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Transitioning from fetal bovine serum to platelet lysate: A novel epoch in stem cell advancement

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Abstract

Culturing of mesenchymal stem cells (MSCs) for different cell therapies requires advancements to enable routine application in clinical environments. The primary concern pertains to the utilization of reagents derived from animals, particularly the incorporation of fetal bovine serum (FBS) into the culture medium. The human platelet lysate (HPL) has emerged as an excellent supplement for a viable animal-free alternative and MSC culture. Most of the researchers focused on the proliferation rates of cells grown with FBS and HPL. Moreover, the HPL was able to enhance the secretion of vascular endothelial growth factor and maintain the immunomodulatory function of various cell types. This mini-review presents novel contributions from recent papers, highlighting the superior efficacy of HPL over FBS, which may facilitate the scientific community's shift towards cellular growth for various clinical applications.

Keywords Platelet lysate, mesenchymal stem cells, regenerative medicine

1. Introduction

The application of mesenchymal stem cell (MSC) therapies is contingent upon implementing standardized *in vitro* expansion protocols. Compliance with the regulations established by the European Medicines Agency is essential for the manufacturing of MSC products intended for clinical use [1]. Traditionally, Fetal Bovine Serum (FBS) has been the standard for cell expansion; its use is associated with concerns regarding xenoimmunization, the transmission of pathogens, and ethical considerations surrounding its collection [2]. This situation has catalyzed a heightened interest in alternatives such as Human Platelet Lysate (HPL), which is a rich source of bioactive molecules. The preference for pooled HPL over FBS in regenerative medicine is influenced by the potential risks of viral and prion infections and their implications for immune responses during MSC culture [3]. Innovative MSC expansion strategies are essential, especially through the incorporation of HPL. Although numerous studies indicate favorable outcomes, obstacles persist regarding disease transmission and cellular proliferation [4]. In this mini review, we seek to provide the most recent studies on the application of HPL in cell culture systems, showcasing the advantages of HPL over FBS.

2. Platelet lysate production and composition

Platelet lysate (PL) is typically obtained from fresh anti-coagulated blood. Briefly, anti-coagulated blood is subjected to mild centrifugation, allowing for the separation of Platelet Rich plasma (PRP) from the hematocrit. Next, the PRP is processed through freeze thaw cycles, following by another round of hard centrifugation and filtration. The resulting product from this filtration is referred as PL [5]. In addition to the abundance of plasma proteins, electrolytes, and minerals, PL contains a variety of growth factors (Platelet derived growth factors (PDGF), Insulin like growth factor (IGF-1) and Tissue growth factors (TGF-β), Vascular Endothelial growth factor (VEGF) and Epidermal growth factors (EGF). It is noteworthy that the repeated freeze thaw cycles of PRP lead to significant disruption of platelet structure, making PL superior to FBS and PRP due to its enhanced stability and better growth factors profile [6].

The main component identified in the PL is Platelet derived growth factor (PDGF), a key protein that resides in the α-granules of platelets. The PDGFR functions as a receptor for PDGF and is integral to the process of cellular differentiation, proliferation and migration, which are essential for embryonic development and healing of tissue damage [7]. Another significant growth factor

prevalent in PL is Vascular endothelial derived growth factor (VEGF), which primarily facilitates angiogenesis. Unlike FBS, the PL is rich in VEGF, thereby validating its preference for widespread applications in regenerative medicine [8]. Platelet derived transforming growth factor beta (TGF-β) is also abundantly present in PL, as it promotes cellular proliferation through the deposition of extracellular matrix and supporting in the differentiation of cells to chondrogenic lineages [9, 10]. Insulin like growth factors (IGFs) serve as another component of PL. They promote overall cell growth and survival, and specifically facilitate the transformation of cells into osteoblasts through the process of collagen synthesis [11]. Apart from the previously discussed growth factors, PL is rich in a variety of minerals, ions, proteins and substances that encourage growth.

