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第４回　生体内進化過程としての老化現象

1. Health, disease and environment for the evolving organism

Before approaching in more detail the question of how environmental pollution affects human health, it might be pertinent to consider what we are and what makes us what we are. Sections 2 to 6 of my paper focus first on body and then mind in setting out to establish some of the basic principles underlying complex life phenomena. We begin with the classic scientific question: how do new species of living organisms originate?

1-1. Darwin's natural selection theory on the origin of species (1859)

The evolution of life on earth is the result of endless competition among a variety of organisms under varying environmental conditions. No organism is unchanging: all evolve through adaptation. We have learned this from Charles Darwin, whose theory of evolution is summarised in the phylogenetic tree diagram pictured in.

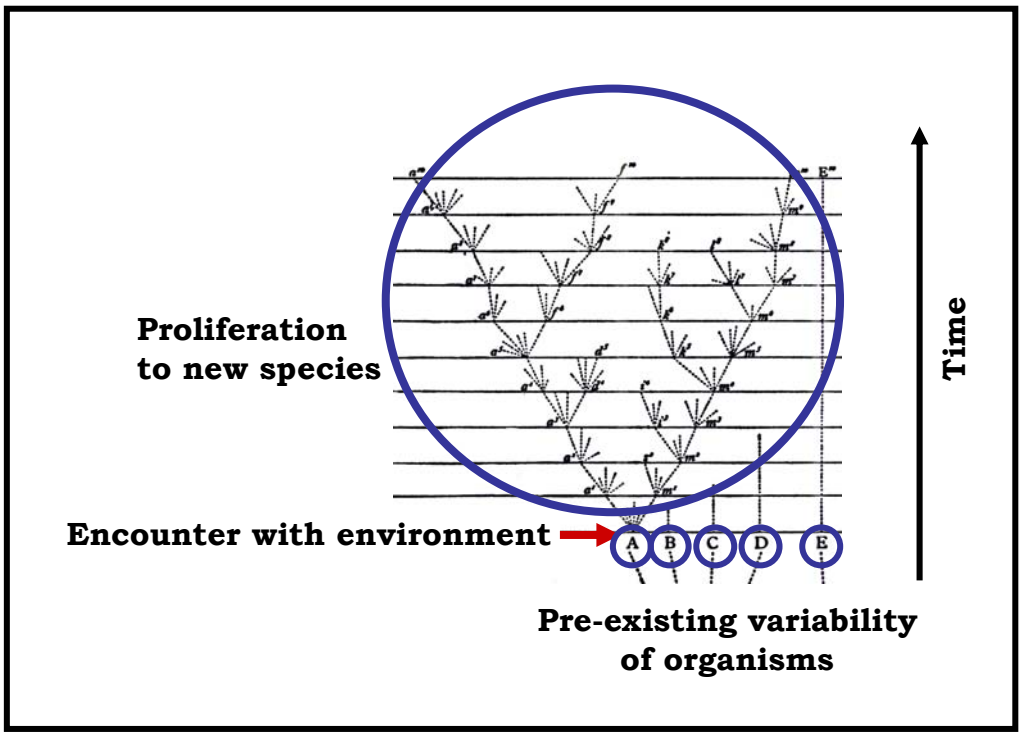

Figure 1: Darwin's phylogenetic tree (modified by Murase)

Darwin's thesis was simple, albeit revolutionary. The phylogenetic tree depicts time as linear, proceeding from the bottom to the top. Preexisting variable organisms are denoted by *A*, *B*, *C*, *D* and *E*, respectively. When preexisting variable organisms encounter a particular environment, the organism best equipped for survival, in this case, organism *A*, is selected. The selected organism then proliferates to build up a new species as time proceeds, one generation succeeding the next, each generation marked by change.

Darwin's natural selection theory rests on three conditions, which must be met for natural selection to occur.

(1) A large repertoire of heritable variability must be generated and preexist at the level of individual organisms. Non-heritable variations do not play a part in the evolutionary process because they cannot be transmitted to later generations.
(2) Each organism encounters the environment that dictates the criteria for selection.
(3) The selected or adapted organism produces offspring.

For Darwin, writing in 1859, new species originated from adapted organisms interacting

with a certain environment. Exactly 100 years later, Frank Macfarlane Burnet applied Darwin's theory within the context of immunology, in doing so, breathing new life into a fascinating question: how does our immune system discriminate the self from the non-self? What, indeed, is the self?

