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Alzheimer's Disease as Subcellular 'Cancer'

—— *The Scale-Invariant Principles Underlying the Mechanisms of Aging* ——

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Alzheimer's disease (*AD*) is characterized by the slow onset of neurodegeneration leading to dementia in many elderly people.[1] The pathological hallmarks of AD are: the extracellular *β-amyloid* deposition in the *senile plaques*;[2] the β-amyloid deposition in cerebral blood vessel walls especially in *hereditary cerebral hemorrhage with amyloidosis of the Dutch type* (*HCHWA-D*);[3] the intracellular *neurofibrillary tangle* formation composed of *paired helical filaments* (*PHF*), the principal component of which is a hyperphosphorylated form of the microtubule-binding protein, *tau*;[4] and neurological dysfuction and neuronal cell death in limited regions and pathways of the central nervous system.[5] Note that β-amyloid is a truncated form of a cell surface integral membrane glycoprotein: amyloid precursor protein (APP).[6] Despite these hallmarks, the pathogenesis of AD has been poorly understood.

In the present paper, a theory of aging is proposed to give a coherent account of the origins and causes of neurodegeneration common to the diverse neurodegenerative disorders such as AD and *prion* (*proteinaceous infectious particles*) *diseases*[7),8] in comparison with the pathogenesis of cancers.[9] Surprisingly, the self-aggregation of denatured proteins —such as β-amyloid, PHF and prions— responsible for neuronal cell death resembles, in many respects, the development (or the clonal evolution) of malignant cells at the expense of the entire organism harboring them. Although neurodegenerative disorders and cancers apparently differ in pathology, they nevertheless seem to follow the same principles regardless of the level and scale of the biological organization. It is the general principles of *heritable variations* and *natural selection*[10] as well as the general principles of *self-organization*[11),12] that operate, not only on different molecules, but also at different hierarchical levels and scales of the biological organization, independent of the details of diseases.

Traditionally, natural selection, along with self-organization, has been thought to underlie 'creative' aspects of biological phenomena such as the origin of life,[13] adaptive evolution of viruses,[14] immune recognition[15),16] and brain function.[17] It therefore must be surprising to find that the same principles will also underlie 'non-creative' aspects, for example, the development of cancer[18),19] and the aging of complex organisms. Although self-organization has extensively been studied in nonliving things such as chemical reactions[11] and laser physics,[12] it is undoubtedly true that the similar sources of the order are available to living things at different levels and scales.[20]

Several paradigm shifts are, however, required to realize how the general principles of natural selection can be extensible to non-DNA molecules which do not possess the intrinsic nature of self-reproduction. One of them is, from the traditional, *genetic inheritance view* that DNA (or RNA) molecules are the *ultimate* unit of heritable variations and natural selection at any organization level, to the *epigenetic* (*nongenetic*) *inheritance view*[21),22] that any non-DNA molecule can be the target of heritable variations and molecular selection to accumulate in certain biochemical environment. Because they are all enriched with a β-sheet content, ready to mostly interact with one another, different denatured proteins like β-amyloid, PHF and prions can individually undergo self-templating or self-aggregating processes out of gene control.[23),24] Other paradigm shifts requisite for a breakthrough in the etiology of neurodegenerative disorders will be discussed.

As it is based on the scale-invariant principles, the present theory also predicts plausible mechanisms underlying quite different classes of disorders such as *amyotrophic lateral sclerosis* (*ALS*), *atherosclerosis, senile cataract* and many other symptoms of aging. The present theory, thus, provides the consistent and comprehensive account of the origin of aging by means of natural selection and self-organization.

Towards the Frontiers of Theoretical Physics

What is life? This long-standing problem has attracted many physicists especially since Erwin Schrödinger published the famous book in 1944. Nevertheless, this problem has not been solved yet. This is not because we lack complete knowledge of elements such as DNA, proteins and other molecules, but because we lack a theoretical framework provided by a new view of life. Indeed, we have been too much familiar with the traditional reductionists' view that requires identifying the elements at different levels of biological organization and understanding the relations between the different levels. On the basis of this traditional reductionism, however, we cannot understand how living things are different from nonliving things, because both are equally made of material molecules. To understand life itself, we must identify not only the 'elements' but also the 'elementary processes' within the organism. Only then, normal states and disease states and even senescent states can be clearly interpreted in terms of dynamic changes in the elementary processes as well as plastic changes in the elements. Regardless of whether the external environment remains constant or not, the organism is continually subject to the intrinsic variability at any level and scale. It therefore must be emphasized that transients and variations are essential and advantageous to life, because changes in the environment are important for successful adaptation. In this sense, we should not always expect that any biological system will show the same responses to the same stimuli. This situation apparently violates the reproducibility of the same events under the same conditions, though it has been central to physics. Now we need paradigm shifts in the theoretical physics as well as modern biology. Along this line, the present paper proposes a theory to attack the problem of aging. Unfortunately, the problem of aging has been largely neglected by most biologists, probably because the aging process is too complicated to seek a simple explanation. It therefore must be surprising that there is a simple explanation of aging, and that the general principles govern not only the aging of higher organisms but also the origin of life and even brain function. Now is the best time to attack the long-standing problem: what is life?

