

undigested materials by phagocytosis. Although scavenger cells are turned over successively, the denatured proteins cannot be removed.

Now let us consider two cases. If, on the one hand, the undigested materials are chemically quite unreactive like lipofuscins, they will merely remain in lysosomes and thus they will not interfere at the chemical level with the proper functioning of the cell. If, on the other hand, the undigested materials have the self-aggregating nature, they will grow like subcellular 'cancer' at the expense of the cell. This progressive acquisition of new structure and function of 'selfish' protein at the molecular level resembles that of new ability (e.g., drug-resistance and metastatic capacity) of 'selfish' cancer at the cellular level. Since denatured proteins are always subject to physico-chemical forces as well as random variations, they undergo successive changes. Consequently, there are a diversity of preexisting variations at the level of molecules.

Here, molecular selection or natural selection plays an important part in molding the denatured proteins, for most of the proteins are degraded not only to prevent the buildup of abnormal proteins, but also to facilitate the recycling of amino acids. At first, natural selection and self-organization occur at the *intracellular* level. However, once the long-lived cells die due to the subcellular 'cancer', they occur at the *intercellular* level. Aging is thus considered as a concerted process of natural selection and self-organization operating at different levels and scales of organization. In other words, aging is an 'evolutionary' process, as cancer can be viewed as 'micro-evolutionary' process.

5.5. *The origin of aging*

The origin of aging cannot be understood without considering the origin of 'irreversibility'. Traditionally, most attempts have been made to derive an arrow of time from 'reversibility' in the physical context of temporal symmetry-breaking. To understand how living organisms undergo the aging process, however, it is not necessary to derive a direction of time, because there already exists the intrinsic irreversibility at the level of molecules. This intrinsic irreversibility, on which proteins undergo unidirectional processes, is of crucial importance not only in regulating chemical reactions, but also in generating cell movements.²⁰⁾

Suppose that DNA molecules are subject to mutations. Although the mutations occur randomly, they are removed by energy-consuming DNA repair systems. This implies the intrinsic irreversibility and hence the direction of time at the level of molecular events. The DNA molecules thus keep time, like a 'molecular clock.' Indeed, this clock shows not only how different two living organisms might be, but also when they began to diverge in the past history. Furthermore, this clock shows the progressive stages of cancer cells in the body, for the evolution of cancer requires the accumulation of mutations.

However, this is not the only case, for there exist many non-DNA molecules. Actually, the biological organization is heterogeneous with respect to its components, so that different molecules keep time in different ways and therefore there must be multiple-time scales. Furthermore, these multiple-time scales will be differently amplified through the cascade of variations and the hierarchy of duality. In this sense, there are a diversity of time-keeping mechanisms at different levels and scales

of biological organization. Different time-keeping mechanisms can be pacemakers to determine the onset of diseases dependent on different diseases: the accumulation of genetic mutations is required for the onset of cancer, whereas the accumulation of β -amyloid triggers the onset of AD.

Along this line, the origin of aging can be specified at the level of individual molecules. In other words, aging is considered as the emergent property or the derived character through the 'differential amplification' of molecular events.

§ 6. Discussion

6.1. *From the origin of life to the aging of higher organisms*

There are a wide variety of complex biological phenomena such as the origin of life, adaptive evolution of viruses, brain function and aging of higher organisms. Traditionally, such a diversity of complex biological phenomena have been discussed in quite different contexts. Indeed, Darwin did not discuss the origin of life at all in the book of "*The Origin of Species*";¹⁰⁾ Maturana and Varela did not discuss the aging of higher organisms in the book of "*Autopoiesis and Cognition*";⁵⁶⁾ Dyson did not discuss the brain function nor consider the aging of higher organisms in the book of "*Origins of Life*";⁴³⁾ Kauffman did not discuss the aging in the book of "*The Origins of Order*".¹³⁾ In this regard, they are only part of the true story, and thus we are still far from fully understanding the general principles of life. For a breakthrough in theoretical biology, an attempt must be made to place such a diversity of the complex biological phenomena into a coherent picture!

