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DISCUSSANT RESPONSE

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to **Jonathan Wells'**

THE HISTORY AND LIMITS OF GENETIC ENGINEERING

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Discussion for the paper on 'The history and limits of genetic engineering' by Dr. Jonathan Wells

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The paper by Dr. Wells has described firstly, the historical background of the development of scientific knowledge on the molecular mechanism of genetic phenomena up to the stage of gene manipulation and secondly the limits of genetic engineering by presenting that the current knowledge of molecular biology is not enough for comprehensive understanding the complex building structure of molecular assembly and differentiation processes of a cell. The paper also did indicate a possible existence of the second informational transduction system independent from the DNA-RNA-protein system, since the shape is not the only variable unspecified by DNA and there is no evidence from any organism that DNA contains a program specifying the temporal sequence of development.

In this discussion, a few comments were made on the informational transduction system regarding to the 3-dimentional assembly of a living organism and the primary aims of genetic engineering as a productive tool in biotechnology under the premise that the current knowledge of gene expression and regulation has certainly a limit for understanding the cellular differentiation and for the modification of a life form.

1. The DNA-RNA-protein system must be a sole information carrying system in living cells since these macromolecules have unique characteristics containing the primary information in the linear sequence of monomers (either nucleotides or amino acids). The informational variations can be accommodated by the number and the order of the monomer sequences in the respective macromolecules. No other constituent of a cell carrys such characteristics.

Then, question is as to how a protein undertake the construction process for the 3-dimensional assembly of a living structure. The answer may not be so simple as one might think. However, the basic force for building the 3 dimensional assembly of proteins can be generated by the active path of protein folding whose information is already programed in the primary sequence of a protein inherited from a given genetic information. This cooperative phenomena can be the vital force of living matters, which is quite different from the passive path such as building a brick house. Thus, it is concluded that the shape is also specified in the code of DNA in such a way that the linear information in a DNA sequence becomes transformed into the 3-dimensional information of a protein.

The primary sequence of a protein will determine, in turn, the secondary, the tertiary, and even further the quaternary structure providing active functional conformation of the protein. Such an active path of protein folding could be extended to the protein-protein interaction between heterogous proteins. It is no doubt that such a process can be effected by various micro-environmental conditions such as pH, temperature, and various effectors in cells. This self association process has been proven by many experimental results of protein subunit interaction and reconstitution study of super-molecular assemblies.

It is conceivable that membrane proteins are responsible for leading cell-cell interaction. As seen in tumor cells, the modification of membrane proteins (ex. phosphorylation by protein kinase) by the expression product of oncogene would cause transformation of normal cells into cancerous cells. The formation of spatial patterns of a cell or an organism would certainly require other structural and functional components provided promptly. The regulatory processes by way of post-translational modification of proteins would also be an important factor for the control of structural assembly of an organism. A protein either structural or functional one has to be primarily expressed in the right time and space to be functionalized properly for the formation of a given structural patterns of a cell. This means that the protein expression must precede in a given sequence during the differential processes of a cell as programed in the genetic information system.

The current experimental results have begun to demonstrate that local cell-cell interactions play central roles in pattern formation in a wide variety of ontogeny. "To understand how cell interactions establish biological patterns, it is necessary to understand both the mechanism by which cells communicate and the logic of the interactions ; that is, how all signaling is regulated. As an increasing number of molecules involved in cell signaling is identified, it is becoming apparent that the signaling machinery has been conserved evolutionarily"(David A. Waring and Cynttia Kenyon, Cell Vol. 60, 123, 1990). Of course, it is not fully understood as to how cell signaling is regulated to generate spatial patterns and whether this logic is also conserved among different species.

2. The knowledge and techniques of molecular biology have definitely become the basis of new breakthrough in understanding cellular differentiation and gene regulation for the spatial pattern realization of a cell. It will certainly become an important tool to unveil the secret laws in developmental biology. It is the field of signal transduction that has provided new concept in understanding the control mechanism of cellular functions.

The recent development in signal transduction has begun to understand mechanisms as to how an external signal transmits to the gene, informational machinery, while the signal generated by genetic code transduces to the extracellular communication systems. The cascade system for signal transduction is yet to be exploited, but the new knowledge of signal transduction processes involved in the cellular differentiation has opened a new field of life sciences by bridging between molecular and developmental biology.

It is of interest to note that the sevenless mutation blocks differentiation of a specific photoreceptor cell in the Drosophila eye. Expression of the sevenless protein in normal flies was precisely restricted in time and space in such a way that the deletion of the gene caused phenotypical defect. This is an evidence that genetic information is certainly involved in the cellular differentiation. Professor H. R. Bourne has stated in his concluding remark at the Cold Spring Harbor Symposium on molecular biology of signal transduction(1988) that "although no one in 2015 will have solved differentiation, learning and memory, or the control of cell proliferation, the vistas accessible to investigators will be incomparably broader and deeper than now. We will understand many signaling pathway of mammalian cells as well as yeast, all the way from cell surface to DNA and beyond."

It is believed that the life phenomena can be governed by the following three transduction processes; 1) the energy and mass transduction to provide vital force for the structural integrity of molecular assemblies of a living cell, 2) the informational transduction to provide pre-determined program for the production of bio-molecules neccessary for the maintenance of existing pattern of a cell, and 3) the signal transduction to control and regulate the above two processes for increased survival efficiency of a living organism. No one can separate these three principles intertwined to keep the cellular vitality effectively and continuously in the dynamic processes for maintaining the given structural pattern of a living organism.

The genetic information encoded in genes is equivalent to the software programed for construction and management of the hardware, i.e. molecular machineries of a living cell. In turn, the hardware provides a carrier vehicle for the structureless software. This means that the characteristic structural pattern of a living organism is nothing but the printout of given genes with molecular materials available on the earth. The gene must have programed the whole pattern of structure and function of a cell in such a way that the program (the software) shall not be destroyed but efficiently preserved in the ever changing environmental conditions. After all, as Richard Dawkins stated, all of the living organisms are "survival machines-robot vehicles blindly programed to preserve the selfish molecules known as genes"(In 'The selfish gene', Oxford University Press, New York, 1982).

The current knowledge of life sciences appears to be barely at the threshhold in comprehending such a complex mechanism of the gene function. It is, thus, far from reality at the present time to consturct an artificial organism, even an uni-cellular organism using of the single gene manipulation.

However, if the evolutionary process of living organisms is to be defined as the process of accumulation of genetic information in DNA, the scientific knowledge could eventually provide a know-how for stabilizing a newly input gene in the intrinsic genetic system and thus consequently creating a new form of life evolutionarily significant.

However, the genetic engineering should not be valued for merely creating a new form of life, but for demonstrating constructive application of the new technology for the benefit of mankinds. The major significance of genetic engineering should be recognized by the fact that the technology was proved to be useful for the increased productivity of a cellular system as a bioreactor and the improved function of cells for the biotechnological uses.

In conclusion, I do not want to argue against Dr. Well's logical presentation of the paper that the knowledge from molecular biology is only a small part and thus a begining of understanding the secret of life. However, I do wish to point out the fact that the pre-existing knowledge in science has always shared its room with new knowledges or concepts as it progresses in the scientific history. Finding of a new scientific fact would not be the end, but another beginning of understanding of the secret of nature. So is the molecular biology in disclosing the secret of life and in its application.