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Enhancing osteogenic differentiation in human umbilical cord mesenchymal stem cells: A review

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Abstract

Background: The article aims to review osteogenic differentiation enhancement in human Umbilical Cord Mesenchymal Stem Cells (hUCMSCs).

Material and Methods: The literature review was carried out in PUBMED with the keywords: human Umbilical Cord Mesenchymal Stem Cells (hUCMSCs) and osteogenic differentiation.

Conclusions: Many research investigated the impact of different substances on the osteogenic differentiation of hUCMSCs and the appliance by which these substances promote osteogenesis in hUCMSCs which are a potential source for bone regeneration.

Keywords: Osteogenic Differentiation; Umbilical Cord; Mesenchymal Stem Cell; Bone Regeneration; Enhancement.

1. Introduction

Stem cells can be found in the human body. These cells have the ability to not only self-renew but also differentiate into every other kind of cell found in the body. To a certain extent, stem cells may be found in both embryonic and adult cells [1]. It is possible to categorize cells as pluripotent, totipotent, oligopotent, unipotent, or multipotent based on their tendency to develop into certain cell types. In animal and human models of regenerative medicine, mesenchymal stem cells (MSCs), which are also often referred to as multipotent stromal cells, have shown a remarkable capacity to produce innovative therapies [2]. Cells that exhibit the presence of CD73, CD90, and CD105 markers, but lacking the presence of CD34, CD14, CD45, or CD11b markers, are categorized as Mesenchymal Stem Cells (MSCs). One notable feature of MSCs is their enhanced ability to transform into multiple types of cells, such as chondrogenic, myogenic, osteogenic, adipogenic, and neurogenic-like cells [3].

Umbilical cords have a plentiful supply of mesenchymal stem cells. When stem cells are cryopreserved immediately after birth, they have a high probability of surviving and may be used in future operations to avoid potentially deadly diseases [1]. The human umbilical cord mesenchymal stem cells, also known as hUCMSCs, have the ability to renew themselves and transform into different type of cells. Genes that are associated with cell specialization, anti-inflammatory response, and immunological regulation are also included in the expression repertoire. The evidence suggests that human umbilical cord mesenchymal stem cells are critically necessary for the regulation of inflammation, cell proliferation, and differentiation. Recently, human umbilical cord mesenchymal stem cells (hUCMSCs) have garnered a lot of attention as a cell source for application in regenerative medicine [4].

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Because of their very high ability for proliferation, human umbilical cord mesenchymal stem cells (hUCMSCs) are also capable of facilitating the creation of osteoblasts. Research has shown that hUCMSCs differentiate into the osteoblast stage more quickly and efficiently compared to different forms of mesenchymal stem cells. Enhancing hUCMSCs with substances may further increase their osteogenic differentiation ability [5] [6]. Therefore, this article aims to review the enhancement of osteogenic differentiation in hUCMSCs.

2. Material and methods

2.1. Search Strategy

For the purpose of this study, we investigated the English-language literature on osteogenic differentiation in human umbilical cord mesenchymal stem cells by using the databases Science Direct, PUBMED, and Google Scholar. Research and literary studies conducted between the years 2019 and 2024 were included. It was determined that osteogenic differentiation, enhancement, and mesenchymal stem cells derived from human umbilical cord were the parameters for the search.

3. Results and discussion

3.1. Metformin enhances osteogenic differentiation in hUCMSCs

The research conducted by Lei *et al.* (2021) revealed that metformin enhances the gene expression related to stem cells, such as SOX2 and NANOG in hUCMSCs. When it comes to regenerative medicine, the ability of stem cells to develop into differentiated cells is very important. Alizarin red-stained calcium nodules were formed in the culture medium by human umbilical cord mesenchymal stem cells that were treated with metformin. It also showed an increase in the levels of osteogenic markers ALP, OCN, and RunX2. The article concludes that metformin promotes osteogenesis and may promote potential application to enhance bone regeneration in the future [7].

