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Production of Human Liver by Intrauterine Xenotransplantation of Human Wharton's Jelly-Derived Mesenchymal Stem Cells to Animal Fetus: A Review

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ABSTRACT

Chronic liver injury and inflammation lead to hepatic fibrosis, cirrhosis, and liver failure. Transplantation of liver is the curative therapy for end-stage liver ailment. The common problem with liver transplantation like any other organ transplantation is organ shortage. The potential role for stem cell therapy to treat liver diseases has become recently topical in medical research because of the self-renewal characteristics expressed stem cells' differentiation potential. Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) are MSCs with multiple differentiations potential. Because of its great resources, without any damage procurement, and less immunogenicity compared with other adult MSCs, WJ-MSCs promise to be a good exogenous cell candidate for tissue engineering. We hypothesize that use of human WJ-MSCs (hWJ-MSCs) xenotransplantation to the rabbit fetus liver to produce human liver tissue in animals' fetus.

Key words: Mesenchymal stem cell, Liver, Transplantation, Heterologous, Human

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INTRODUCTION

The central organ for homeostasis is liver and performs extensive functions, such as glycogen storage, drug detoxification, metabolism, production of variant serum proteins, and bile secretion [1]. Liver ailments such as fibrosis, hepatitis, and cirrhosis cause morbidity and mortality as liver functions are required for homeostasis. The liver is inimitable in its great potential to generate again from variant injuries. Liver tissue can be transplanted from a living donor due to the liver's capability to recover its major mass after surgical removal of a considerable portion [2]. Transplantation of liver is the only curative therapy for end-stage disease, but access to sufficient donors is problematic, the procedure

costly, and life-long immune suppression is required [3].

Transplantation of cell has proposed another promising method for liver-based treatments [4, 5]. Stem cells from different intra- and extra-hepatic sources has been studied for the hepatic diseases therapy [6]. Stem cells are almost simple to harvest and have the potential of proliferation and differentiation to various lineage [7]. Additionally, stem cells show immunotolerogenic properties reducing the risk of graft rejection [8]. In contrary, the method is hampered by the limited number of donors and invasive harvesting methods. Also, the yield of stem cell, in vivo repopulation potential, and the differentiation capacity decline with aging [9].

We hypothesize that use of human Wharton jelly-derived mesenchymal stem cells (hWJ-MSCs) xenotransplantation to the rabbit fetus liver to produce human liver tissue in animals' fetus. Therefore, we reviewed the potential of this cells and xenotransplantation method for liver production in this article.

MSCs differentiation to liver tissue

The MSCs possess similar features including favorable proliferative capability, self-renewal, and differentiation potential. These cells were separated from bone marrow [10-18], adipose tissue [19, 13, 20, 21], endometrium [22, 23], dental pulp [24], umbilical cord [25] and menstrual blood [26]. They possess multilineage properties differentiating to osteoblasts [19], adipocytes [23], chondrocytes [19] and neuronal-like cells [10].

Among multiple sources of stem cells human umbilical cord matrix (WJ) is the best source of stem cells, because of non-invasive collection, speedy availability with a great donor pool, no ethical limitations, great in vitro expandable values, and multi-potent differentiation [27, 28]. Because of immunomodulatory effects, WJ-MSCs are assumed desired agents not only for autologous, but also for allogeneic cell treatment methods for hematopoietic and non-hematopoietic, malignant and non-malignant, inherited, and acquired diseases [29-31].

MSCs may be differentiated into endoderm-derived generic cells, like hepatocytes [32]. A marker used to differentiate MSCs into hepatocyte-like cells is albumin secretion with the evaluation of metabolic enzymes, α- fetoprotein, and cellular skeleton proteins [33-35]. They are a good source of MSCs for autologous and allogeneic applications [27]. WJ-MSCs have the stem cells' characteristics [36]. The WJ-MSCs express the liver productive markers and the enzyme genes involved in liver metabolism. After 3 stages of full hepatogenetic induction (liver genes), the MSCs of the umbilical cord differentiate and show a quasi-liver morphology [32, 37]. Several regulating liver markers store glycogen and produce urea and induce CYP3A4 activity [38]. According to previous studies it was shown that WJ-MSCs can express several liver markers, such as alpha-fetoprotein, cytokeratin 18, cytokeratin 19, glucose-6-phosphatase [25, 37]. Furthermore, WJ-MSCs as a very young source of MSCs with no ethical concerns and low immune responses have the characteristics of both embryonic and adult stem cells [27].

Intrauterine xenotransplantation for liver production

On the other hand, because of the scarcity of liver donors, it has increased the incentive to use animal resources for organ or tissue transplantation [39]. As the rabbit is an animal that is physiologically and phylogenetically close to humans and during a short period of pregnancy (35 days), and during pregnancy having a great number of fetuses (5 to 8), it can be assumed to be a good candidate for intrauterine xenotransplantation.

By "xenotransplantation", we directly transplant the cells', tissues', or organs' from one species to another. Current enthusiasm in xenotransplantation originates from the global deficiency of human tissues, organs and cells to be used in transplantation. The imbalance between demand and supply can be addressed if tissues, organs, or cells of other species can be transplanted into humans [40]. Because the inhumane mammals were the closest relatives to humans, for the first time, it was considered as a source of potential organ for xenotransplantation. In principle, chimpanzees were the best option due to the similarity of organ size with humans. They also have good blood compatibility with humans which has led them to consider potential candidates for xenotransplantation. However, chimpanzee as an endanger species, other potential donors have been raised [41].

