving living conditions and improved medical care. It is especially important to prevent chronic inflammation, which is an important source of Misrepair. An improved repair system by gene-manipulation can reduce the chance of Misrepair. However, the theory of complex systems together with basic physical principles such as the *Second law of Thermodynamics* teach us (10-13) that entropy-increase and equivalently Misrepair accumulation and as a consequence aging are inevitably imposed by nature on living beings. Theories ignoring these basic principles by making dubious



promises on the possibilities of sensational extension of longevity must be considered as “wishful thinking” rather than as serious theories.

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