3.2. Liu’s Zhenggudan No. 2 Formula enhances osteogenic differentiation in hUCMSCs

In the study that Deng et al. (2022) conducted, they investigated the effectiveness of Liu's Zhenggudan No. 2 Formula (LZF2) in enhancing osteogenic differentiation. It is a drug called Liu's Zhenggudan No. 2 (LZF2) that assists in the healing of fractures. It is made up of the following ingredients: Caesalpinia sappan, Rehmannia glutinosa, Syzygium aromaticum, Acacia catechu, and Costustoot. LZF2 was administered to rats, and subsequently the serum that contained the medication was extracted. Under carefully monitored and regulated laboratory circumstances, the purpose of this treatment was to stimulate the osteogenic growth of human umbilical cord mesenchymal stem cells, also known as hUCMSCs. When compared to the group that served as the blank control, the groups that were treated with COI or high-concentration LZF2 exhibited significantly greater levels of ALP activity, a rise in the number of calcified nodules, and a higher percentage of OCN content. Consequently, it may be deduced that there is an increasing capacity in osteogenic differentiation [8].

3.3. Asperosaponin VI enhances osteogenic differentiation hUCMSCs

Asperosaponin VI (ASA VI), the primary active component of Radix Dipsac, was the subject of research conducted by Niu et al. (2022) to determine whether or not it has the ability to stimulate osteogenic differentiation in hUCMSCs. The authors used the quantitative reverse transcription-PCR technique to evaluate the levels of gene expression related to bone formation. The levels of osteogenic mRNA (OPG, OPN, TGF-β, and RUNX2) in hUCMSCs were considerably upregulated following three or five days of exposure to ASA VI. The researchers also investigated the way in which the oestrogen signaling system influenced the process by which these cells transformed into bone cells throughout the period of development. For the purpose of preventing ASA VI from binding itself to the oestrogen receptor, fulvestrant was used. The levels of expression of the bone marker genes CML2 and ESR2 were found to be considerably different between the groups that were treated with ASA VI and those that served as the control. This discovered difference was judged to be statistically significant. The modifications were substantial according to statistical analysis. On the other hand, the group that was given fulvestrant showed much lower levels of these markers. According to the findings of this study, ASA VI can be used for the purpose of stimulating human umbilical cord mesenchymal stem cells. It is very conceivable that this will result in the synthesis of MMP2 as well as the development of osteoblasts. Fulvestrant, on the other hand, is accountable for ensuring that similar undesirable outcomes do not materialize in the future. The study's findings suggest that ASA VI stimulated osteogenic differentiation in hUCMSCs [9].

3.4. Decellularized Periosteum-Derived Hydrogels enhances osteogenic differentiation hUCMSCs

An example of a possible use for periosteal hydrogels is to stimulate osteogenesis in human umbilical cord mesenchymal stem cells (hUCMSCs). This study made use of a hydrogel that was produced from periosteum that had been decellularized, which means that its cells had been removed altogether. Hydrophilicity, rheological characteristics, microstructure, and gelation rate were some of the physicochemical aspects that were taken into account in this investigation. The purpose of this study was to evaluate the cellular activity and osteogenic growth pathways by growing human umbilical cord mesenchymal stem cells (hUCMSCs) on coverslips that were coated with dPH and Matrigel. This particular work was carried out in order to accomplish this aim. Compared to Matrigel, the growth of human umbilical cord mesenchymal stem cells (hUCMSCs) on dPH revealed significantly greater levels of osteopontin (OPN), runt-related transcription factor 2 (RUNX2), osteocalcin (OCN), and alkaline phosphatase (ALP). These results were seen in comparison to the development of hUCMSCs on Matrigel. Alizarin red S staining (ARS) measurements were taken over a period of time, and they indicated that the mineralized matrix in the dPH group was 9.74 times larger than the Matrigel group. In addition, quantitative analysis assisted in providing support for the findings. The results of this research suggest that the incorporation of dPH into stem cells that have been extracted from human umbilical cord may be able to trigger the production of osteogenic cells in these cells [10].

