Chapter 1

Introductory chapter: Pluripotent stem cells

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Stem cells are defined as those that have potential of self-renewal and differentiation into specific cells. In 1961, Till et al. transplanted bone marrow cells to recipient mice whose bone marrow is damaged with irradiation [1]. After bone marrow cells are transplanted to the irradiated mice, they colonize and recapitulate the bone marrow of the recipient mice. These results suggest that stem cells perform self-renewal and differentiation. This type of stem cells, hematopoietic stem cells, produces only hematopoietic cells. This concept has been developed and now is clinically applied to hematopoietic stem cell transplantation [2].

Pluripotent stem cells have two properties: self-renewal and pluripotency. Self-renewal has the potency to produce daughter cells with the same character through infinite cell division. Pluripotency is the characteristic to produce specialized cells of three layers: endoderm, mesoderm, and ectoderm.

Pluripotent stem cells are totally different from other cells, such as cancer cell lines and primary cells. Cancer cells divide infinitely, but their differentiation status does not change. Primary cells divide only into limited numbers and change their characteristics as they divide. Pluripotency, therefore, has been the main focus of stem cell research.

Regenerative medicine is to replace or transplant cells or tissues to restore normal function. For the generation of cells or tissues, cell source has been a major problem. Pluripotent stem cells produce cells of three germ layers. That is all the somatic cells could be derived from pluripotent stem cells virtually. Embryonic stem (ES) cells have been expected to be a cell source for the transplantation of patients with organ failure.

Embryonic carcinoma (EC) cells, extracted from teratocarcinoma, have such characters. EC cells not only divide infinitely, but also produce cells of three germ layers [3]. These characters fulfill the criteria of pluripotency. EC cells are the first cells that have been reported to exhibit pluripotency. EC cells are successful in the formation of chimera in germ line and in the production of chimera mice. Researchers were excited about the results expecting that genetically modified mice would be produced. Disappointingly, cancer develops in the

chimera mice. Researchers speculate that one of the major reasons of cancer is the formation of EC cells.

With the experience of EC cells, researchers attempted to derive cells from a healthy embryo. Mouse embryonic stem cells were first extracted in 1981, and human ES cells were first extracted in 1997 [4, 5]. ES cells are derived from the inner cell mass of preimplantation embryos. ES cells have been used to produce knockout mice.

To produce ES cells, embryos need to be broken. This raises ethical issues. The transplantation of cells or tissues produced from ES cells causes graft-versus-host disease (GVHD). Ethical issues and GVHD are innate obstacles to develop regenerative medicine.

To overcome these problems, methods to produce human-induced pluripotent stem (iPS) cells have been developed by Professor Yamanaka et al. with the introduction of reprogramming factors, such as Oct3/4, Sox2, Klf4, and c-Myc [6]. One of the most important features of iPS cells is that they can be derived from cells of the patients who are potential recipients. Ethical issues and GVHD, thus, do not arise from iPS cells. Currently, a clinical trial is underway for retinitis pigmentosa with iPS cells derived from the patients [7].

iPS cells are useful not only in the application of regenerative medicine but also in stem cell research. Researches on the networks of expressed genes and stem cell niche are underway [8].

For the clinical application of iPS cells, new problems arise, that is, culture methods. To transplant somatic cells differentiated from iPS cells, the iPS cells should be manipulated under xeno-free condition. Another problem with manipulation is that a good-medical-practice (GMP) level should be realized.

Practically, the extraction of iPS cells from a patient requires plenty of time and labor. If iPS cells are stored and provided upon request, time and labor would be saved. Patients would be subjected to regenerative medicine promptly and smoothly. iPS cell banks have been under development with dental pulp [9].

From a pharmacological point of view, somatic cells and tissues are necessary for the evaluation of toxicity of certain types of drugs. Human cells or tissues are very hard to obtain for the investigation of toxicity. iPS cells are expected to be useful for “toxicology” because they would produce somatic cells in the toxicological experiments.

To innovate a drug for the treatment of a disease, the mechanism of the disease should be clarified. As mentioned earlier, it is difficult to obtain somatic cells or tissues from the patients. iPS cells are again expected to be useful for the investigation of the mechanism of the disease because they would differentiate into somatic cells.

With the above discussions, the differentiation of iPS cells has been the main focus of the investigation. There have been plenty of literatures on differentiation protocols of iPS cells. Unfortunately, some somatic cells are difficult to obtain from iPS cells.

During the investigation of differentiation protocols, a new concept arises, that is, self-organization [10]. iPS cells differentiate into various types of cells forming an organ. The

resultant cells finally form the organ. This procedure is particularly useful for not only the production of specific types of cells but also for the production of organs.

Mesenchymal stem cells (MSCs) are usually obtained from bone marrow. MSCs have the potential to differentiate into adipose cells, chondrocytes, and hematopoietic cells. MSCs can be obtained from a potential recipient and differentiated into target cells. MSCs, therefore, are considered interesting and useful for the scientific and clinical applications.

This book demonstrates the current status of stem cell research, new concepts, and solutions to the problems of pluripotent stem cells. Finally, it is shown how the issues are addressed, and horizons of accumulated and broadened knowledge.

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