3. Platelet lysate use in cell culture systems

There is undeniable fact that FBS maintains its position as well-established cell culture supplement, however, due to concerns regarding animal welfare, the transmission of zoonotic disease and other factors as outlined in Table 1, PL is highly preferred and recommended as a cell culture supplement. When compared with FBS, incorporation of autologous PL in MSCs culture did not adversely impact cellular proliferation and viability, but instead augmented their genetic potential for multilineage differentiation [12]. To fully leverage PL, *Rashid et al*. have advocated the utilization of autologous PL for the *in vitro* culture of MSCs. In this study, the treatment groups enriched with 7.5% and 10% autologous PL exhibited significantly improved ($p < 0.001$) cellular viability, growth, PDGF profile and cell migration in comparison to the treatment groups that received same doses of FBS [13]. Moreover, another study illustrated how stem cells harvested from Wharton's jelly grow more efficiently and rapidly than those sourced from umbilical cord blood in a 100% to 60% ratio of HPL [14]. In HPL culture, the cells show a shiny, small, and round morphology and proliferate faster [15], whereas in FBS culture, the cells are larger, more diverse, and proliferate more slowly. Not only for the *in vitro* culture, but the utilization of HPL for cell growth is beneficial for regenerative purposes, as it is economical, safe, and has strong proliferative properties [15]. A recent study explored the importance of heparinized HPL in the MSC differentiation protocol in which the authors indicated that both types of HPL, regardless of the presence of heparin, promote osteoblast proliferation, viability, and mineralization required for hydroxyapatite formation, facilitate rapid population doubling, and simultaneously enhance the efficiency of osteoblast culture for therapeutic uses. Notably, the addition of heparin to HPL enhanced osteogenic markers in cultured osteocytes, emphasizing the need to modify formulations to meet different clinical specifications [16].

In another research, human umbilical vein endothelial cells (HUVEC) were used with HPL, indicating that the use of HPL is both a cost-efficient and proficient means for enhancing the proliferation of endothelial cells, while also holding significant potential for research and therapeutic applications. Additionally, the efficacy of HPL surpassed that of commercial proliferative media, allowing these cells to be maintained in culture for a long period [17]. Furthermore, *Wendland et al*. [18] significantly advanced the field of platelet derivatives by devising a method for the production of Lyophilized HPL (L-HPL). Their evaluation of L-HPL against fresh HPL indicated no significant discrepancies in quality control parameters, concentrations of growth factors, or functionality of hMSCs, thus affirming lyophilized HPL's viability as a cell culture supplement. These results highlight the potential of lyophilized HPL as a sustainable and ethical alternative to animal serum in biomedical research and drug development. According to *Lim et al*. [19] the method used for preparation plays a crucial role in influencing the biological properties of HPL and the effectiveness of MSC culture. The addition of calcium chloride for HPL production [15], serve as a promising results in the umbilical cord derived MSC size, and overall morphology as compared to fibrinogen depleted HPL and FBS in the field of regenerative medicine. This investigation emphasizes the critical nature of preparation methods in the optimization of HPL for cell culture and therapeutic use, suggesting that the mechanical method could lead to a reduced quantity of growth factors as a result of damage sustained during freezing and thawing. Based on the essential role of platelets in tissue repair, HPL's richness in bioactive components has increasingly found its way into regenerative medicine and clinical practices. The major limitation of HPL use in MSC differentiation is the lack of their standardization in manufacturing and cytokines, growth factors, minerals and vitamins presence. As early as 2019, the International Society of Blood Transfusion (ISBT) Cell Therapy Working Group issued a position statement regarding the production and quality criteria for HPL (summarized in Figure 1) [20]. Consequently, the diverse benefits of HPL render it essential for the progression of regenerative therapies.

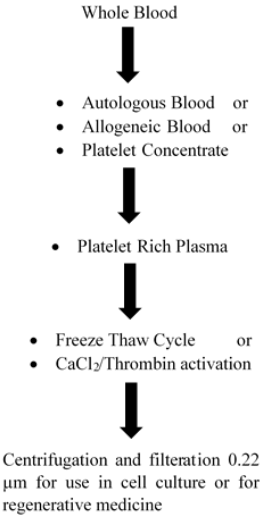

Figure 1 Preparation procedure of allogeneic/autologous platelet concentrate and platelet lysate.

