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Research Article

The Safety Profile of a Bone Marrow-Derived Mesenchymal Stem Cell Extracellular Vesicle Isolate Product

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Abstract

Bone Marrow Derived Mesenchymal Stem Cells (BM-MSCs) and perinatal (placenta, amnion, umbilical cord, and Wharton's jelly) tissue derived cells are the current primary cell sources for commercial regenerative medicine products. Several companies are marketing their perinatal products claiming equivalent or superior safety and efficacy profiles to BM-MSCs with little data to support these claims. The scientific literature clearly indicates that not all mesenchymal stem cells are created equal. Understanding the critical primary attributes of the cell source may provide the end user important information to evaluate and compare the quality, safety and potential efficacy of the product based on its source. A BM-MSC Extracellular Isolate Vesicle Product (EVIP) has recently been developed. The purpose of this paper is to evaluate the safety profile of this BM-MSC EVIP compared to all perinatal products in terms of potential allergic reaction, infection, carcinogenicity, and clinical efficacy.

Introduction

Currently, the field of regenerative medicine is utilizing first generation technology and therapies [1]. Autogenous treatments rely on obtaining extremely rare viable Mesenchymal Stem Cells (MSC) from the patient's bone marrow or adipose tissue [2]. The problem inherent to any autogenous source is donor variability. Young donors have higher MSC numbers as well as stem cell vitality with fewer co-morbidities. However, mostpatients seeking treatment with regenerative medicine are older. How clinically efficacious are the few thousand MSCs obtained from the adipose or bone marrow of a 75-year-old with diabetes? Additionally, is the cost and morbidity of obtaining autogenous MSCs from any source worth it?

Non-expanded allogeneic sources for the MSCs are from tissues such as amniotic fluid [3,4], the umbilical cord [4], Wharton's jelly [5] or the placenta [6]. Unfortunately, the number of MSCs from these sources isminimal. The vast majority of stem cells from these sources are hematopoietic, not mesenchymal. The FDA requires these products to be sterilizedprior to usage.Usually, this is achieved by radiation. During sterilization, gamma rays eliminate microorganisms but also significantly alter the molecular structure of fragile biologics such as cytokines, chemokines, and growth factors as well asinstigatemutations of DNA and RNA.

How clinically efficacious are radiated growth factors? These sources all share the inherent problem of donor and thus, product variability. Every donor is genetically unique, making every product batch a "one of a kind." Do the products contain viable cells at the bedside or not? If they do, what are the long-term effects of introducing foreign DNA into a patient? How safe are allogeneic cellular products for regenerative purposes? How safe is the DNA and RNA of any radiated placental, umbilical cord, or amniotic product [3-6]?

A second-generation regenerative medicine product has been developed and is currently in use. The Extracellular Vesicle Isolate Product (EVIP) is derived from the bone marrow of a single young healthy adult female donor. The donor screening and testing was performed by a CLIA licensed laboratory for the presence of any virus or infective agents. Her MSCs have been fully characterized and have a master record filed with the FDA. The donor has been tested for any chromosomal abnormalities. The product is SAFE based on the quality in which is produced and lack of any reported clinical adverse events. The end product from these cells contains over 800 different active GFs and cytokines and well over 30 billion exosomes per cc. The product can currently be usedonly in a frozen form, to ensure biomolecular stability, which is then thawed to room temperature just before use. The EVIP sterilization is achieved through ultrafiltration, not radiation using cGMP manufacturing methods to ensure the highest possible safety profile achievable. This can be accomplished because GFs and exosomes are less than 150 nanometers while all bacteria and any cell are microns in size (1,000 times larger). The bone marrow-derived MSC (BM-MSCs) growth factorsand exosomes are created with a proprietary method to maximize the numbers of specific anti-inflammatory and tumor suppressor growth factors and RNAs. The exosomes do not contain DNA. EVIP concentration and GF biomolecule content is evaluated for each production batch to verify every vial meets product specifications [7].

A literature review was performed to ascertain the safety profile of a bonemarrow-derived MSC active growth factor and exosome product [7]. The literature review focuses on exosome carcinogenesis and disease transmission potential. The purpose of this paper is to evaluate the safety profile of this BM-MSC EVIP containing over 800 different growth factors and over 30 billion exosomes per cc [7].