As explained above, because of the immune system function it was thought that xenotransplanted described as coordinated or incompatible

harmonious species should be phylogenic close to each other because the incompatible recipient loses the xenograft tissue or cell in a few minutes to a few hours [41]. A new approach has been recently rose which is production of human tissue in another species under a natural immunosuppression condition without considering the relationship between the donor and receptor species.

DISCUSSION

There are in vitro animal study, that differentiated umbilical cord stem cells to the hepatocyte-like cells , but generating functional hepatocytes are still under debate [42]. In in vivo condition, it has been found in studies that multiple weeks after the MSCs' transplantation into the damaged livers of rats with liver fibrosis induced by carbon tetrachloride, a significant reduction in liver fibrosis with lower levels of glutamic oxaloacetic transaminase, glutamate-pyruvate transaminase and growth factor-B1 transfer were observed in the liver [35]. an study has shown that the injection of the MSCs of human umbilical cord into hepatectomized SCID rats causes the expression of human albumin and alpha-fetoprotein under in vivo conditions [38]. According to the recent study it is essential to evaluate the xenotransplantation of WJ-MSCs into rabbit's fetus.

It is assumed that intrauterine transplantation of WJ-MSCs to rabbit fetus (Figure 1) by ultrasonography of the uterine wall compared to laparoscopic surgery in the midline is better [43, 44]. It increases the chance of transplantation in the rabbit's fetus. It was shown that the ratio of fetal death was high in the intrauterine transplantation of stem cells into the liver of sheep embryos due to the perforation and suction in the liver [45]. Therefore, it is important that the needle insert into the peritoneal cavity to prevent damage and increase the possibility of continued pregnancy to the end and birth of the newborns.

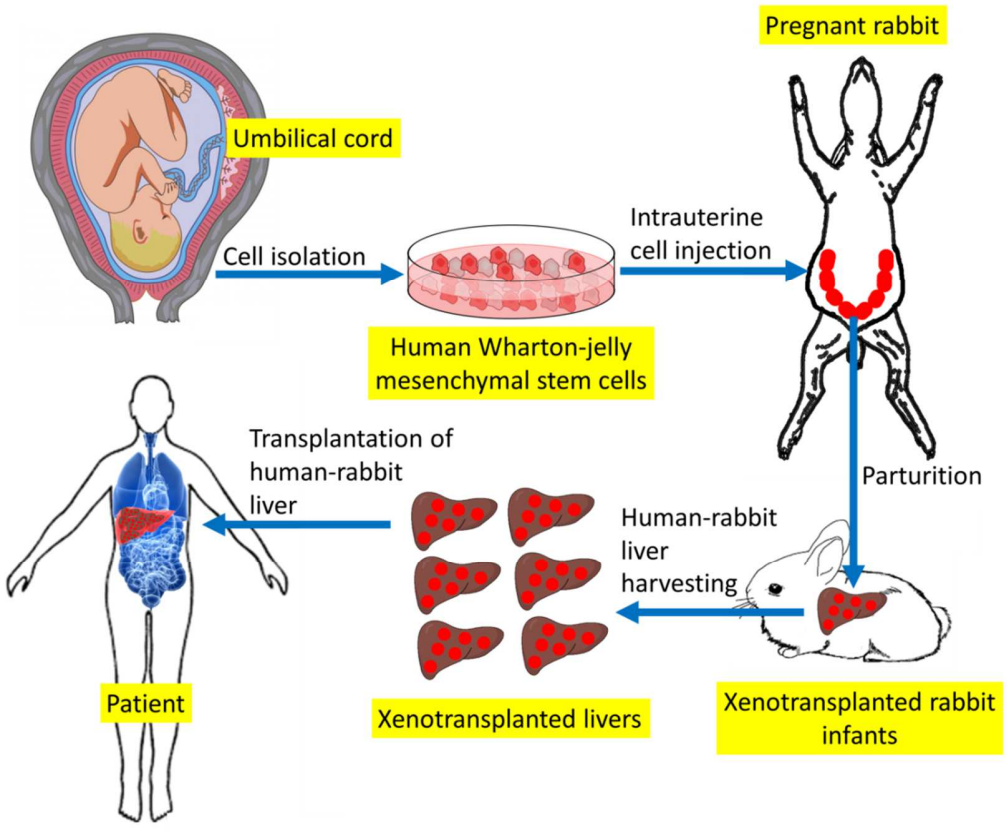

Figure 1. A sketch for production of human liver by intrauterine xenotransplantation of human Wharton's jelly-derived mesenchymal stem cells to rabbit fetus.

CONCLUSION

The rabbit is assumed the most suitable species due to its physiological suitability, breeding characteristics, anatomical similarity and for the sake of ethics [46]. Thus, the plan currently hypothesized to provide a novel therapeutic strategy, xenotransplantation of the WJ-MSCs, is responsible for the reconstruction of the human liver in the rabbit's fetus. This review suggest that, it would be possible to produce human liver tissue in an animal embryo, such as rabbits, in order to provide a valuable medical aid to patients with liver dysfunction. The hWJ-MSCs xenotransplantation to the rabbit fetus liver can be a candidate to produce human liver tissue in animals' fetus.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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