§ 1. Introduction

The pathogenesis of AD has been a long-standing mystery since first described by A. Alzheimer in 1907. This is not because we lack complete knowledge of components —such as molecules, organelles, cells or individuals— at different levels of organization, but because we lack a global view integrating the fragments of knowledge at all levels and scales. Since life has become *hierarchically* organized during both evolution[25] and development,[26] we need the global view to understand the pathogenesis of AD and many other complex biological phenomena. Lessons learned from past breakthroughs in biology and medicine can give insights into better understanding of how we attack the long-standing mystery of AD.

Without complete knowledge of molecules or cells, we have indeed made successive breakthroughs in immunology and oncology in the context of natural selection since Charles Darwin's book[10] of "*The Origin of Species by Means of Natural*

Selection" in 1859. It has progressively been understood that Darwin's principles of heritable variations and natural selection —which govern the long-term evolution of all living organisms on the earth— can also govern the short-term evolution of all dividing cells in the multicellular organism. The paradigm underlying this genetic inheritance view is that any self-reproducing entities —such as living organisms and dividing cells— adaptively evolve through successive rounds of mutations and natural selection acting *ultimately* on genes. *Clonal selection theory*[15] in immunology and *clonal evolution theory*[18),19] in oncology have been proposed in this context. Of course, this is not a result of the simple application of the general principles of natural selection to immunology and oncology, but a result of the independent rediscovery of the same principles in the cellular society.

Here we have to appreciate two important points. First, the general principles indeed govern adaptive evolution of biological organization regardless of its hierarchical level. Although life has become hierarchically organized during evolution and development, it nevertheless must be a surprise that the same principles govern adaptive behavior of biological organization at different hierarchical levels. Second, adaptive evolution of dividing cells, for example, at a hierarchically lower level is not always promised to favor the hierarchically higher organism harboring them, as in the case of cancer. It seems to be paradoxical! However, understanding this paradox will advance investigations of many symptoms of aging as well as normal living states.

1.1. *Paradigm shifts in modern biology*

One purpose of this work is to realize that Darwin's principles of natural selection can and should be extended to the intracellular society involving complex biochemical reactions of molecular metabolism. This, of course, requires several paradigm shifts, though they are more or less dependent on each other and thus it may not be appropriate to consider each of them separately. For convenience, however, eight important paradigm shifts are mentioned in order.

The first, concerning the relevance of variations among components of the biological organization, is from the *instructionists' view* to the *selectionists' view*.[17),27),28] The instructionists' view is that the construction and ongoing operation of the biological organization require the instruction from its genes and/or its environment. According to this view, variations are simply noise with little essential importance. The selectionists' view, in contrast, is that the biological organization takes advantage of preexisting variations for successful adaptation to changes in its environment through natural selection. Thus variations are functionally important for adaptive behavior of the biological organization. This issue, referred to as "instructionist versus selectionist", will be discussed in § 2 in the context of aging.

The second, concerning the selectionism, is from the *genetic inheritance view* to the *epigenetic inheritance view*.[21),22] Since the astonishing discovery of the self-templating structure of DNA molecules,[29] we have been too much familiar with the *central dogma*[30] that all amino acid sequences are determined by DNA base sequences via RNA templates. It is therefore considered that all the infectious pathogens, like viruses in the simplest microbes, must contain DNA or RNA as genetic material for

the self-replication and transmission of themselves.[31] Although the genetic inheritance view that DNA (or RNA) molecules are the *ultimate* unit of heritable variations and natural selection has been successful in biology as discussed in § 3, the central dogma as well as the traditional view of infectious pathogens[31] appears to be no longer complete enough, because there is increasing evidence for infectious prions[7),8] lacking nucleic acids. We therefore need the epigenetic inheritance view that non-DNA molecules potentially become direct targets of heritable variations and molecular selection. This will be intensively discussed in § 4.