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Materials and Methods

Within the field of stem cell biology, it has become increasingly understood by researchers and clinicians that the clinical efficacy of Mesenchymal Stem Cells (MSCs) for regenerative medicine is not dependent on the living cells but the paracrine signaling of Growth Factors (GFs) and exosomes produced by those cells [8,9,10,11]. If enough signaling proteins and exosomes can be collected and protected from enzymatic degradation, live MSCs are not required. These acellular products are the future of regenerative medicine [12,-15]. A cellular exosomes, derived from BM-MSCs, provide a consistent product with extensive characterization which includes advanced particle analysis, proteomic evaluation, and USP<71> sterility assurance. Cytokine and growth factor identification and quantification are also performed. Think of acellular exosomes as a therapeutic quality product that is consistent, standardized, and quality tested regarding dose and activity [16-19].

The MSC produces numerous growth factor proteins capable of treating orthopedic pathology [20,21]. However, the most crucial paracrine method by which the MSC functions may be through the creation of the acellular structure of the exosome [22-27]. The exosome is a 30 to 150 nanometer (1 billionth of a meter) bi-phospholipid membrane-enclosed structure created by the endosome. An MSC (12 to 18 microns) is 1,000 times larger than an exosome. For comparison, the diameter of a hair is 80,000 nanometers. Exosomes contain growth factors, signaling lipids, and microand messenger RNA. The RNA contents in exosomes mediate most of their anti-inflammatory effects. The RNA is placed into an exosome along with numerous peptide growth factors and signaling lipids by the endosomes within the donor MSC [11,28-30]. The exact type and amount of growth factor proteins, signaling lipids, and RNA placed into an exosome are dependent on the surrounding microenvironment of the MSC [31]. The exosomes are released into the extracellular matrix and taken up by a receptor cell. The exosome RNA is then taken into the receptor cell ribosome where the RNA is translated to create numerous anti-inflammatory growth factors, chemokines, cytokines, and secretomes. Exosomes do not elicit acute immune rejection, and there is no risk for tumor formation [12-15]. The effects of exosome RNA may last months or longer as the receptor cell ribosomes continue to translate the donor RNA [8,9,15,32].

This the mechanism by which exosomes have shown safety and efficacy in treating orthopedic pathology [8,10,11,28,33]. This is illustrated in figure 1 and figure 2.

Results

To ascertain whether the BM-MSC exosome product has carcinogenic potential, a literature review was performed to determine the biologic mechanisms ofcancerous transformation ofa normal cell. Once the biology of this transformation is understood, we can evaluate the safety profileand carcinogenic potential of the BM-MSC exosome product.

What causes a cell to become cancerous?

Unlike bacteria or viruses, which infect the body from the outside, cancer originates in the body's own cells. The disease begins deep within the cell nucleus, in the chromosomes that contain our genes.

Of the approximately 22,000 genes in human cells only several hundred are involved in the process of cell division. These few genes ensure that cell division occurs in an orderly consistent manner. Each step in the process must occur in the right order, at the right time, with the right prompts, at the right pace and after a certain number of divisions the cell must undergo apoptosis [34].

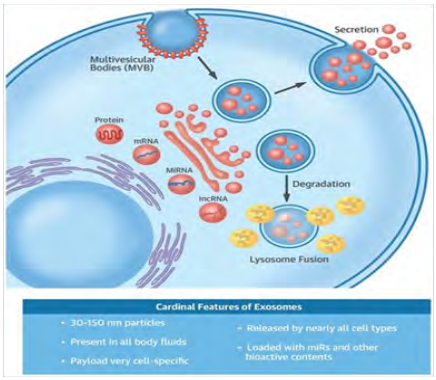

Figure 1: (Top) Schematic of exosome biogenesis. Exosomes arise from the fusion of surface membrane invaginations (multi-vesicular bodies) and the products of the Golgi apparatus. The resulting vesicles are either degraded by lysosomes or secreted as exosomes. (Bottom) Cardinal features of exosomes.

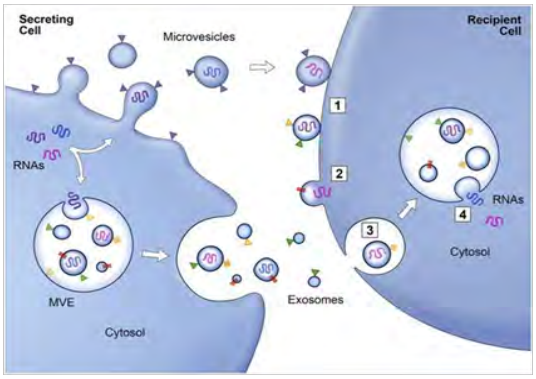

Figure 2: Exosome secretion and uptake.

