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INCORPORATION OF PLACENTA EXTRACT INTO LIPOSOMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Recent Innovations of Liposomal products in Pharmaceutical science for Drug Development, A number of drug candidates which are highly potent and have low therapeutic indication can be targeted to the required diseased site using the liposomal drug delivery system. Drugs encapsulated in liposomes can have a significantly altered pharmacokinetics. The efficacy of the liposomal formulation depends on its ability to deliver the drug molecule to the targeted site over a prolonged period of time, simultaneously reducing its (drug's) toxic effects. The drugs are encapsulated within the phospholipid bilayers and are expected to diffuse out from the bilayer slowly. The placental extract can be incorporated in the liposomal drug delivery system. The placenta is an organ with the role of protecting and nurturing the baby in a mother's womb. Naturally, it serves as an interface for the supply of oxygen and nutrients from the mother to the baby, but in order for the baby to grow healthily within the womb, the placenta works in a truly range of ways, including digestion and excretion in place of the internal organs of the still developing baby, the secretion of hormones, and the provision of an immune system to make it difficult for the baby to contract illnesses. On the other hand, the placenta is also an organ that synthesizes "cell growth factor", a substance that controls the growth and replication of cells. Fetal membrane stem cells are presently preserved mainly for research. However, as these cells gain interest for their regenerative and immunomodulatory properties

KEYWORDS: Liposome and Phospholipids, Application of Liposome, Placenta Extract and it's Applications.

INTRODUCTION

Liposome's are colloidal, vesicular structures composed of one or more lipid bilayers surrounding an equal numbers of aqueous compartments1. The sphere like shell encapsulated a liquid interior which contain substances such as peptides and protein, hormones, enzymes, antibiotic, anti-fungal and anticancer agents. A free drug injected in bloodstream typically achieves therapeutic level for short duration due to metabolism and excretion. Drug encapsulated by liposome achieve therapeutic level for long duration as drug must first be release from liposome before metabolism & excretion. They are small artificial vesicles of spherical shape that can be created from cholesterol and natural non-toxic phospholipids.[1]

Classification of liposomes

The liposome size can vary from very small (0.025 μm) to large (2.5 μm) vesicles. Moreover, liposomes may have one or bilayer membranes. The vesicle size is an acute parameter in determining the circulation half-life of liposomes, and both size and number of bilayers affect the amount of drug encapsulation in the liposomes9. On the basis of their size and number of bilayers, liposomes can also be classified into one of two categories: (1) multilamellar vesicles (MLV) and (2) unilamellar vesicles. Unilamellar vesicles can also be classified into two categories: (1) large unilamellar vesicles (LUV) and (2) small unilamellar vesicles (SUV). In unilamellar liposome's, the vesicle has a single phospholipids bilayer sphere enclosing the aqueous solution. In multilamellar liposome's, vesicles have an onion structure.[2]

Key Features of Liposomes

- Unique systems for solubilizing new generation of small molecules.
- Can be produced synthetically and in large quantities
- Well-characterized lipids available
- Surge of activities in developing a pharmaceutically-acceptable liposomal product.
- Numerous clinical trials ongoing.

Applications of Liposomal DDS.[3]

1. Gene therapy
2. Liposomes as carriers for vaccines
3. Liposomes as carrier of drug in oral treatment
4. Liposomes for topical applications
5. Liposomes for pulmonary delivery

6. Against Leishmaniasis
7. Lysosomal storage disease
8. Cell biological application
9. Metal storage disease
10. Ophthalmic delivery of drugs.
11. Liposomes in anticancer therapy

Human placental extract

Human placenta, besides playing a fundamental and essential role in fetal development, nutrition, and tolerance, may also represent a reserve of progenitor/stem cells. Considering the complexity of the structure of the placenta, we have focused our attention on cells isolated from the amniotic and chorionic fetal membranes and reached a consensus on the minimal criteria for definition of mesenchymal cells derived from both of these membranes.

Four regions of fetal placenta can be distinguished: amniotic epithelial, amniotic mesenchymal, chorionic mesenchymal and chorionic trophoblastic. From these regions, the following cell populations are isolated: human amniotic epithelial cells (hAEC), human amniotic mesenchymal stromal cells (hAMSC), human chorionic mesenchymal stromal cells (hCMSC) and human chorionic trophoblastic cells (hCTC).

Cells from each layer demonstrate variable plasticity. Because of their plasticity, the term stem cell has been used in the literature to describe a number of cells isolated from placenta..[4,5]

According to criteria recently proposed by Dominici et al. for bone marrow-derived mesenchymal stromal cells[6,7], mesenchymal cells isolated from fetal membranes should be termed mesenchymal stromal cells (hAMSC and hCMSC).

