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Mini Review

Application of Stem Cells in the New Drug Development for Evaluating the Organ Toxicity

Palanisamy Sankar[1]* and Ramya Kalaivanan[2]

[1]*Department of Veterinary Pharmacology and Toxicology, Veterinary College and Research Institute, Namakkal, Tamil Nadu, India*
[2]*Department of Veterinary Microbiology, Veterinary College and Research Institute, Namakkal, Tamil Nadu, India*

***Corresponding Author:** Palanisamy Sankar, Department of Veterinary Pharmacology and Toxicology, Veterinary College and Research Institute, Namakkal, Tamil Nadu, India.

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Abstract

Stem cell has opened a new avenue in the area of drug discovery and development. Stem cells are capable of renewing themselves. However, they can be continuously cultured in an undifferentiated state, giving rise to more specialized cells of the human body such as heart, liver, bone marrow, blood vessel, pancreatic islet, and nerve cells. Potential use of stem cells instead of the primary cells for the research related to the drug discovery and its screening will certainly be a resourceful tool as formulating drugs are more diverse and complex. Therefore, stem cells are an important new tool for developing unique, *in vitro* model systems to test drugs and chemicals and a potential to organ toxicity. This review provides an overview of the applications of stem cell in the area of organ toxicity in drug development process.

Keywords: Stem Cells; New Drug Development; Organ Toxicity

Introduction

Stem cells are a dynamic and versatile system that can be used in identification and validation of novel drug targets, metabolism and safety testing, compound evaluation for genetic variants, identification of clinically relevant biomarkers and to predict the potential toxic effects of drugs. Stem-cell technology offers superior methods to format predictive and high-throughput screening of thousands of compounds in a very short span of time, provides greater accuracy and reduces the amount of *in vivo* testing. Many drugs that were introduced into the market as cures for various ailments were withdrawn later because of their nonspecific effects on other bodily functions. For examples, nimesulide was withdrawn from the US market because of its potential for producing fatal liver failure, mibefradil for its non-specific inhibition of the hepatic cytochrome P450-dependent enzymes and more recently, rofecoxib for its capability of causing serious cardiovascular complications. Conventional screening of chemical libraries for potential target molecules is a costly and time-consuming affair with the current estimate put at approximately 1 billion US$ and 15 years from the identification of a lead compound to its introduction into the market. This has put enormous pressure on the pharmaceutical companies to introduce cheaper and high-throughput screening protocols in their research programs. Advances in stem cell biology and fabrication technology have established the foundation to develop organ-inspired high-throughput *in vitro* assays. A critical breakthrough in biology was the discovery of stem cells, which can be used for disease modeling and drug toxicity screening [1].

Stem cells to evaluate cardiotoxicity

Cardiomyocytes have been derived from human embryonic stem cells that resemble functional cardiomyocytes in every aspect, but, the controversy surrounding this type of stem cells has limited their application. Adult stem cells, for example, derived from the bone marrow now represent a feasible alternative for obtaining functional cardiomyocytes and there has been rapid progress in this field. Human adult stem cells can be expanded *in vitro* and this has provided unlimited potential for producing large quantities of cardiomyocyte progenitors. These can then be used to assess Kv11.1 potassium ion channel activity (sometimes simply denoted as hERG: human ether-à-go-go-related gene - a novel potassium channel found mainly in the heart and the blockade of which is supposed to cause prolongation of the QT interval), other K^+ and $Ca2^+$ channel activity through high-throughput automated patch-clamping. The net result of this endeavour would be improved screening of potential harmful compounds at very early stages of the drug development [2].

Stem cells to evaluate hepatotoxicity

Placenta is a source of multipotent stem cells and efforts are now on to use this as a source of hepatocytes. The placental stem cells can propagate relatively easily and when incubated in the presence of dexamethasone begin differentiating into hepatocytes. Such placental stem cell-derived hepatocytes express most of the drug-metabolizing enzymes, including CYP3A4, CYP2C9

and CYP2E1 that are most vital in drug metabolism. Placental stem cells are now being investigated for producing several different cell types, like hepatocytes or pancreatic islets that can be used as replacement therapy in cases of cirrhosis or diabetes. The placental stem cells are relatively easy to obtain and not associated with any ethical issues; therefore, use of such stem cells will be increasing in drug testing and replacement therapy in the days to come.

Stem cells to evaluate genotoxicity

Genotoxicity and reproductive toxicity tests are important parameters in the identification of lead compounds. Animal testing for these parameters have met with fierce resistance and the cell culture-based systems are less perfect because most cell lines react differently to a potential toxicant than in vivo situation. Stem cells are increasingly being used in such studies. The potential toxicant is tested directly on the human adult stem cell lines. Stem cells like the bone marrow cells are present in the adult body and represent an important source of normal cell rejuvenation. Therefore, any compound that is able to affect the differentiation or proliferation of adult stem cells can be considered as potentially genotoxic. For example, thalidomide has no side effects in normal adults but can cause severe fetal deformities, viz., phocomelia. Such a potential toxicant cannot be detected by normal screening methods even by using cell cultures because many of such compounds inhibit signaling pathways that are only active during the early stages of embryogenesis. However, such pathways are also active in proliferating stem cells. Therefore, this toxic effect of thalidomide would become clearly evident in stem cell cultures. Using of stem cell cultures, phenobarbital, DDT and gossypol were also shown to be either genotoxic or have reproductive toxicity.

Stem cells and *in vitro* toxicology

A major limitation in using embryonic stem cells or adult stem cells for *in vitro* toxicology studies is the fact that during differentiation, these cells tend to form a heterogenous cell population consisting of cells of different lineages [3]. This complicates results and data analysis. To solve this problem, extensive studies have been carried out on cell-specific surface markers. Another method is the introduction of transgenes into the stem cells before differentiation. These transgenes are expressed only when the stem cells differentiate into a particular lineage. For example, these transgenes can be designed such that they are introduced into a region of the genome that contains genes that are expressed only in cardiomyocytes. So, when the stem cells differentiate into cardiomyocytes, the transgene is also expressed along with the genes specific for cardiomyocytes. The transgene usually confers antibiotic resistance to the lineage of stem cells and, therefore, can be isolated from other cell lineages based on their resistance to an antibiotic that would be toxic to any other cell. The transgene can also be engineered to express a unique plasma membrane surface protein. This way when the protein gets expressed, a specific antibody labeled with a fluorescent probe can be allowed to interact with the protein and then only the cells showing fluorescence can be separated from a heterogenous cell population using the fluorescence activated cell sorter (FACS). A transgene conferring neomycin resistance was introduced into the region that contained the cardiomyocyte specific promoter. This allowed the neomycin resistance gene to be expressed whenever the myosin heavy chain of the cardiomyocyte was expressed. Subsequently the cells (cardiomyocytes) that expressed the neomycin resistance gene were separated from rest of the cells by antibiotic selection [4]. This gave a cardiomyocyte population that was 99% pure. Similarly, hepatocytes could be separated when a transgene expressing hepatocyte nuclear factor was introduced into the embryonic stem cells.

Conclusion

The feasibility and accuracy of research with stem cells have prompted many private companies to set up production facilities and now many pure cell lineages are readily available. Although ESTs could not replace prevailing evaluation protocols *in vivo*, these could, however, reduce or refine the use of animal procedures. In addition, the continuous utilization of stem cells in drug discovery will only be possible by collaborative research. Sharing knowledge between academic research and industry, as well as investment from pharmaceutical companies in basic and translational stem cell research are key to develop successful drug development.

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