Because life has hierarchically and heterogeneously organized through the course of evolution since its origin, there must be the common principles underlying a diversity of life phenomena. Once the common principles are specified, different phenomena can be understood in the light of these principles. It is therefore really important to find that there are some general principles of life.

Throughout the present paper, I have repeatedly suggested that there must be the scale-invariant principles of 'natural selection' and 'self-organization' that govern a diversity of biological phenomena ranging from the origin of life to the aging of higher organisms. Unfortunately, the words 'natural selection' and 'self-organization' are full of meaning, so that the mechanisms underlying different phenomena remain to be detailed. To attack this difficulty, I strongly emphasized that we need paradigm shifts and hence new views (see § 1).

It is true that the genetic inheritance view and the selectionists' view have been extremely successful in many fields of biology, for Darwin's theory of natural selection in ecology, Burnet's theory of clonal selection in immunology and Nowell's theory of clonal evolution in oncology have successfully proposed on these traditional views. (Of course, Darwin did not understand the basis of heredity. However, it is no matter in this context.) These traditional views, however, appear to be nothing but useless concepts in understanding the complex biological phenomena such as neurodegenerative disorders (e.g., AD and prion diseases) and many other age-related diseases.

With new views following the paradigm shifts, we have fully understood how people are exposed to a threat of neurodegenerative disorders in the light of the scale-invariant principles. Although there are different mechanisms in different life phenomena, it nevertheless must be emphasized that the scale-invariant principles hold in all cases regardless of the details of biological organization. Along this line, I will briefly sketch the whole story of life from the origin of life to the aging as follows, though the details remain to be written in a series of papers and books.

The origin of life: In the abiotic conditions, the genetic inheritance systems as well as the self-reproducing molecules such as RNA or RNA-like molecules had not yet been established. The major sources of the order must be self-organization. It is therefore very important to consider the emergence and evolution of self-reproducing molecular systems lacking genes. Suppose that a collection of molecules has the property that the last step in the formation of each molecule is catalyzed by some molecule in the system. When the molecular diversity exceeds a certain critical level of complexity, the phase transition occurs, by which a connected web of catalyzed reactions spanning the molecular species spontaneously arises in the system. This molecular system lacking genes is collectively self-reproducing and eventually evolving.

Along this line, the theory of the origin of life has been proposed by Kauffman.¹³⁾ As it is not necessary that any molecule reproduces itself, Kauffman's theory of the origin of life is robust in the sense that the conclusions hold for a wide variety of assumptions about abiotic chemistry such as the kinds of molecules involved. Because the present-day life has complex networks of controls that regulate protein behavior and cellular behavior without direct controls of genes (see §§ 4 and 5), the intracellular and extracellular society of molecules extremely resembles the abiotic society and thus both will be understood in the light of the common principles.

The adaptive evolution of viruses: Many viruses such as human immunodeficiency viruses (HIV) have mutation rates that are six orders of magnitude higher than for autonomous microorganisms such as bacteria. For such extremely high mutation rates, the genetic inheritance systems are no longer accurate. In this regard, the viral society is analogous to the abiotic society, for both have no reliable gene-inheritance systems. To understand the viral behavior, therefore, we need a theoretical framework provided by new views.

Indeed, the theory of a viral quasi-species has been proposed by Eigen, in which viruses are successfully treated as a quasi-species that is defined by a local population distribution in sequence space.¹⁴⁾ Such a distribution can spontaneously form and dissolve by phase transitions, and then adaptively evolve as a whole. The adaptive evolution of this viral quasi-species is in principle similar to that of the above-mentioned, self-reproducing molecular system without genes. On the basis of Eigen's theory of a viral quasi-species, the origin and evolution of HIV has been progressively understood.

The brain function: What is the biological basis of mental and psychological phenomena? What principles underlie the formation of movement patterns and synergies during motor development? How does our memory work? There remain

so many problems about our brain function. Among them, variability is the most mysterious:²⁷⁾ while different persons respond differently to the same environmental challenge; the same persons not only respond differently to varying environmental challenges, but also show transient responses to sustained input. What are the sources of such transient responses even under stable conditions? A clue to this problem would be found in the fundamental problems: 'the origin of aging' and hence 'the origin of irreversibility'.