The third, concerning the information-rich molecules, is from the *genetic information view* to the *epigenetic information view*. Consider cellular constituents at the molecular level. Besides nucleic acids, there are other cellular constituents such as proteins, sugars and lipids: proteins serve as the main machineries of molecular recognition[32] and catalysis[33] and also determine the shape and structure of the cell;[34] sugars are energy stores and structural fibers and also serve as markers for molecular recognition[35] as well as tags for intracellular protein transport;[36] lipids aggregate to form membranes and serve as second messengers for signal transduction.[37] It therefore turns out that cells are so *heterogeneous*. Of course, as established by the genetic information view, DNA stores the genetic information required to make enzymes acting on metabolic pathways of these molecules. It has, however, little direct influence not only on regulation of the metabolic pathways but also on dynamic processes such as intracellular transport and signal transduction. These cellular constituents are thus considered as information-rich molecules. This opens up the epigenetic information view, in which cellular constituents themselves store the epigenetic information out of genetic control. It is therefore important to emphasize that —just like nucleic acids are continually subject to genetic mutations and natural selection during evolution of life— all the other information-rich molecules are potentially exposed to epigenetic mutations and natural selection at any process within living organisms.

Though the rest of this paper will mostly focus on proteins, it should be kept in mind that the same logical structure of the following arguments can be applied to other information-rich molecules such as sugars and lipids, which will provide us with deep insights into the mechanisms underlying many symptoms of aging. This will be discussed in § 5.

The fourth, concerning the sources of the order found in living organisms, from the *single-force view* to the *multiple-force view*.[13] From the single-force viewpoint, either natural selection or self-organization is considered as the dominant sources of the order depending on the time scale. When natural selection acts on individuals of a population, as in the case of the origin of species, the order will emerge gradually, for evolution takes place gradually through the changing composition of populations from generation to generation.[38] When self-organization occurs, the order emerges spontaneously by phase transitions, as in the case of crystallization of a collectively self-reproducing molecular system.[13] In contrast with this single-force view, the multiple-force view is that both forces are considered at the same time as the sources of the order. Consider the long-lived cells: for example, nerve cells and muscle cells. As they are nondividing cells (i.e., permanent cells), both natural selection and

self-organization are potentially capable of operating in the intracellular society, with cumulative effects. The observed cellular states (which reflect the emergent order through natural selection and self-organization) therefore depend on the cell's past history. An important point to be stressed here is that the emerging 'order' will not always favor the preexisting cellular states.

The fifth, concerning the states of nondividing cells such as nerve cells, is from the *static view* to the *dynamic view*. The static view is that adult nervous system is static because of the inability to generate new nerve cells, and that the plasma membrane of nerve cells is dismissed as a passive, permeable barrier. This static view is far from the truth. The dynamic view, on the contrary, is that neurons undergo dramatic changes in the morphology during early childhood as well as late adulthood in response to environmental influences. The plasma membrane not only plays a dynamic role in an intracellular signal pathway,[36] but also undergoes the *endocytic-exocytic cyles*. Indeed, a bit of the plasma membrane is continually internalized in the process of *endocytosis* and it is also added to the cell surface in the converse process known as *exocytosis*.[39),40] Such dynamic cellular processes — responsible for the remarkable adaptability of nerve cells to environmental stimuli — are, of course, not determined by immediate gene instructions. Instead, they are driven by the coordinated activity of a complex network of protein metabolism, since proteins serve as the main machineries of molecular recognition and catalysis, and also determine the shape and structure of the cell. This issue will be discussed in § 5.

The sixth, concerning the approach to living organisms, is from either the *reductionists' view*, as practiced by molecular biologists, or the *holists' view*, as practiced by ecologists, to the *unified view*[41] involving both of them interactively. As life has become hierarchically organized during both evolution and development, it is necessary to have this unified view to understand complex biological phenomena.

The seventh, concerning the reductionism, from the *elementary unit view* to the *elementary process view*. In the elementary unit view, most attempts are made to identify the elementary units (or simply, the elements) at different levels of biological organization. This view, however, cannot provide useful insights into understanding of how living things are different from nonliving things, for both are composed of the material elements. Also, it is very difficult to understand how disease states emerge out of living organisms, if there is no difference at the level of the elements even after the onset of the disease. In the elementary process view, attempts are made not only to identify the elements but also to understand how the elementary processes are organized into the functions of living organisms. On the basis of this view, we can understand how disease and senescent states differ from normal states, and also grasp the general principles underlying the functional mechanisms of different organisms at different levels and scales.

The eighth, concerning the origin of life and its evolution, is from the *simple self-reproducing molecule view*[42] to the *complex self-regulatory network view*.[13),43] The simple self-reproducing molecule view, on the one hand, is that life started as simple self-reproducing RNA or RNA-like molecules and such simple molecules were organized into complex networks of biochemical reactions over the course of evolution. The complex self-regulatory network view, on the other hand, is that life started as

complex self-regulatory (or self-sustaining) networks of biochemical reactions and simple self-reproducing molecules, like DNA and RNA, evolved later out of such complex networks.