3.5. Static magnetic field enhances osteogenic differentiation hUCMSCs

The effects of a continuous magnetic field on the proliferation and differentiation of human umbilical cord mesenchymal stem cells (hUCMSCs) were explored by Chang et al. (2020). When it came to the culture of human umbilical chord mesenchymal stem cells (hUCMSCs), it was found that a magnetic field of 0.4 T was the most effective. For the purpose of conducting research on human umbilical cords, cells were extracted from the cords. Procedures involving alkaline phosphatase activity and alizarin red staining were carried out in order to achieve the objective of correctly measuring osteogenic differentiation. After doing study for a week, specialists probed further into the two different civilizations. Alkaline phosphatase (ALP) activity is an early indicator of bone tissue formation, despite the fact that exposure to SMF has no effect on this process. When human umbilical cord mesenchymal stem cells, also known as hUCMSCs, were exposed to an osteogenic medium, which was then followed by a stationary magnetic field (SMF), it was demonstrated that the activity of human umbilical cord mesenchymal stem cells, the activity of which was also known as hUCMSCs, was significantly increased. In addition, cells that had been treated with SMF produced ALP genes at a higher level. Upon completion of seven days of growth, the findings of alizarin red staining demonstrated that cells treated with SMF had a greater concentration of calcified nodules in comparison to cells treated in a sham method. The results of this study demonstrate that the application of a constant magnetic field to mesenchymal stem cells isolated from human umbilical cords has the potential to induce their osteogenic differentiation [11].

3.6. Arginyl-glycyl-aspartic acid (RGD) functionalized polyurethane scaffolds enhances osteogenic differentiation hUCMSCs

An arginyl-glycyl-aspartic acid (RGD) peptide has the capability to attach to proteins that are present in the extracellular matrix. These proteins have the ability to bind to the peptide. The most essential thing is that this peptide could influence the activity of stem cells when they are in a biomaterial environment. This study was conducted with the intention of investigating the method by which RGD molecules adhere to porous polyurethane scaffolds that have a "real thickness" of 5 millimeters by 5 millimeters by 5 millimeters. In the course of this investigation, one of the most important goals is to ascertain whether or not mesenchymal stem cells derived from umbilical cord may grow into osteogenic cells. The survival, activity, and mineral synthesis of the hUCMSCs were evaluated utilizing a gene expression study on scaffolds made of polyurethane-RGD (PU-RGD). A total of two unique sets of PU-RGD were evaluated during the length of the trial, with doses of 100 and 200 μg/ml. Additionally, a control group and a benchmark for the PU scaffolding were included into the evaluation. The researchers implanted scaffolds that contained 160,000 mesenchymal stem cells that were extracted from the umbilical cord of a human individual. These cells were collected from the umbilical cord. For a period of seven days, it was required to culture these cells in the maintenance medium. This was done so that the potential for development that these cells had could be used to its fullest extent. The authors conducted research to study the link between the functionalization of RGD and the proliferation of mesenchymal stem cells derived from human umbilical cord. The findings demonstrated that there is a correlation between the two. During the course of the experiment, the authors made the revelation that scaffolds that contained 100 μg/ml of RGD exhibited a bigger number of osteogenic genes and caused the production of proteins. After twenty-one days had passed, the R100 group had achieved results that were superior to those acquired by the R200 group as well as the control group. The p-value for collagen type I was found to be 0.01 after 21 days, while the p-value for osteonectin was found to be 0.05. Both of these values were determined to have significant. On the basis of statistical analysis, it was found that both of these values are significant. Given the findings of this study, it would seem that PU-RGD has the ability to function as a stimulant for the osteogenic differentiation of hUCMSCs [12].

3.7. METTL3 enhances osteogenic differentiation of hUCMSCs by up-regulating m6A modification of circCTTN

A variety of pathological processes may be affected by the alteration of certain circRNAs by N6-methyladenosine (m6A). The protective mechanisms of the immune system, the differentiation of cells, and the development of cancer are all processes that are included in these processes. The methyltransferase-like 3 (METTL3) enzyme is responsible for osteoclast bone resorption. This is accomplished by methylating circ_0008542 on the basis of the m6A level. There was a strong correlation between osteogenic differentiation and METTL3, which is a protein that had a role in the alteration of m6a. The researchers decided to overexpress METTL3 in order to study the effect that this would have on the levels of circCTTN m6A and the osteogenic differentiation of cells. In order to determine the extent to which the recombinant adenovirus influenced the osteogenic differentiation of hUCMSCs after its application to boost METTL3 expression, Western blotting and quantitative real-time PCR measurements were carried out. It was shown that the levels of Runx2, ALP, and COL1 were significantly different between the control group and the hUCMSCs overexpressing METTL3 group. This difference was statistically significant. These findings indicate that METTL3 enhances the osteogenic differentiation in hUCMSCs [13].