We already know that there is the intrinsic irreversibility at the level of molecules in our body, for any molecule is exposed to the successive rounds of random variations and energy-consuming repair processes (see § 5.5). Through both the hierarchy of duality and the cascade of variations, the intrinsic irreversibility will be amplified. The intrinsic irreversibility, thus, implies instability and transient responses to sustained input at a higher level of organisms.

Of course, there is little doubt that there are genetic constraints on the basic structure of nervous organization. Even so, however, the structure is subject to variations during the development and ongoing operation of neurons and neural networks. (Indeed, there are a number of plastic changes at many sites in the nervous system during or after stimulation; these plastic changes may contribute to learning and memory.) Such structural variability can additionally give rise to dynamic variability at the level of neural networks. What is inherited is thus a capacity to learn, invent and instruct.⁴⁰⁾ This capacity to vary in a way is no longer controlled by immediate gene instructions. In this regard, I think that both the brain function and the aging are understood in the light of the common principles, because aging also reflects the capacity of higher organisms.

Although neural networks apparently differ from biochemical networks in components, they must share the essential features especially at the level of dynamic processes. Interestingly, the selectionists' view has provided a theoretical framework of the brain function.¹⁷⁾ Astonishingly, there is increasing experimental evidence for the general principles of 'natural selection' operating at various levels in the nervous system.²⁸⁾

The aging of higher organisms: A cell is an environment extremely concentrated by a diversity of proteins such as molecular chaperons, proteolytic enzymes and other catalytic enzymes. The chaperons help to guide both the folding of newly synthesized proteins and their assembly into macromolecules. Proteolytic enzymes degrade denatured or misfolded or unassembled proteins. Catalytic enzymes act on steps of metabolic reactions, though some of them are further activated or inhibited by the binding of other control proteins. Consequently, a diversity of proteins are organized into a complex network of self-sustaining biochemical reactions, in which different constituent proteins are turned over in different rates.

This self-regulatory system does not explicitly require self-reproducing molecules such as DNA or RNA, though different cell types reflect different regulatory states of DNA. Nevertheless, the self-regulatory system shows remarkable adaptability to changes in internal and/or external environment, as in the case of nerve cells and muscle cells. Such a remarkable adaptability at the level of individual cells contrib-

ute to not only 'creative' aspects of life such as brain function, but also 'non-creative' aspects such as aging. This duality must be the intrinsic character typical of life and perhaps nature.

In summary, although phenotypic diversity is evident, there are the general principles underlying all the profound life phenomena ranging from the origin of life to the aging of higher organisms. The theory of aging proposed in this paper thus not only accounts for most of age-related diseases, but also provides important insights into better understanding of many other life phenomena such as the origin of life and brain function. To understand 'non-creative' or 'defective' aspects of life is to understand more and more 'creative' aspects. Now is the best time to attack not only the long-standing mystery of brain, but also that of aging and many other life phenomena.

6.2. *Evidence for natural selection and self-organization in aging*

First of all, it is emphasized that natural selection is completely different from self-organization, for natural selection implies 'gradual' emergence of order through evolution, whereas self-organization implies the 'spontaneous' emergence of order through phase transition. Despite such a clear distinction, there is the close relationship between natural selection and self-organization.

Suppose complex systems composed of heterogeneous, mutually interacting elements. In such complex systems, variations in any one element may preclude or require changes in another element. Now, we should recognize the dual effects of self-organization. On the one hand, there are constraints on changes within the system arising from interactions among system elements. Such constraints may limit the number and kind of variations to be generated. Natural selection can act on the constrained variations. Here, self-organization or self-ordering mechanism cannot only generate new order, but also reduce the capacity of variability within the system.