1-2. Burnet's clonal selection theory of acquired immunity (1959)

The human body is composed of two different classes of cells: dividing, inter-differentiated cells, such as immune and liver cells; and non-dividing, post-differentiated cells, such as nerve and muscle cells. Both dividing and non-dividing cells are subject to change in different ways as we see in sections 2.3 and 2.4. Where Darwin considered the ecological system as a society of descendants of proliferating organisms, Burnet depicted our immune system as a society of clones of dividing cells. Because variations and heritability are held in the cell lineages within the immune system, the general principles of natural selection known to govern the adaptive evolution of organisms in an animal society are also capable of governing the adaptive behaviour of dividing cells as members of a cellular society.

As long as dividing cells exist, the body is inevitably exposed to different clones of variant cells through successive rounds of genetic mutations and natural selection. Our immune system takes advantage of this preexisting pool of variant immune cells, allowing natural selection — or clonal selection — to immunise the self against non-self factors such as invading antigens from the external environment.

Figure 2 – a summary of Burnet's clonal selection theory – shows the cell lineages within the immune system. Like Darwin's natural selection theory, Burnet's clonal selection theory stands on three conditions:

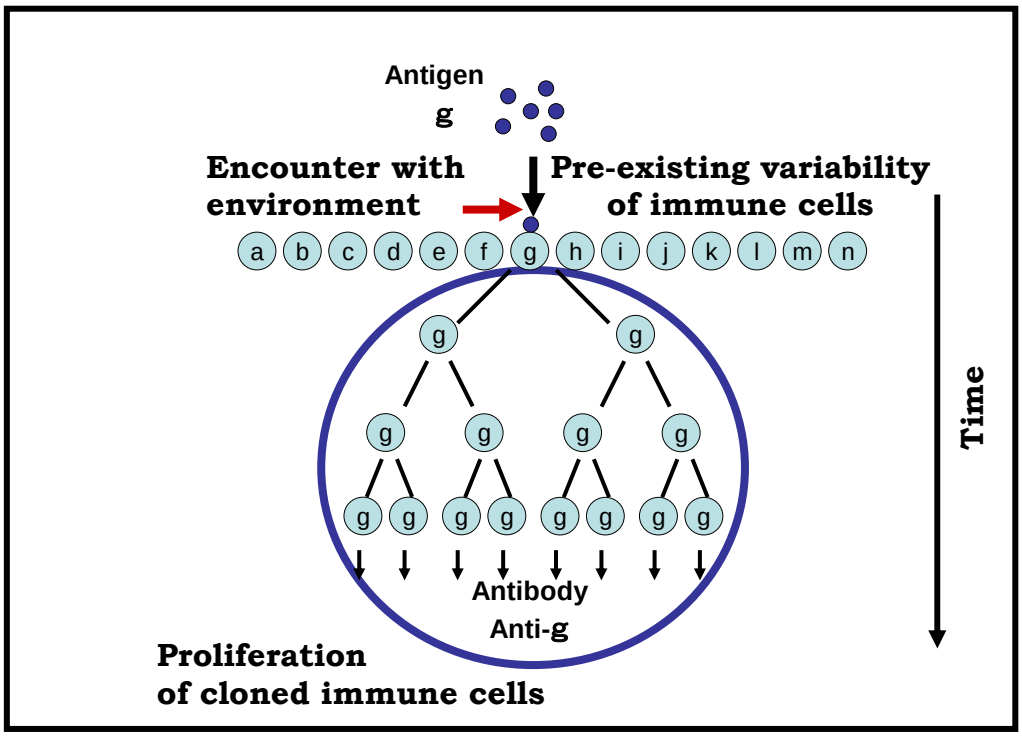

Figure 2: Burnet's clonal selection theory

(1) A large repertoire of variable immune cells must be generated and pre-exist. These are denoted *a* to *n* in the figure.

(2) Pre-existing variable cells encounter new environmental conditions in the form of an antigen, which dictates the criteria for selection. In the figure, cell *g* is selected since it has a receptor — an antibody – that can attach specifically to the antigen g.

(3) The selected immune cell *g* responds to the given antigen g by producing clones. A large amount of the antibodies – anti-g – are produced when the clones start to proliferate.

Although the scale of this immune system is quite different from that of the ecological system, the underlying principles are the same.

