Blasetti N, et al., J Stem Cell Res Dev 2020, 6: 034
DOI: 10.24966/SRDT-2060/100034

HSOA Journal of
Stem Cells Research, Development and Therapy

Review Article

Culture Media Supplements for *In vitro* Expansion of Umbilical Cord MSCs

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Abstract

Stem cell therapies are continually emerging to treat many diseases. Umbilical cord tissue has been shown to be a good source of stem cells, but the number of cells obtained is low, so *in vitro* expansion is needed to obtain good quality cells for clinical applications. The use of animal-free culture supplements is mandatory; so many alternatives are being investigated. In this brief review, we describe different culture supplements used for in vitro stem cell expansion and summarize our previous work in which we developed a methodology to obtain human serum and platelet lysate to be used as culture supplements.

Introduction

Stem cells or Mesenchymal Stem/Stromal Cell (MSCs) as they are commonly named have the capacity to replicate themselves into two identical cells or to proliferate and differentiate into specialized cells of different tissues [1-4]. They can be obtained from different tissues in the adult human body: bone marrow, adipose tissue, synovial tissue, dental pulp [3-10]. Nowadays MSCs derived from perinatal tissues such as placenta and umbilical cord areconsidered functionally better than stem cells derived from adult tissues because of their superior proliferation and engraftment capacity [11-13].

All of them have two main functions: regenerate damaged tissue (after trauma or disease) and regulate immune response. The mechanisms used by stem cells to regenerate or repair tissues are still being investigated. It is thought that besides the differentiation capacity, they stimulate resident stem or progenitor cells in the tissue to proliferate, differentiate and repair the damaged tissue [2,3,14]. This response is regulated by direct cell interaction and by secretion of bioactive factors.

Unfortunately, the number of stem cells obtained from different sources is low, so *in vitro* expansion is needed to reach the number of cells necessary for clinical application or preclinical research.

Tissue and Cell Culture

Tissue and cell culture was developed as a method to study animal cells behavior *in vitro*, free of *in vivo* variations. Even though it was stablished more than one hundred years ago, culture techniques are still being improved. To proliferate *ex vivo*, cells need to be fed with culture medium supplemented with growth factors and proteins, generally obtained from animal sources such as Fetal Bovine Serum (FBS) or Calf Serum (FCS). There is still no consensus on the best method of isolation and expansion of tissue and cells *in vitro*. Although with significant differences in the culture method, MSC expansion techniques must guarantee genetic stability and differentiation capacity after standard culture conditions [15].

Culture Supplements

Generally, the culture medium for cell expansion is supplemented with Fetal Bovine Serum (FBS), which provides all the growth factors necessary for cells to proliferate. But if these cells are intended for use in clinical applications, the use ofanimal derived components is discouraged by regulatory authorities, as there is a risk of animal disease transmission and immunological reactions [16-18]. So other supplement alternatives such as plasma, AB serum, platelet lysate and serum-free synthetic supplements are being investigated [19,20].

Current investigations recommend that cells should be grown in serum-free synthetic media or using human platelet lysate as a supplement [20,21]. Unfortunately, serum-free supplements are not approved by regulatory authorities in many countries, so many laboratories use in house prepared platelet lysate. Although it is recommended to obtain a pool of at least 10 units of platelets to eliminate the variability that may exist between units [22], the main disadvantage of this method is the increased risk of transmission of diseases by viruses not detected in serological examinations carried out in platelet units individually [23]. Therefore, individual platelets units should be used if cultured cells are intended for use in humans.

Wharton´s Jelly Derived Mesenchymal Stem Cells Expansion Using Human Serum or Platelets Lysate

Within the past years, umbilical cord tissue was found to be a source of mesenchymal stem cells with attractive advantages: noninvasive collection, low risk of infection, multipotency, higher growth rate when cultured in vitro and low immunogenicity with good immunosuppressive ability. Umbilical Cord Mesenchymal Stem Cells (UCMSCs) are obtained from Wharton's jelly tissue, which is located between the veins and artery inside the umbilical cord.

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Citation: Blasetti N, Rico JP, Colman D, Contreras IM, Chillik I (2020) Culture Media Supplements for *In vitro* Expansion of Umbilical Cord MSCs. J Stem Cell Res Dev Ther 6: 034.

Received: April 07, 2020; **Accepted:** April 28, 2020; **Published:** May 05, 2020

In previous work we compared the use of human serum and platelets lysate for UCMSCs expansion. Briefly, we developed a methodology to obtain human serum and platelet lysate and we used them as culture media supplement. Morphology, immunophenotype and self-renewal capacity of cells grown in human serum or platelets lysate were compared. Cells grown in both culture conditions were positive for the expression of mesenchymal stem cells markers (CD73, CD90 and CD105) determined by flow cytometry. Cultures with platelets lysate supplemented mediaproduced higher cell numbercompared to serum supplemented media [24].

We were able to obtain a culture media supplement derived from human platelets that is a better choice than other supplements like human serum. Moreover, the use of platelets lysate allowed to establish cell cultures free of animal components, so they are suitable for cell therapy.

Conclusion

Since adult stem cells were discovered in human tissues, stem cell therapies have continually emerged to treat many different diseases, regenerate damaged tissues or regulate immune function. By April 2020, a total of 7834 clinical trials comprising stem cells treatments are registered at clinicaltrials.gov database, which lists privately and publicly funded clinical studies conducted around the world (search words: “stem cell”), and a total of 466 clinical trials for treatments using umbilical cord stem cells treatments (search words: “umbilical cord stem cell”). So, it is important to develop new and safer cell and tissue culture methods to obtain good quality cells to be used in clinical applications. This includes the use of GMP culture media, animal free media supplements, good quality flasks and plastic consumables, as well as safe cryogenic technologies.

The use of animal free media supplements is mandatory if cells are intended to be used in human cell therapies, so many options arose in recent years. Platelets derived growth factors obtained after platelets lysis have shown to be a good option because they are easy to obtain, safe and provide good quality growth factors for cells in culture.

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