On the other hand, the opposite is true as well. Although self-organization can provide new order, it also can give rise to new class of variations among system elements. Consider the case of self-aggregation of β -amyloid, which is one of the hallmarks of AD. Before the operation of self-organization, natural selection may act on variations among the 'inherent' elements. As a result of self-organization, system elements can acquire new structure and new function. The 'ordered' elements emerge out of the 'inherent' elements and the emergent, 'ordered' elements are in turn subject to random variations. Then, natural selection can act on new class of variations among the 'heterogeneous' elements. In this sense, self-organization can increase the 'heterogeneity' of system elements, and natural selection is a result of this self-organization.

On the basis of this discussion, let us consider evidence for natural selection and self-organization in the aging process.

(1) A high degree of variability at different levels and scales

The present paper stresses that aging is a concerted process of natural selection and self-organization at various levels and scales of biological organization. As individual persons get old even under the same circumstances, they will show a diversity of age-related changes and eventually develop quite different diseases.

Those who have the same disease show different processes as they get old. Because all of the proteins in the complex network of the self-sustaining biochemical reactions in a cell are the targets of variations, defects in any protein may perturb the whole network system, resulting in a diversity of the developmental processes of diseases. Such a diversity of age-related changes and diseases, along with the slow onset of diseases, are indirect evidence for natural selection operating at any level and scale of organization, for it is well known that the evolution of different animal species living in the same habitat will often result in divergent modes of behavior and different adaptive strategies through natural selection. For the same reasons, there must be different classes of variability that will reflect complexity of living organisms as follows.

(i) There are a diversity of neurodegenerative disorders such as AD, Parkinson's disease, prion diseases, ALS and so on.⁵⁾ Although different denatured proteins cause different diseases, there are remarkable similarities in all the diseases (see § 5.4).

(ii) There are different human prion diseases such as GSS, CJD and Kuru.⁸⁾ From studies of familial prion diseases, it is now clear that there are different genetic mutations in PrP gene (located on the short arm of human chromosome 20) depending on different prion diseases,

(iii) There are different ways in which the same disease arises.⁸⁾ CJD, for example, may arise not only from mutations in PrP gene, but also from post-translational modification of wild-type prion protein, PrP^c, referred to as epigenetic mutations. Though it is rare, CJD occurs by infection as well. In the case of AD, several mutations in the APP gene, positioned on the midportion of the long arm of human chromosome 21, are linked to disease characterized by deposition of amyloid in the brain.⁸²⁾ In *Down syndrome*, those who are born with an extra copy of this chromosome (i.e., trisomy of chromosome 21) develop β -amyloid deposits at a relatively early age.¹¹⁸⁾ Furthermore, AD can be caused by defects in different chromosomes: defects in chromosomes 14 and 19 are associated with early- and late-onset diseases, respectively.⁸²⁾

(iv) The prions consisting of a single kind of protein can cause multiple effects on different animals.⁷⁾ Some prions cause disease quickly, whereas others do so slowly.

(v) Deposits are highly heterogeneous.⁵¹⁾ The varied forms of pigment granules such as lipofuscin granules comprise a diverse and heterogeneous group of molecules. Likewise, different constituent molecules of the cells such as proteoglycans or lipids could act as heterogeneous seeds for the polymerization of amyloid.

(vi) In addition to various ways of genetic mutations, there are a wide variety of epigenetic mutations in producing denatured proteins such as transformation, oxidation, glycosylation, racemization and so on.⁵⁾

(2) Transients or dynamic changes

Traditionally, scientists emphasize the reproducibility of the same event to the same input. However, living organisms show transient responses not only to the changing environment but also to the sustained environment. During the cellular process at every level and scale, as in the above discussion, an immense amount of

new variations are produced, which in turn results in the reorganization of a new intracellular society involving new class of constituents. The intracellular society is thus exposed to continuous changes in its endogenous composition, and it shows transients in response to not only a dramatically changing environment but also an entirely stable environment. Such transients in any environment are essential for adaptive behavior of a cell, regardless of whether it is dividing or not. In relation to the transients, it is possible to view the following things as indirect evidence for the operation of natural selection.

