BIKEN JOURNAL Vol. 28 37–38, 1985

COMMEMORATIONAL LECTURE

CELL FUSION AND CELL ENGINEERING

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I would like to congratulate The Research Institute for Microbial Diesases of Osaka University on the occasion of their 50th anniversary. It is a great honour for me that the commemoration Committee of this Institute kindly invited me to be a guest lecturer.

About thirty years have passed since the discovery of cell fusion through virus HVJ (that is the Heamagglutinating virus of Japan, also known as Sendai virus). At that time I was working in this Institute in the Department of Preventive Medicine under Proffessor K. Fukai. The HVJ that we used for cell fusion was a strain that Dr. Y. Okuno and Dr. K. Fukai had isolated from mice and it was provisionally called Z virus at that time. This kind of virus was also isolated in other several laboratories in Japan at about that time and the Society of Japanese Virologists identified all these strains as HVJ, so our virus then became called HVJ Z strain.

When I first observed cell fusion by HVJ, I remenber thinking that this phenomenon was going to be useful in cell biology and genetics. But, progress to date utilizing this cell fusion phenomenon has far surpassed my initial expectations. I have been surprised at how much has been accomplished in natural sciences as the result of the development of this one technique. It is as if it has changed the basic concept of the field. Somatic cell genetics and cell biology of mammals suddenly emerged as modern sciences when the phenomenon of cell fusion was established. It is truly wonderful to me that the virus was isolated in Japan and that the phenomenon was discovered and established in this country also. However, the progress that has been made in this field since these findings has, of course, also been due to the cooperation of many distinguished scientists in other parts of the world.

In classic genetics, an individual animal body is understood to be composed entirely of only the phenotype of the genomes of the fertilized egg from which it developed. In this sense, a somatic cell is only one member of the whole body. However, after since the demonstration by Carrel in 1912 that cells could grow from chick embryo tissue in vitro, it has been possible to handle a somatic cell as an autonomous individual in a Petri dish. We know that each somatic cell contains a complete set of genomes derived from the parents and that a somatic cell at the level of genomes is equivalent to a fertilized egg as Gurdon pointed out in 1963. Unfortunately, however, technical freedom in genetic analysis of somatic cells in culture has been

limited by the fact that these cells do not show phenomena such as male and female confugation of germ cells. Fortunately, development of the technique of cell fusion has solved this largest problem and led to the establishment of somatic cell genetics.

The first advance in somatic cell genetics was gene mapping of individual human chromosomes. In 1967, Weiss and his coworkers made the important discovery in a hybrid of human and mouse cells that the chromosomal balance is unstable and that the human chromosomes disappeared gradually in the hybrid, depending on the genes of the human chromosome. Over the past 15 years, about 350 human genes have been mapped by this technique, and one or more phenotypic markers have been indicated on each human chromosome.

The next advance was in analysis of genetic control corresponding to luxury functions of somatic cells. We can modify the expression of some luxury functions by fusion or hybridization of a cell expressing a luxury function with another cell not expressing this function. From this type of experiment, we have learned that substances controlling gene expression are actually present in the cell, although in limited amount, and that the substances controlling genes do not show species-specificity of function.

The third advance was in human hereditary diseases. A genetic complementary test is possible by fusion of somatic cells. It has been shown that some complementary groups are present in patients suffering from the same syndrome. For example, Exoderma pigmentosum (XP) cells show a defect in the system for excision repair of damaged DNA. By studies involving cell fusion with HVJ, complementary groups have been identified in XP patients. This means that ten or more genes participate in the excision repair system of humans and that on marriage of two XP patients the children will not have XP provided their parents belong to different groups.

The fourth advance was the development of the great technique of producing monoclonal antibodies utilizing hybridomas of B-lymphocytes and myeloma cells. This technique has resulted in major advances in the fields of biology and medicine.

Recently, new techniques for introducing macromolecules into living cells have also been established on the basis of the cell fusion phenomenon in my laboratory. One method is a technique utilizing diffusion of macromolecules through the cell membrane, which occurs at an early stage of the cell fusion reaction. Using this method, we demonstrated that the defective function of XP cells could be restored to normal by the introduction of endonuclease V of T4 bacteriophage into the cells. A second method involves fusion of cell membranes with viral envelope vesicles, in which macromolecules have been trapped. Selective killing of Subacute sclerosing panencephalitis (SSPE) cells has been succesfully achieved by this method. Liposomes containing diphtheria toxin fragment A could fuse with SSPE cells but not with normal cells. A third method employs the fusion of cells with erythrocyte ghosts in which macromolecules have been trapped. In this way we can easily introduce DNA, RNA or high molecular weight proteins into living cells. This method will be useful for modification of living cells.