3.8. Linc02349 enhances osteogenic differentiation of hUCMSCS

Through the use of human umbilical cord mesenchymal stem cells, researchers Cao et al. (2020) investigated the manner in which the IncRNA profile Linc02349 affects osteogenic differentiation. Over the course of seven days, the researchers monitored the levels of alkaline phosphatase (ALP), which is an enzyme that plays a role in the process of osteogenic differentiation. According to the results of this analysis, there is far more ALP activity than was anticipated. Experiments were carried out on the twenty-first day in order to confirm the existence of calcium nodules that were elevated, which were also related with Linc02349. A staining with alizarin red S was conducted as part of the procedure. The levels of Dlx5, OPN, and OSX proteins were found to be greater in cells that had been overexpressed using Linc02349. In spite of this, the presence of Linc02349 knockdown cells results in a decrease in both the activity of ALP and the number of calcium nodules. According to the results, Linc02349 promotes osteogenic growth in human umbilical cord mesenchymal stem cells (hUCMSCs) [14].

3.9. Calcium hydroxide enhances osteogenic differentiation of hUCMSCs

It is hypothesized by researchers Priyo et al. (2021) that calcium hydroxide would be able to provide assistance to human umbilical cord mesenchymal stem cells throughout the process of bone regeneration. For the purpose of this investigation, human umbilical cord stem cells (hUMSCs) were cultured in alpha MEM with 0.1 μg/ml of calcium hydroxide included in the composition. Following the twenty-first day, the use of red S staining allowed for the observation of osteogenic differentiation. According to the findings, the group that received hUCMSCs had a considerably greater incidence of mineralization nodules in comparison to the group that served as the experimental control. Therefore, it is possible to make use of calcium hydroxide in order enhance the osteogenic differentiation capacity of human umbilical cord mesenchymal stem cells [15].

3.10. Royal jelly enhances osteogenic differentiation of hUCMSCs

Royal jelly is said to be one of the numerous products that worker bees are responsible for manufacturing. Because the protein concentration is high, it promotes the proliferation and growth of cells. The primary objective of this experiment was to ascertain whether or not royal jelly had an impact on the osteogenic growth of human umbilical cord mesenchymal stem cells. In order to produce the royal jelly (RJ) groups, 10% fetal bovine serum (FBS) was combined with RJ dosages of either 0.075 mg/ml or 0.150 mg/ml. In addition to the minimum essential medium (MEM), the control group was given a 10% supplement of fetal bovine serum (FBS). After twenty-one days, the findings of the alizarin red staining make it abundantly evident that there were significant differences between the two groups, which were the treatment group and the control group. According to the results of the research, royal jelly may be able to enhance the osteogenesis of hUCMSCs [16].

3.11. Epigallocatechin-3-gallate-loaded chitosan microspheres incorporated with chitosan/carboxymethyl cellulose/montmorillonite scaffolds enhance osteogenic differentiation of hUCMSCs

To determine how the green tea flavonoid epigallocatechin-3-gallate (EGCG) affects osteogenic development in human umbilical cord mesenchymal stem cells (hUCMSCs), Wang et al. conducted research in 2022. The chitosan microspheres were of higher quality as a result of the use of emulsified EGCG. Building scaffolds out of montmorillonite, carboxymethyl cellulose, and chitosan was the first step in the technique, which was followed by the addition of EGCG-packed chitosan microspheres (ECM). Both the alizarin red staining and the ALP activity were used in order to investigate the osteogenic differentiation. Calcium nodules were found to have formed, and the results showed that the activity of the ALP enzyme had risen. In addition, a quantitative real-time polymerase chain reaction, which is often referred to as QRT-PCR, was

explored in order to study the genes that are associated with osteogenic differentiation. This category contains a number of genes, including OPN, Runx2, Col-1, ALP, and OCN, among others. As a result of the administration of EGCG, there was seen to be a significant increase in the expression of genes. The potential of EGCG to promote the growth and maturation of human umbilical cord mesenchymal stem cells has been demonstrated to be favorable, as revealed by research [17].