Sometimes, a gene will acquire an abnormality that interferes with its ability to function. These abnormalities can take several forms:

- A mutation in which the DNA within the gene is miscoded or misspelled.
- A copying error, in which too many or too few copies of a gene are present.
- A translocation, in which a gene or portion of the gene gets sewn into the wrong section of the genome.

These errors can occur in a variety of ways. In some cases, they may be inherited from a parent. More often, however, they arise during one's life as a result of exposure to environmental hazards such as ultraviolet light from the sun or harmful chemicals such as those found in tobacco, or simply bad luck-a mistake made during the process of DNA duplication during cell division [35] (Figure 3).

Most of the time, these non-inherited errors-known as somatic mutations-can be corrected by the cell. Cells have a variety of

mechanisms for "proofreading" their DNA, for verifying that the letters of the genetic code are in the proper order and, when they are not, replacing them with the correctletters. Theproofing process is performed by polymerases that identify mismatches of the genetic code and then excise and repair theaberrations. When genetic derangements are so extensive in which normal cell function or cell division threatens to veer out of control, select genes order the cellto die for the good of the body as a whole (apoptosis or programmed cell death) [29].

Figure 3: DNA Sequencing can identify genetic defects and errors in the code.

When these corrections are not made, or when a diseased cell fails to self-destruct, cell growth and division can begin to break free of their constraints. As more mutations occur, affecting more aspects of cell life, a cell may grow without restraint, invade nearby tissue, drift to other parts of the body, hide from the immune system, the long-livedcell, in effect, becomes a cancer cell. The process usually occurs over several years [36].

Two primary types of genes that play a role in cancer are oncogenes and tumor suppressor genes.

Oncogenes

Proto-oncogenes are genes that typically help cells grow. When a proto-oncogene mutatesorbecomes overly abundant, it becomes a "bad" gene that can become permanently activated and thus unable to respond toroutine feedback checks and balances. When this happens, the cell can grow out of control, which can lead to cancerous growth. This mutated gene is called an oncogenes [36,37].

It may be helpful to think of a cell as a car. For it to work correctly, there need to be mechanisms to control its speed. A proto-oncogene functions much like a gas pedal. It helps the cell grow and divide. An oncogene could be comparedto a gas pedal stuck in the down position, which causes the cell to divide out of control.

A few cancer syndromes are caused by inherited mutations of proto-oncogenes that cause the oncogene to be continuously activated. However, most cancer-causing mutations involving oncogenes are acquired by external causes and not inherited. They generally activate oncogenes by:

- Chromosomal rearrangements: Changes in chromosomes that put one gene next to another, which allows one gene to activate the other.
- Gene duplication: Having extra copies of a gene, which can lead to the overproduction of the specific proteins?
- External radiation or chemical exposure resulting in defective gene sequences or gene promoter regions.

Tumor suppressor genes

Tumor suppressor genes slow cell division, repair mistakes in DNA or initiate programmed cell death. When tumor suppressor genes do not work properly, cells can grow out of control, which can lead to cancer.

A tumor suppressor gene is analogous tothe brake pedal of a car. It normally keeps the cell from dividing too quickly, just as a brake keeps a car from going too fast. When something goes wrong with the gene, such as a mutation, cell division can get out of control. A significant difference between oncogenes and tumor suppressor genes is that oncogenes are the result of proto-oncogene activation, but tumor suppressor genes cause cancer when they are inactivated.

Inherited abnormalities of tumor suppressor genes have been found in some cancer syndromes. They cause certain types of cancer to run in families although most tumor suppressor gene mutations are acquired, rather than inherited. For example, abnormalities of the *TP53* gene (which codes for the p53 protein) have been found in more than half of human cancers. Acquired mutations of this gene appear in a wide range of cancers [35-37].

The only published literature on whether cells used for regenerative medicine can cause cancer is by Hernigou [1]. The cells they analyzed were Bone Marrow-Derived MSCs. There is currently NO literature examining the risk of cancer from any other source including adipose, placenta, umbilical cord, or amniotic fluid [3-6].

There areconcerns regenerative cell-based therapies could result in an increased risk of tumor formation. Hernigou investigated the long-term risks for systemic and site-specific cancers in patients who had received bone marrow-derived stromal progenitor cells to treat orthopedic lesions [1,38].

