Cell Engineering Division

Cell Engineering Division in RIKEN BioResource Center is a not-for-profit public bank that accepts donation and deposit of human and animal cell materials developed by life science research community. It examines, standardizes, amplifies, preserves, and provides cell materials to the interested scientists in all over the world. The major cell material has been cultured cell line, i.e., immortalized clone cells. Regarding human cell lines, the majority of them are derived from tumor cells. There is no doubt that the demand of supply of these cell lines will never cease in the field of biology. In addition, the demand for supply of non-immortalized cells has recently increased especially in the fields of developmental biology, transplantation medicine, regenerative medicine, and so on. To meet these demands, we have recently started the banking of primary human cells including somatic stem cells, such as human umbilical cord blood cells and primary cultured human mesenchymal cells. The staffs conduct not only banking of cell materials but also research and development relating to cell materials, such as establishment of novel human and animal cell lines and development of new technology to utilize cell materials.

History

RIKEN Cell Bank was established in June 1987 when a committee of scientists recognized a need for a central collection of animal cell materials that would serve scientists. In 2001, RIKEN BioResource Center (RIKEN BRC) was established and then Cell Bank was reorganized to Cell Engineering Division. In 2002, our division was recognized as the central archive for collection of “human and animal cell materials” in the National BioResource Project (NBRP) program, sponsored by the Ministry of Education, Culture, Sports, Science, and Technology.

Activities relating to cell banking

1. Cell Banking: Human and animal cell lines
2. Cell Banking: Human B cells transformed by EB virus
3. Cell Banking: Human mesenchymal stem cells
4. Cell Banking: Human umbilical cord blood cells
5. Quality control by STR profiling analysis for human cell lines
6. Ethical matter relating to human cell materials
7. Good manufacturing practice (GMP) facility
Activities relating to development of new cell resources

1. Development of technology to culture primate embryonic stem (ES) cells
2. Development of technology to obtain human feeder cells that maintain ES cells
3. Development of technology to establish human and animal cell lines possessing multi-potency
4. Development of technology to improve cell culture
5. Development of technology to immortalize human primary cells

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Activities relating to cell banking

1. Cell Banking: Human and animal cell lines

Cell lines are very useful materials in all fields of biology and they have been utilized in many kinds of experiment. We possess approximately two thousands cell lines, of which approximately one thousand lines are available for distribution. Approximately a half of the cell lines were derived from human cancer cells. These cancer tissue-derived cell lines are very precious for oncology and tumor immunology. Another half of the cell lines were derived from animals. In addition to animal cell lines derived from somatic cells, we possess several kinds of mouse embryonic stem (ES) cell line including C57BL/6-derived ES cell line. In recent years, nearly three thousands ampoules have been distributed in a year (Figure 1), mostly to not-for-profit organizations (80%) and approximately 10% overseas. We will continue to accept deposits and donations of cultured animal cell lines and expand the collection, since the significance of those cell lines in the field of biology will never cease.

2. Cell Banking: Human B cells transformed by EB virus

In order to analyze the causes of certain specific diseases at the level of genome, many genome samples are required. However, it is not so easy to collect many samples. Thus the collection of many genome samples and/or cell lines containing the genome is very important and useful for researchers in the field. We are collecting human B cell lines immortalized by Epstein-Barr virus transformation. The donors of B cells are not only volunteers possessing certain disease but also healthy volunteers.
3. Cell Banking: Human mesenchymal stem cells

Compared to obtaining primary cells derived from experimental animals, it is very difficult to obtain human primary cells. Current researches in life science, however, require human primary cells, such as stem cells, especially in the fields of transplantation and regenerative medicine. We succeeded to establish a system to provide such human primary cells efficiently. By collaborating with researchers who developed technologies to expand human mesenchymal stem cells in vitro very efficiently, we are supplying human mesenchymal stem cells to researchers. Mesenchymal stem cells can differentiate to bone, cartilage and reportedly also to neurons and cardiomyocytes (Figure 2).

4. Cell Banking: Human umbilical cord blood cells

Umbilical cord blood is a source of not only hematopoietic stem cells but also other somatic stem cells (Figure 3). Human umbilical cord blood cells are readily available, but usually discarded if they are not used in transplantation. Provided the mother of a newborn baby agrees to allow the umbilical cord blood cells to be used in research, the material can provide a valuable resource without the complicating factor of ethical concerns. By collaborating with “Japanese Cord Blood Bank Network”, we are supplying human umbilical cord blood to domestic researchers in order to contribute for the fields of transplantation and regenerative medicine (Figure 4).