3.12. Rutin enhances osteogenic differentiation of hUCMSCs

Using human umbilical cord mesenchymal stem cells (hUCMSCs), this study investigated the influence that the naturally occurring bioflavonoid rutin has on the process of osteogenesis. The goal was to get a deeper comprehension of the function that rutin plays in the formation of osteogenic processes. Through the investigation of gene expression patterns associated with bone tissue formation, the researchers aimed to determine the extent of their influence. Runx2, OPN, and OCN are all increased at the cellular level as a result of treatment with rutin. When stained with alizarin red, the experimental group exhibited a considerably greater number of calcified nodules in comparison to the group that served as the control. Considering these data, it seems that rutin may hasten the osteogenic process of human umbilical cord mesenchymal stem cells [18].

3.13. Total flavonoids from Arachniodes exilis enhances osteogenic differentiation of hUCMSCs

There were a variety of doses of total flavonoids extracted from Arachnium exilis (TFAE) that were administered to the hUCMSCs. For the purpose of this research, there were four treatment groups, each of which had a different quantity of TFAE. These concentrations were 0μg/mL, 1μg/mL, and 5μg/mL. An additional group that was included in the research was a control group. On the ninth day, alizarin red was used in order to determine the level of calcification that had occurred. During the course of the tests, it was determined that the ideal concentration of TFAE was 5μg/mL. The findings of the alizarin staining were supported by the fact that the activity of alkaline phosphatase (ALP) was greatly raised by the administration of TFAE at a dosage of 5μg/mL during the third and seventh day. On the ninth day, a comparison was done between the human umbilical cord mesenchymal stem cells (hUCMSCs) that were treated with 5μg/mL TFAE at the same concentration and the control group, which exhibited significantly higher levels of expression of Col2s2, OPN, Osx, and Runx2. There is a possibility that TFAE has the capacity to enhance osteogenesis in hUCMSCs [19].

3.14. Aligned PLGA/SrCSH composite scaffolds enhance osteogenic differentiation of hUCMSCs

From the findings of this study, it has been shown that the incorporation of strontium-doped α-calcium sulfate hemihydrate (SrCSH) into poly(lactic-co-glycolic acid) (PLGA) scaffolds has the potential to enhance the osteogenic capacity of human umbilical cord mesenchymal stem cells (hUCMSCs). Increases in Runx2 expression and ALP activity were seen when a-Plaga/SrCSH scaffolds, which contain a high concentration of Sr, were used in the experiment. Morover also promoting the expression of OCN and COL-I. These findings indicate that aligned PLGA/SrCSH composite scaffolds enhance osteogenic differentiation of hUCMSCs. [20].

4. Conclusion

Scholars have conducted research to determine how the osteogenic growth of human umbilical cord mesenchymal stem cells, also known as hUCMSCs, is affected by a number of different substances. These cells have the potential to be used in the future to enhance bone regeneration. Metformin, rutin, asperosaponin VI, calcium hydroxide, royal jelly, epigallocatechin-3-gallate, and Liu's formula for zhenggudan number two have all been put through their paces in the laboratory. At specific concentrations, these substances raise the expression of osteogenic markers and mineralization, which in turn improves the osteogenic characteristics of human umbilical cord mesenchymal stem cells (hUCMSCs) both in vitro and in vivo. In addition, the study investigated the ways in which these substances enhance osteogenesis in human umbilical cord mesenchymal stem cells (hUCMSCs), suggesting that they might be valuable agents for enhancing the capacity for bone regeneration of hUCMSCs.

Compliance with ethical standards

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All author acknowledged their equal contribution, read the manuscript, and gave their approval.

Disclosure of Conflict of interest

We declare that there was no major conflict of this article.

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