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Mesenchymal Stem cells derived from human perinatal tissues as a model for drug screening and toxicity testing – A perspective

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Perspective

Mesenchymal Stem cells derived from human perinatal tissues as a model for drug screening and toxicity testing – A perspective

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Backgroud

Stem cells have a great potential for basic research and hold the future for clinical applications. These cells have characteristic features quite unique from other cells i.e., they are capable of self-renewal and differentiating into any cell type. The two types of stem cells being considerably worked on are the embryonic stem cells (ESCs) and the adult stem cells[1].

ESCs are pluripotent cells and hence capable of differentiating into all three germ layers viz., endoderm, mesoderm, and ectoderm[2]. Adult stem cells are generally regarded as multipotent having the capability of differentiating into limited cell types. However, some reports show evidence of having pluripotent nature in adult stem cells like mesenchymal stem cells (MSCs) [3], though it is not generally accepted. In general, MSCs are capable of differentiating into adipocytes, chondrocytes, and osteocytes[4].

MSCs vary significantly in their paracrine secretions based on the tissue of origin[5,6]. This difference is probably required for the maintenance of the tissue homeostasis in which they are residing. All the MSCs have immune regulatory properties[7]. Area of mesenchymal stem cells (MSCs) has flourished lately. Mesenchymal stem cells can be isolated from perinatal and postnatal tissues. MSCs are present in almost all the postnatal organs viz., liver, skeletal muscle, adipose tissue, heart, lung, brain etc. making their presence ubiquitous. However, it is not possible to recover these MSCs for research purposes as it evokes ethical issues and technical difficulties. Hence, the best choice left to researchers is perinatal tissue available as biological waste. Perinatal MSCs can be harvested from various sources viz., cord blood, umbilical cord, placenta, amnion, and chorion[8]. These MSCs are the promising resources for autologous stem cell transplantation because they are the biological wastes that are easily available with negligible legal issues. The most important features of these MSCs are that they are human origin and represent normal diploid cell population having finite life. Human diploid cells have been employed in viral vaccine preparation such as rabies. It is very difficult to prepare and establish human diploid cell culture such as MRC5 and MRC9 derived from human fetal lung and kidney respectively. Under this scenario, human tissue derived MSCs come to our rescue to form a novel alternative/ substitute for drug screening [9]. A study performed by Petlzer et al., highlighted the importance of elaborated predictive *in vitro* test to screen between-donor variability of perinatal tissues for banking allogeneic standardized MSCs. Perinatal MSCs are useful for *ex vivo* expansion of hematopoietic progenitor cells as they have the potential to modulate the *in vitro* immune response [10]. Umbilical cord MSCs and placenta-derived MSCs are considered to be genetically stable under hostile *in vivo* situations, demonstrating their suitability to be used for therapy [11].

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The screening of genotoxic compounds are done by a widely known micronucleus test. To reduce the number of animal experiments carried out; high throughput screening of compounds can use MSCs as a substitute to peripheral lymphocytes and cancer cell lines [12].

Pharmacological investigations include screening the compounds on both *in vitro* and *in vivo* models. *In vivo* models involve a lot of animals and ethical clearances. *In vitro* model on the other hand comprise the primary cell culture, established cell lines, organ culture, embryo culture and three-dimensional cultures for specialized cells. All have their own advantages and disadvantages. The most widely used ones are the established cell line, which are either primate or non-primate origin. If it is a primate cell line i.e., a human cell line, it is mostly the cancer cell line. If one has to study an *in vitro* phenotypic instability of hepatocytes, there are some limitations in harvesting liver cells from human, which raises an ethical concern, non-availability of the fresh liver from humans for harvesting cells and hepatocyte preparation from different donors will have high batch to batch variation in the assessment of drug toxicity.

To overcome the above limitations, different models using the cell lines derived from human have been proposed for screening; one of the classic examples being HepG2 (human hepatoma cell line), they show minimal levels of drug metabolizing action and do not establish a real alternative to primary hepatocytes. Pharmaceutical companies progressively make use of cell lines to speed up the selection of new drugs with promising pharmacokinetic and metabolic properties [13]. Cell lines serve as the most feasible alternative even though they tend to exhibit problems in stability [14]. The development of cell line based model that exactly mimics the human *in vivo* conditions is lacking and there are various factors, which need to be looked at before selecting a cell line for screening. None of the models discussed above depicts the actual human physiological conditions. Therefore, stem cell based model is the best option. Stem cells may also be a source for the generation of various cell types *in vitro*. Such *In vitro* models have an advantage of being used as an alternative to animals and the application includes transplantation, tissue engineering and in drug and vaccines research. Based on the previous reports, it is established that MSCs especially from perinatal tissues and their differentiated progeny can be used as a model for screening drugs and toxicity assays. The employment of perinatal tissue derived MSCs prove the concept of "Trash to Treasure" and provide suitable substitute for animal experimentation serving three "R" principle of Replacement, Refinement, and Reduction in animals. In the modern era of stem cells, MSCs and their differentiated progeny, such as islets, hepatocytes, cardiomyocytes etc. can be used as a novel means for screening drugs for cell specific disease thereby minimizing the cost of procuring the specific cell lines and using that for the experiment as depicted in Figure 1:

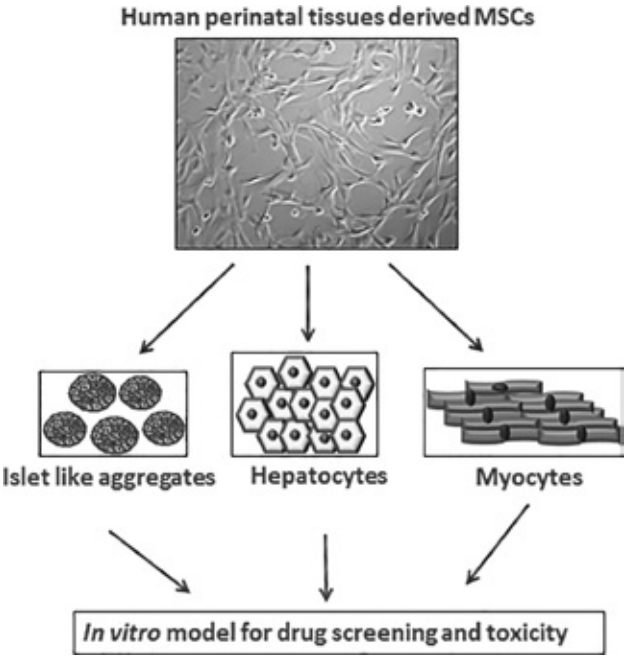

Figure 1: Stem cells and their progeny as In vitro **model for drug testing**

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