5. Quality control by STR profiling analysis for human cell lines

Cross-contamination between cultured cell lines can result in the generation of erroneous scientific data. Hence, it is very important to eliminate cell lines that are of an origin different from that being claimed. Inter-species contamination can be detected by various established methods, such as karyotype and isozyme analyses. However, it has been impossible to detect intra-species cross-contamination prior to the development of technology that detects differences between cell lines at the molecular level. Recently, profiling of short tandem repeat (STR) polymorphisms (STR profiling) has been established as a method for the analyses of gene polymorphism. STR profiling is a simple and reliable method to identify individual cell lines. All human cell lines we are currently providing were analyzed by STR profiling to authenticate its identity. We found that more than ten human cell lines out of approximately 400 were misidentified. We conclude that STR profiling is a useful and powerful method to eliminate cell lines that have been misidentified by cross-contamination or by other causes. Through this unfortunate lesson, we have established a method for rigorous quality control.

6. Ethical matter relating to human cell materials

Cell banking of human cells requires strict regulation about ethical matters. We only accept the donation of human cells that are approved by the Institutional Review Board (IRB) at RIKEN Tsukuba Institute. Furthermore, RIKEN BRC contracts Material Transfer Agreement (MTA) with the organization that donates human cells to RIKEN BRC. In the MTA, RIKEN BRC confirms that the human cell resource was obtained after a proper informed consent. An approval by the IRB in the organization that donates human cells to RIKEN BRC is also necessary. When RIKEN BRC distributes human cells to user, RIKEN BRC also contracts MTA with the user. As for certain human cells, such as umbilical cord blood, an approval by the IRB at the user organization is also required.
Activities relating to development of new cell resources

1. Development of technology to culture primate embryonic stem (ES) cells
   Embryonic stem cells have a lot of potential not only in the field of basic biology but also in the field of clinical science. Before human ES cells are applied to clinical science, many kinds of experiment using primate ES cells are required. Therefore, we are planning banking of primate ES cells. At the moment we are establishing the technology to culture primate ES cells using cynomolgus monkey ES cell line.

2. Development of technology to obtain human feeder cells that maintain ES cells
   To our knowledge all human ES cell lines existing at the moment are cultured on the feeder layer derived from mouse embryo, i.e., Mouse Embryonic Fibroblast (MEF). Considering the application of human ES cells to clinical science, the cells cultured on MEF are not appropriate. Feeder cells derived from human resources are necessary and required, however the technology to obtain human feeder cells constantly is not established yet. We are planning to establish such technology using fibroblastic cells derived from placenta and umbilical cord.

3. Development of technology to establish human and animal cell lines possessing multi-potency
   Human and animal cell lines possessing multi-potency and/or tissue-specific character are very useful for developmental biology and the basic research of regenerative medicine. We are trying to establish such cell lines by various approaches. First, identification and purification of tissue-specific stem cell may lead to establishment of such cell line by immortalizing the stem cell. Second, induction of ES cell’s differentiation may lead to such cell line. Third, reprogramming of somatic cells may lead to such cell line. We are investigating these possibilities.

4. Development of technology to improve cell culture
   All kinds of cell are affected by many humoral factors both in vivo and in vitro. Analyses of functions of these humoral factors are essential for improvement of cell culture and cell differentiation. Search for novel humoral factors is also one of the most important researches in this field.

5. Development of technology to immortalize human primary cells
   It is very difficult to immortalize human primary cells. This fact makes the difficulties of using human cells in many fields of research. To immortalize human primary cells efficiently, we are analyzing mechanisms associating with cell mitosis and apoptosis.
Figure 1. Accumulated numbers of provision of cell materials.

Figure 2. Usefulness of human mesenchymal stem cells. Human mesenchymal stem cells that are originally donated for regenerative medicine etc. and expanded in vivo will be supplied to researchers depending on the informed consent of patients.
Figure 3. Flow chart of human umbilical cord blood samples.

Development of technology to expand hematopoietic stem cells in vitro
Development of technology to induce other somatic stem cells from cord blood

Figure 4. Scheme of banking of human cord blood. Human cord blood that is originally donated for transplantation but is not suitable for the purpose will be supplied to researchers depending on the informed consent of donators.
Publications

Original Papers (* Peer reviewed Journal)


2. Kaoru Saijo, Mayako Kato, Takashi Oomori, Isao Yoshimura, Tadao Ohno: The Validation study which leads organizers “cry”: So many points you must follow. AATEX 9: 54 (2003) *


7. Eiichi Ishikawa, Koji Tsuboi, Shingo Takano, Eiji Uchimura, Tadao Nose and Tadao Ohno:


Oral Presentations


