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

Jicun Wang[1], Thomas M. Michelitsch[2*], Arne Wunderlin[3] and Ravi Mahadeva[1]

[1]Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom
[2]Institut Jean le Rond d'Alembert CNRS UMR 7190, Université Pierre et Marie Curie (Paris 6), 4 Place Jussieu, 75252 Paris cedex 05, France
[3]1. Institut für Theoretische Physik, Pfaffenwaldring 57/4, D-70550 Stuttgart, Germany
*Send correspondence to: Dr. Thomas M. Michelitsch, Email: michel@lmm.jussieu.fr

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ABSTRACT

It is now increasingly realized that the underlying mechanisms which govern aging is 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 (7). 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 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 which is 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 which is introduced here gives also 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; 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-accumualation. The **gene-controlling theories** emphasize the genetic regulation on aging. 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 explainable only by the slow accumulation of damage, as the non-living substance. Therefore we suggest here some crucial modifications of this theory and to 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 destroying the integrity of structure, no matter whether the damage is at 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 sometime 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 scar formation. The term 'Misrepair' appears applicable 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 changed structure before any reparation has taken place whereas "Misrepair" is the change in structure as a result of incomplete or defective reparation. In contrast to a damaged structure a misrepaired structure is invisible for the reparation system and remains hence irreparably defective. Since not any more reparable the defective structure of Misrepair accumulates with time. Distinguishing these two concepts are necessary for understanding 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 repair and maintenance is, since repairing – many steps of biochemical reactions need time. A misrepaired structure cannot be 'repaired' any more (restored to the pre-damage state) and persists as a 'scar'. Therefore we emphasize it is the Misrepair and not the original damage that accumulates. Therefore the term of *Misrepair-accumulation* seems to be 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 death of hepatocytes. Misrepair is a result of the active repair processes beneficial for survival. Therefore the maintenance and repair system does NOT SLOWDOWN but PROMOTES the occurrance of 'Misrepair', although more powerful repair means lower rate of occurance of Misrepair. Misrepair sacrifices long-term

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survival over the immediate survival of individual – which is more important for the survival of species. Therefore this misrepair mechanism was selected by nature by its evolutionay 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 a just a price to be paid.

Table 1. Comparison of damage and Misrepair

Damage	**Misrepair**
Physical and chemical injury on cells/ECM	Imperfect reconstruction of structure of cells/ECM
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

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 at a 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 distingwishing of damage and Misrepair makes it clearer what the cause (damage) is and what the effect (Misrepair) is in aging process. Misrepair as a (inperfect) repairing result links the functions of gene-controlling and damage-exposure in aging. The concept of tissue-Misrepair couples aging and development, which have the similar mechanism: tissue-(re)construction. Therefore this theory unifies the multi-factors in aging mechanism.

Our interpretation is in agreement 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 (Misrepair accumulation). Entropy actually characterizes the degree of disorganization. Living

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beings continuously need to release entropy to protect them from running into thermodynamic equilibrium (death) (10-12). However the entropy increases due to the permanent accumulation of misrepaired defective structures which cannot be any more removed from the body since they are invisible for the reparation system. In addition, in the spirit of the physical theory of complex systems, living beings must be conceived complex. The characteristics for 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).

INTERPRETION OF AGING PHENOTYPES AND LONGEVITY IN THE LIGHT THE 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 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-(re)constructuion* of tissue/body. On this point, the aging and development procedures are regulated by a similar genetic mechanism (3,4). This *mis-(re)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 will breakdown; therefore, the potential of tissue is the key point for longevity. The maximum potential lies in the complexity and maintenance of the structure. Genes predetermine this potential by controlling the development. The time it takes to develop, plus to breakdown the structure is the lifespan of tissue/body. 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. elegnas*, 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.

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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 a possible source of Misrepair. An improved repair system by gene-manipulation can reduce the probability of Misrepair. However, the physical theory of complex systems teaches us (10-13) that entropy-increase or equivalently Misrepair accumulation and as the 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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FIGURE 1

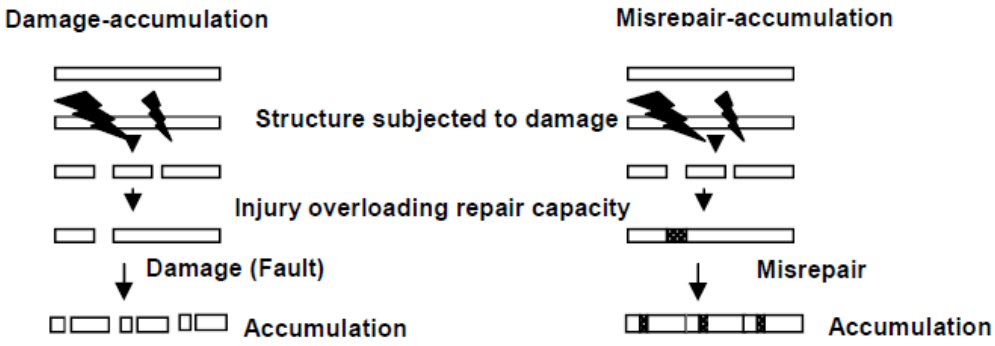

FIGURE LEGEND

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**: serous 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.

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