Table 1 Comparative features between FBS and HPL.

Characteristics/ Features	Fetal Bovine Serum (FBS)	Human Platelet Lysate (HPL)
Origin/source	Extracted from the blood of bovine fetuses obtained during the slaughter process	Developed from pooled human blood platelets, confirming that it is a xeno-free, or animal product-free, supplement that is appropriate for clinical therapies.
Composition	A sophisticated blend comprising more than 1,000 distinct components, which encompasses a diverse range of growth factors, proteins, hormones, and vitamins	This formulation features a highly concentrated combination of human-specific growth factors, hormones, and proteins that are naturally liberated from lysed platelets. Notable constituents include VEGF, IGF-1, TGF-β, and PDGF
Consistency	Generally demonstrates a more stable composition and established quality assurance measures as a result of its extensive utilization in research	Possibility of high variability from batch to batch due to the pooled sources from human donors; however, this can be addressed by employing standardized production method
Immunogenicity	Includes foreign, xenogeneic proteins that may elicit an immune response when cells cultured in it are utilized in clinical application	Presents a reduced likelihood of inducing an immunological reaction, particularly in allogeneic contexts involving human cells. Although allogeneic hPL may still pose certain risks, it is typically regarded as a safer alternative to FBS for human cell therapy
Pathogen risk	There exists a potential risk of transmitting zoonotic disease	As a product derived from humans, it poses a risk of transmitting infectious diseases, including HIV, hepatitis B, and C, despite the implementation of stringent testing protocols designed to reduce this risk
Ethical concerns	The production of this raises considerable ethical issues pertaining to animal welfare	It encompasses ethical considerations concerning consent and the possible health risks faced by human blood donor
Cell proliferation	Facilitates the growth and proliferation of cells, yet is frequently surpassed by hPL when it comes to human cell	Typically exhibits enhanced proliferative effects on hMSCs in comparison to FBS, allowing for more rapid expansion
Cell morphology	Typically accommodates a more standard cell size and shape	It can encourage a distinct cell morphology in comparison to FBS, frequently leading to smaller, more elongated cells
Functional properties	Exhibits well-documented and effective, albeit occasionally less potent, effects in comparison to hPL for certain human applications	Demonstrates the ability to preserve or improve essential cellular characteristics, including differentiation potential and immunomodulatory functions, across a range of human cell types
Cost and availability	It is readily and consistently obtainable from various suppliers, rendering it a dependable and typically more affordable choice for fundamental research	The production process can be intricate and expensive and may have restricted commercial availability, contingent upon the supplier and the manufacturing method

5. Conclusion

This mini review presents reviews and original research articles that illuminate the progress made in stem cell development using PL, paving the way for future regeneration studies. PL provides a safer, more ethically responsible, and frequently more effective alternative to FBS, especially when cultivating human cells for clinical and therapeutic applications, owing to its human origin and high, consistent levels of regenerative growth factors. Nevertheless, the challenges associated with the production and application of PL must not be overlooked. Currently, the range of PL applications is extensive for autologous regenerative purposes; however, for large-scale *in vitro* use, it requires the establishment of widespread standardized protocols and validation. The production of PL on a large scale, along with the consistency across different batches and the applications of both autologous and allogenic types, calls for further exploration to identify their potential future uses in research and translational medicine. Nonetheless, as we investigate the inherent complexities of stem cell biology and its applications, cell growth and Good Manufacturing Practices (GMP) are critical to fully realizing the capabilities of this groundbreaking field. With careful handling of the scientific, ethical, and regulatory frameworks, stem cell research has the potential to open new horizons in medicine and improve the quality of life for countless people around the world.

Author Contributions

The tasks of conceptualization, writing, and the preparation of the original draft were carried out by ES and MAS. Both authors have reviewed and consented to the final version of the manuscript.

Conflict of Interest Statement

Not Applicable.

Data Availability Statement

The main manuscript file contains all the necessary data.

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