(i) Like cancers, neurodegenerative disorders and other age-related diseases show their slow onset.⁷⁾ Because evolution occurs gradually at any organization level and scale, there is long delay between the initial event and the onset of disease.

(ii) No predetermined aim is present at any organization level and scale. As a consequence, there are always dual, seemingly conflicting, effects: on the one hand, successive construction of new types of adaptations would occur, resulting in open-ended evolution; on the other hand, the disintegration of the phenotypes into components would occur, leading to devolution. The open-ended evolution could play an important role in the origin of brain or mind. In contrast, devolution suggests that new disease will evolve in association with changes in our culture and habits. In this sense, brain function and aging — though apparently differ from each other — should be considered as general phenomena typical of higher organisms.

6.3. *Speculations and future studies*

(1) Roles of PrP genes and APP genes

Proto-oncogenes are favorable early in life but have cumulative bad effects later on. In the light of this evidence of proto-oncogenes, roles of PrP genes and APP genes could be speculated. Probably, PrP genes and APP genes may operate early in the determination and cell differentiation toward neurons. Indeed, the evidence of the highest concentrations of PrP mRNA in neurons⁸⁾ and the abundance of APP in the brain⁸²⁾ indicates that PrP genes and APP genes play important roles in the biology of nerve cells.

The surprising findings that a protein, called Ure2p found in yeast,¹¹⁹⁾ might sometimes change its conformation suggest that prion diseases are rooted in the primitive living organisms, and that other prions unrelated in amino acid sequence to the PrP protein could exist. Likewise, there are a large family of APP and APP-like proteins in evolutionary divergent organisms such as *Drosophila* and *Caenorhabditis elegans*.⁸²⁾ All these findings indicate that prions, APP and APP-like proteins play important roles in living organisms, though details remain to be solved.

(2) Therapies

Several therapies may prolong the onset of age-related diseases due to the accumulation of denatured proteins. Of course, there are many ways in which diseases occur. Therefore, first of all, it is necessary to identify localization of defects in cellular processes. Then, it is possible to consider the best way to reduce the bad effects.

(i) If proteins are denatured due to conformation changes, denatured proteins

may be transformed into the normal ones when appropriate chaperons or enzymes are activated.

(ii) If genetic mutations occur to produce an excess amount of denatured proteins, drugs that prevent them from interacting with one another may be effective.

(iii) Activation of scavenger cells such as macrophages and microglia may be generally efficient to remove denatured proteins, independent of the exact causes of diseases.

(3) Emergence of new age-related diseases

Because aging reflects the capacity of complex organisms, new age-related diseases are potentially capable of evolving in the future. For example, new types of prions will evolve. What can we do? Since our body itself is the complex environment allowing any element or any elementary process to be altered, it is impossible to suppress any potential illness which will evolve in the future. Only way for us to survive is not to live against diseases, but to live together.

Since complex organisms are potentially subject to a threat of new age-related diseases, nature evolved an ultimate strategy of a single-celled beginning:²²⁾ the ontogeny of multicellular organisms always starts from a single cell. This strategy is advantageous to the survival of species because the single-celled condition can reduce and reset the variations arising within the organism in the past history.

§ 7. Conclusions

Although aging is highly complex biological phenomena, the underlying principles are very simple: aging is a concerted process of natural selection and self-organization operating at various levels and scales of biological organization. In this sense, there is no difference among diverse living phenomena such as the origin of life, brain function and aging. Of course, we need paradigm shifts and thus new views to specify the underlying mechanisms of 'natural selection' and 'self-organization.' Living organisms are always exposed to variations in different ways such as genetic mutations and epigenetic mutations. Nature, therefore, evolved many sophisticated systems to reduce and remove accumulated errors or variations within the organisms. Examples include DNA repair systems, protein-repair systems, protein-degradation systems, scavenger systems and many other fail-safe systems. Actually, these systems can reduce and remove the accumulated errors. However, they themselves are the targets of natural selection. This relationship poses a serious dilemma. To solve this dilemma, life eventually evolved the strategy of a single-celled beginning.

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