Hernigou treated a total of 1873 patients from 1990 to 2006, with bone marrow derived concentrated MSCs. Patients were monitored for cancer incidence from the date of the first operation (1990) until death, or until December 31, 2011. The mean follow-up time was 12.5 years (range, five to twenty-two years). The average number of colony-forming unit fibroblasts returned to the patients was 483,000 fibroblasts (range, 62,000 to 2,095,000 fibroblasts). The primary outcome was to evaluate with radiographs and/or magnetic resonance imaging the risk of tumorigenesis at the cell therapy treatment sites. The secondary outcome was to assess the risk of cancer diagnosed in areas other than the treatment site during the follow-up period. The relative risk of cancerwas expressed as the ratio of the observed and expected number of cases, that is, the standardized incidence ratio, according to the cancer incidence in the French population.

No tumor formation was found at the treatment sites on the 7306 magnetic resonance images and 52,430 radiographs among the 1873 patients. Fifty-three cancers were diagnosed in areas other than the treatment site. On the basis of cancer incidence in the general population during the same period, the expected number of cancers was between ninety-seven and 108 for the same age and sex distribution. The range of the standardized incidence ratio for the follow-up period was between 0.49 and 0.54 (95% confidence interval, 0.30 to 0.80).

This study found no increased cancer risk in patients after application of cell-based therapy using bone marrow-derived stromal progenitor cells either at the treatment site or elsewhere in the patients after an average follow-up period of 12.5 years [1].

The EVIP created from BM-MSCs are created in a cGMP laboratory to produce an abundance of specific anti-inflammatory growth factors, RNA, and tumor suppressor proteins such as PTEN, TGF-b, and the following (Table 1).

CTACK	CCL27-Cutaneous T cell attracting chemokine	**Tumor Suppressor & Cell Survival**
DAN	**Differentially Aberrant in Neuroblastoma**	**Tumor Suppressor & Cell Survival-BMP Signal inhibitor**
FAS-L	CD95L	Tumor Suppressor, TNF Family & Immune System
HCC-4	CCL16 or LMC	Tumor Suppressor and Anti-Apoptosis
IGFBP4	Insulin Growth Factor Binding Protein #4	Tumor Suppressor & Cell Survival
IGFBP6	Insulin Growth Factor Binding Protein #6	Tumor Suppressor & Cell Survival
MSP	**MST1-Macrophage Stimulating 1**	**Tumor Suppressor**
OPN	Osteopontin	Tumor Suppressor, ECM Production, Inflammation Mediation

Table 1: List of tumor suppressor proteins present in the bone marrow derived MSC exosome product [35].

Discussion

Once the biology of carcinogenesis is understood, it becomes obvious BM-MSC derived exosomes cannot contribute to this process [29-31]. The BM-MSC exosomes are an ACELLULAR product. The EVIP is from a single 22 year old female donor who is registered with the FDA master file. The EVIP is filter sterilized. Based on the fact growth factors and exosomes are less than 150 nanometers while bacteria and cells are microns in size the EVIP can not contain any bacteria. The donor has been tested for the presence of any virus. The donor has been tested for any chromosomal abnormalities. The product is SAFE. The BM-MSCsgrowth factors and exosomes are created with a proprietary process to stimulate the production of specific anti-inflammatory and tumor suppressor growth factors and RNAs. The exosomes do not contain DNA or genes and CAN NOT cause cancer.

Peer reviewed published studies comparing BM-MSCs versus perinatal (Placenta, amniotic, Wharton's jelly or cord blood) derived MSCs clearly indicate that BM-MSCs have a much higher safety profile and yield higher quality exosomes that deliver a more favorable profile of signaling factors. Bone marrow derived MSCs are a much more characterized cell source. Over 63,000 peer reviewed papers have been published on bone marrow derived MSCs. This compares to 1,200 on perinatal derived MSCs. We are unaware of any IRB sponsored study utilizing a product from a perinatal source because of their lacking safety profile data.

Given the reported differences in safety, quality, and efficacy of exosome products, physicians MUST investigate the exosome product being considered beyond the sales and marketing brochures to ensure they provide their patients with the best chance for a safe and successful clinical outcome. Demand to know if the product contains any bovine derived proteins. Any detectable level of animal proteins in a product carries severe potential risk to the patient. Is the product sterilized with radiation? Is each batch of product from a different donor? Is the donor of each batch of product registered with the FDA? Does the product contain any maternal proteins? Does the product contain any DNA? These questions need to be accurately and honestly answered before any ethical physician can make the decision to use them on their patients.

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