1-3. Clonal evolution theory and the origins of malignancy

Clonal selection theory presents us with a serious dilemma. The same principles of natural selection that make dividing cells essential to the body's immune system, can also allow any dividing cell to be malignant within the same body. Clonal evolution theory explains how cancer cells develop in accordance with the principles of Darwin's

natural selection, applied at the cellular level (Cairns 1975; Nowell 1976).

This can be seen in Figure 3, in which time's progression is shown from left to right, and the development of malignant cells is depicted as a micro evolutionary process. In the figure, a large repertoire of newly emerging variable cells denoted by *a*, *b*, *c*, *d*, *e* and *f* occur as a result of heritable mutations. One of these cells – *d* in the figure – clones itself by cell division when it comes into contact with endogenous factor *x*. Further rounds of mutation and selection result in the development of different kinds of cells, denoted by *d*, *f*, *g*, *h*, *i* and *j*. When the latter encounter an environment, denoted by exogenous factor *y*, a selected cell – *f* in the figure – clones itself through cell division. Through successive rounds of heritable mutation and selection, originally benign cells may in this way become increasingly malignant under the varying environment.

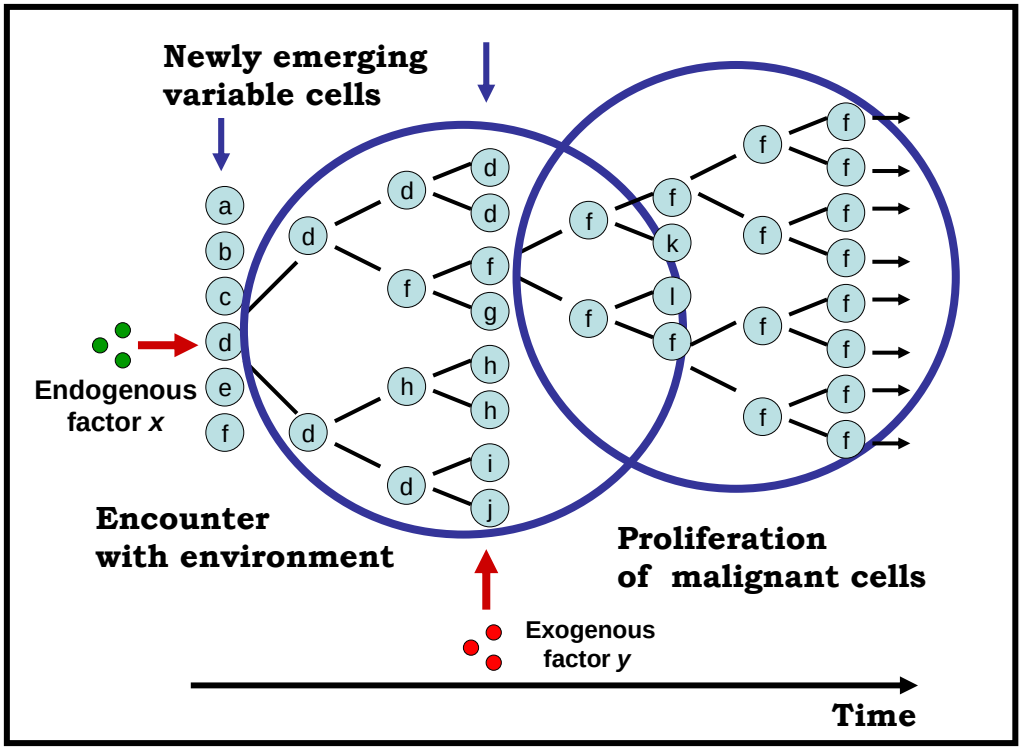

Figure 3: Clonal evolution theory and cancer development

It is essential here to observe the role played by environment – the internal environment of the body itself, as well as the external environment in which the body lives. Cancerous cells can occur as a response to endogenous factors such as hormones, as well as exogenous factors like environmental chemicals and, ironically, anti-cancer drugs. In each case, environment plays a crucial role and the principle of natural selection is revealed as a double-edged sword that can work both for and against the body. Here we see two opposing evolutionary processes, both conducted by the clonal

selection process written into the immune system. The same mechanism that promotes health may also end in disease, in this case cancer. From a hierarchical point of view, these evolutionary processes occur within the still-evolving organism. The organism's identity is challenged by both its 'internal' and 'external' environments, and the unity or coherence of the self is seen to depend on the delicate balance negotiated by within-body competition in the face of environmental variation.

So far, we have learned two ways in which dividing cells may behave. What can we learn with regard to non-dividing cells?