The complex self-regulatory network view strongly suggests that any molecule does *not* necessarily have the self-reproducing nature *a priori* as long as reaction networks, as a whole, are self-sustaining and hence ultimately self-reproducing.[13] *Why? Because there is no essential difference between constituent molecules and their biochemical environment concentrated by many kinds of molecules, independent of whether molecules or their environment would be self-reproducing.* It is such 'relativity' that seems to be a Copernican revolution in the modern biology as well as in the origin of life. An immediate consequence of this revolution is that a self-reproducing molecular system lacking genes can adaptively evolve through heritable variations and natural selection.

According to the emerging view reflecting a convergence of these new views mentioned above, I got some idea to frame a theory of aging. The main idea of my theory is this: Life has become not only hierarchically organized but also heterogeneously organized during both evolution and development in such a way that a number of molecules other than genes (DNA or RNA molecules) are embedded in biological organization as its necessary components. Most of them are organized into complex self-regulatory networks of metabolism. Unlike DNA (or RNA) molecules, non-DNA molecules themselves are not intrinsically self-reproducing. Even then, the environmental networks are continually acting on some particular non-DNA molecules through the self-regulatory nature of the networks themselves. Such non-DNA molecules can be the targets of heritable variations and natural selection as if they were the self-reproducing molecules. They can be selfish through natural selection like subcellular 'cancer'.

1.2. *What is aging?*

Another purpose of this work is to open up new vistas into fundamental mechanisms underlying not only normal states but also disease states and even senescent states, for all these states have evolved since the origin of life. Rather than considering each of them separately, as previously appreciated, we should now consider such a diversity of biological states as general phenomena characterized by their degree of cohesiveness among different levels of organization. On the basis of the main idea mentioned above, I will propose a theory of aging to attack the long-standing mystery of AD, prion diseases and other neurodegenerative disorders. This new theory will also account for the pathogenesis of quite different diseases such as amyotrophic lateral sclerosis (ALS), atherosclerosis, senile cataract and many other symptoms of aging.

Although aging or senescence is a widespread phenomenon, it has been largely neglected by most biologists and thus it remains one of the most poorly understood of biological phenomena. (Most gerontologists have traditionally stressed the difference between 'aging' and 'senescence'.[5] Throughout this paper, the term 'aging' is not distinguished from the term 'senescence' like most biologists.[44]) What is aging? Burnet (1976, p. 86)[45] wrote: "*No one has yet produced a satisfactory explana-*

tion of the whole process, and probably no one ever will". Kirkwood[46] also wrote: "*Aging is a complicated process and it may be a mistake to seek too simple an explanation*". However, my answer is very simple: Aging is a concerted *process* of natural selection and self-organization operating on different components — such as molecules, organelles, cells and organs — at different hierarchical levels of biological organization. This is the conclusive account of the origin of aging by means of natural selection and self-organization. In this sense, the aging of higher organisms is not the special phenomena; instead, it is one of the general phenomena typical of life like the origin of life and its evolution and even the brain function.

To date, many theories of aging have been proposed.[5),44)~55)] I think it, therefore, important to point out briefly how my theory is different from others especially the *evolutionary theories of aging*,[44),47)~50)] for they also are based on the general principles of natural selection. Assuming that genetic variation(s) would affect *age-dependent characters* like survivorship and fecundity, the evolutionary theories suggest that evolution of aging occurs as a *result* (not a process) of natural selection modifying the *time* of onset of the variant gene(s). However, these theories must be circular or incomplete as they already assume 'aging' in a general sense in terms of age-dependent characters. It is not chronological 'age' or 'time',[56)] but living states emerging out of the complex networks of molecular metabolism that determine the time of action of gene(s).[46)] The evolutionary theories of aging are therefore viewed as a simple application of the general principles of natural selection to aging. In contrast, as I stressed before, my theory proposes that aging itself is a concerted process of natural selection and self-organization acting on different components at different hierarchical levels. This is one of the rediscoveries of the general principles of natural selection operating at various levels in different biological systems. In an extreme sense, therefore, *aging itself is considered as an 'evolutionary' process*.

§ 2. Instructionist versus selectionist

The issue "instructionist versus selectionist" has been discussed in biology. However, such an issue has never been discussed in gerontology, probably because so many theories of aging have been proposed along quite different lines of evidence and they seem to be so complicated. In this section, I will discuss how the present theory of aging is different from others in the light of this issue.

All the theories of aging proposed so far are considered to be situated between the two extreme instructionists' views. The one is the *gene instructionists' view* that aging, like development, is directly controlled by genes. The *programmed theories* such as the evolutionary theories of aging are based on this view since they ultimately require deleterious genes, though the evolutionary theories also stress the importance of the effects of natural selection upon genetic variations affecting age-dependent characters.[44),47)~50)] However, as discussed before, assuming such life-history characters falls into a circular argument because it is essentially equal to assuming some time-keeping mechanisms responsible for aging. Furthermore, it turns out that most biological processes — even cell differentiation, for example, during development — are no longer directly controlled by immediate gene instructions (see § 4 in more