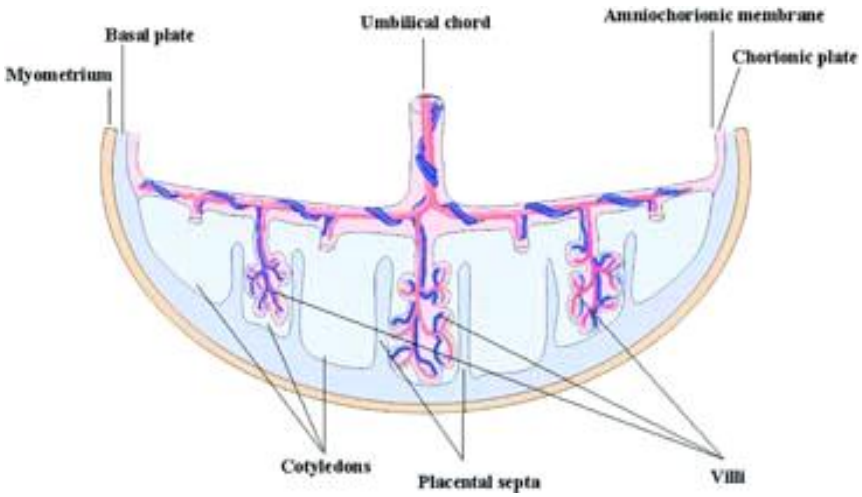
A specific pattern of surface antigen expression (Table 1);

Table 1. Specific surface antigen expression at passages 2–4 for amniotic mesenchymal stromal cells and human chorionic mesenchymal stromal cells

Positive (≥95%)	Negative (≤2%)
CD90	CD45
CD73	CD34
CD105	CD14
	HLA-DR

Placental Compartments

The fetal adnexa is composed of the placenta, fetal membranes, and umbilical cord. The term placenta is discoid in shape with a diameter of 15–20 cm and a thickness of 2–3 cm. From the margins of the chorionic disc extend the fetal membranes, amnion and chorion, which enclose the fetus in the amniotic cavity, and the endometrial decidua. The chorionic plate (Fig. 1) is a multilayered structure that faces the amniotic cavity. It consists of two different structures: the amniotic membrane (composed of epithelium, compact layer, amniotic mesoderm, and spongy layer) and the chorion (composed of mesenchyme and a region of extravillous proliferating trophoblast cells interposed in varying amounts of Langhans fibrinoid, either covered or not by syncytiotrophoblast). Villi originate from the chorionic plate and anchor the placenta through the trophoblast of the basal plate and maternal endometrium. From the maternal side, protrusions of the basal plate within the chorionic villi produce the placental septa, which divide the parenchyma into irregular cotyledons (Fig. 1).



Fetal Placenta Tissue Cell Populations

Human Amniotic Epithelial Cells:-Recent reports indicate that hAEC express stem cell markers and have the ability to differentiate toward all three germ layers. These properties, the ease of isolation of the cells, and the availability of placenta as a discard tissue, make the amnion a potentially useful and noncontroversial source of cells for transplantation and regenerative medicine. For isolation of epithelial cells, the amniotic membrane is stripped from the underlying chorion and digested with trypsin or other digestive enzymes.[8], [9], [10]–[11] Epithelial cells are specifically released by brief trypsin digests of 20–40 minutes each.[12] Isolated cells readily attach to plastic or basement membrane-coated culture dishes. Culture is commonly established in a simple medium such as Dulbecco's modified Eagle's medium

supplemented with 5%–10% serum and epidermal growth factor (EGF), where the cells proliferate robustly and display typical cuboidal epithelial morphology.[10, 11, 13] Additional cell surface antigens on hAEC include ATP-binding cassette transporter G2 (ABCG2/BCRP), CD9, CD24, E-cadherin, integrins α6 and β1, c-met (hepatocyte growth factor receptor), stage-specific embryonic antigens (SSEAs) 3 and 4, and tumor rejection antigens 1-60 and 1-81.[11, 14] Surface markers thought to be absent on hAEC include SSEA-1, CD34, and CD133, whereas other markers, such as CD117 (c-kit) and CCR4 (CC chemokine receptor), are either negative or may be expressed on some cells at very low levels. Although initial cell isolates express very low levels of CD90 (Thy-1), the expression of this antigen increases rapidly in culture.[11, 14]