1-4. Neurodegenerative disorders as intracellular 'cancer'

The above section identified cancer in terms of the micro-evolutionary process of dividing cells within our body. In this section, we look at the origins of neurodegenerative disorders such as Alzheimer's and prion diseases, both of which are caused by the selective cell death of non-dividing neurons in the brain. In 1996, I proposed a theory of aging that explored the origins and causes of neurodegenerative disorders and suggested that the self-aggregation of abnormal molecules responsible for neuronal cell death resembles, in many respects, the development of malignant cells. Although neurodegenerative disorders and cancers differ in pathology, they nevertheless obey the same principles of natural selection regardless of the level and scale of their biological organisation.

We can begin by considering how natural selection operates at the level of molecules within a single non-dividing cell. A 'normal' intracellular environment is shown in Figure 4a. Here, a number of different circles are used to denote a variety of molecules in different states of synthesis and degeneration. Together, they form a dynamic stable-state. All cell molecules in a dynamic intracellular environment are possible targets of variation and natural selection. Targeted molecules, which have become non-degenerative in nature, may begin to accumulate within the cell. This situation can be seen in Figure 4b, which starts with a single molecule that has deformed from ○ to ■ through mutation or external influences. The resultant deformed molecule causes nearby normal molecules to become abnormal and, in doing so, acts very much like a kind of intracellular cancer. Eventually, the accumulation of abnormal molecules destroys the cell. This process is the origin of all neurodegenerative disorders.

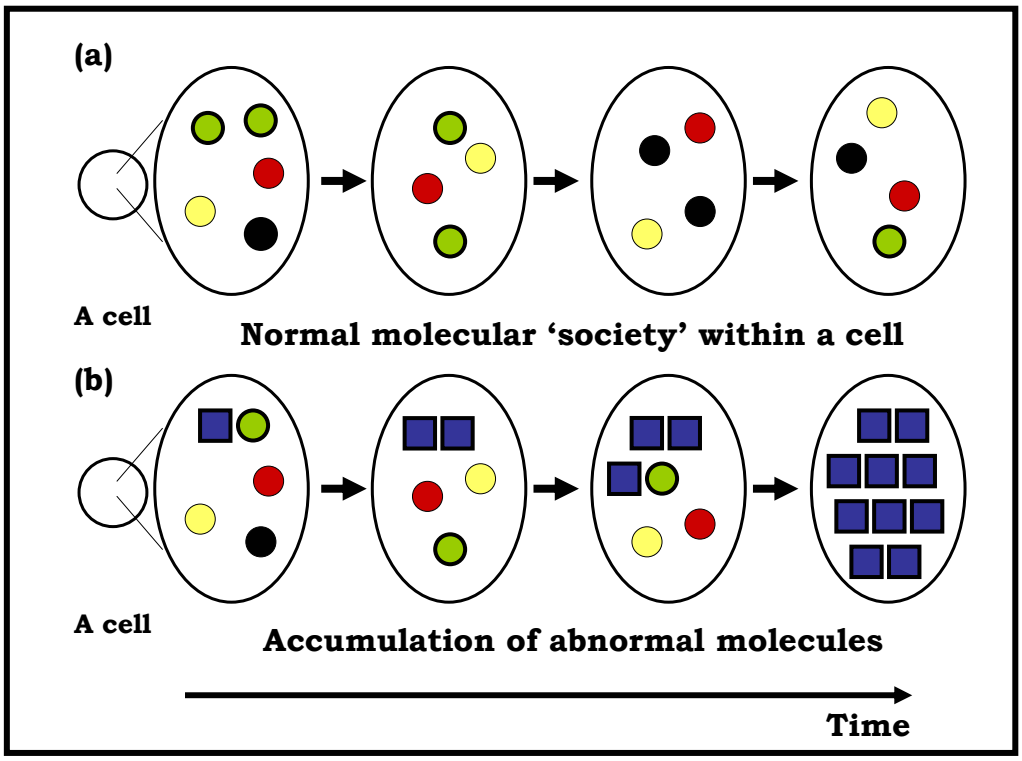

Figure 4: Molecular society within a single non-dividing cell in (a) normal and (b) abnormal cases. ○ and ■ denote normal and abnormal molecules, respectively

We have now seen that all the cells have the potential for variation and selection, regardless of whether they are dividing or non-dividing. Health and disease, or life and death, are conducted under the same principles, although different processes occur at different levels and scales of biological organisation.