Preclinical Studies in Animal Models

Hepatic Regeneration

The large number of hepatic genes and functions identified in human amniotic epithelium (hAE) suggest that if effective and efficient methods were developed to induce complete hepatic differentiation, hAE could be a useful source of cells for transplant procedures. Preclinical investigations with hepatic differentiation of hAEC have been promising. In vitro, differentiation procedures have yielded cells that express a number of liver functions, including the transcription factors HNF3γ, and C/EBPα, HNF1, HNF4α, pregnane x receptor, and constitutive androstane receptor, and differentiated liver genes, including albumin, α1-antitrypsin (A1AT), glucose-6-phosphatase, carbamoyl phosphate synthase I (CPS-I), glutamine synthase, phosphoenolpyruvate carboxykinase, tyrosine aminotransferase, transthyretin and the drug metabolizing genes CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2D6 2E1, 3A4, 7 and 7A1.[11, 14, 20, 21] Following transplantation into the liver, successful engraftment and survival of human[19, 25] or rat amniotic epithelial cells (AEC)[26] has been demonstrated.

Cardiac Repair

Myocardial infarction, ischemia, and stroke are important consequences of end-stage occlusive vascular disease. Present-day therapies are inadequate and palliative, so stem cell therapy has been investigated. Coculture experiments with neonatal rat heart explants have confirmed that hAMSC integrate into cardiac tissues and differentiate into cardiomyocyte-like cells. After transplantation into myocardial infarcts in rat hearts, hAMSC survived for 2 months and differentiated into cardiomyocyte-like cells.[22]

Placenta Derived Stem Cells for Treating Neurological Disorders

Human AEC have shown particular potential for treating central nervous system disorders. Since the discovery that hAEC have stem cell properties[11], express neural and glial markers and neural-specific proteins, and also have the capacity to produce and secrete neurotransmitters[9, 16], cell therapy with these cells has been considered.[9, 15] Successful transplants of hAEC into caudate nucleus.[17, 18, 27], hippocampus[28], and spinal cord[24] have been reported. Transplantation of hAEC in a rat model of Parkinson's disease reversed the condition and prevented neuronal death.[17, 18] When hAEC were transplanted into ischemic hippocampus, they differentiated into "neuron-like" cells.[28] Following transplantation into the transected spinal cord of monkeys, hAEC aided a robust regeneration of host axons and prevented death of axotomized neurons of the spinal cord.[66]

Cell Tracking

In preclinical studies, tracking of transplanted cells is essential. Using cell labeling together with imaging, cells can be traced noninvasively.[29], [30], [31], [32], [33], [34], [35], [36]–[37] Stem cells from different sources have been labeled using radionuclides, magnetic nanoparticles, or reporter genes, in both preclinical and clinical studies.[30, 38, 39] In contrast to other imaging techniques, luminescence imaging detects live cells, since the reporter gene, luciferase, generates photon emission only in the presence of ATP, luciferin, and oxygen.[40] Reporter gene transfection protocols established for adipose-derived stem cells have been successfully applied in hAMSC.[37], allowing luminescence imaging of their survival, migration, and distribution in preclinical in vivo models.

Cell and Tissue Banking

Cell Banking

So far, most experience in preservation of placental tissue-derived cells has been gained with cord blood, which contains both hematopoietic and mesenchymal stem cells. When cord blood transplantation proved effective, many cord blood banks were established, offering collection and banking for public (allogeneic) or private (autologous or allogeneic) use. Cord blood is procured from natural births or caesarean sections.[41] Different methods for the reduction of red blood cells, plasma volume and cryopreservation exist.[42] Cord blood products containing cryoprotectants (e.g., dimethyl sulfoxide [DMSO]) are frozen at a controlled-rate and can be stored in liquid nitrogen for at least 15 years without the loss of their engraftment potential in vivo.[43]

Tissue Banking

The use of amniotic membrane has history spanning almost 100 years. The first reported clinical use of amniotic membrane was in 1910, when it was applied in skin transplantation.[44] Shortly after, application was expanded to treat burned and ulcerated skin[45, 46] and conjunctival defects.[47] Since its rediscovery in 1995[48], it has been widely applied in ophthalmology, surgery, and wound healing.[49] Besides its nearly unlimited availability, easy procurement, and low processing costs for therapeutic application, many beneficial properties of this tissue, including bacteriostatic, anti-inflammatory, analgesic, wound healing, reepithelialization, reduced scarring, and anatomical and vapor barrier properties, have been reported.[23, 50, [51]–52]

CONCLUSION

Future medical needs may require concomitant application of cord blood and placental cells from the same donor. The liposome can be used as a vehicle for administration of nutrients and pharmaceutical drugs. In this review, we have presented recent advances in this field, with the aim of defining the placenta derived cell subpopulations and their plasticity, as well as providing protocols for their isolation and differentiation. Finally, the preclinical studies reported strongly support the hypothesis that placenta holds much promise for the development of cell-based therapies for clinical applications in the future in the field of targeted “Liposomal Drug Delivery System”.

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