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Therapeutic Potential of Rat White Adipose MSCs: Phenotypic Stability and High Immunomodulatory PGE2 Secretion

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Abstract | Mesenchymal stem cells (MSCs) represent promising therapeutic agents in regenerative medicine, with adipose tissue emerging as an advantageous source due to its accessibility and high stem cell yield. Despite extensive research on MSCs, significant knowledge gaps persist regarding rat white adipose-derived MSCs (RWA-MSCs), particularly their phenotypic stability during extended culture and immunomodulatory prostaglandin E2 (PGE2) secretion capabilities. This study aimed to characterize RWA-MSCs immunophenotypically and evaluate their therapeutic potential through PGE2 secretion analysis. White adipose tissue was isolated from rats (*Rattus norvegicus*). Immunocytochemistry assessed surface markers (CD105, CD90, CD73, CD45) at third passage following International Society for Cellular Therapy criteria. PGE2 levels were quantified using ELISA in standard and secretome media conditions. Cells demonstrated robust growth characteristics, 70-80% confluence at fourth day of first passage and maintained consistent proliferation which demonstrated 60-70% confluence at second day of thirth passage. Immunophenotypic analysis revealed high expression of mesenchymal markers: CD105 (96.2%), CD90 (99.3%), CD73 (95.7%), with minimal hematopoietic marker CD45 (1.7%). Notably, secretome media induced significantly higher PGE2 production (5.6865±0.492 ng/mL) compared to standard serum-supplemented media (4.9428±0.098 ng/mL), representing 15.1% increase exceeding therapeutic immunomodulation thresholds. RWA-MSCs exhibit exceptional phenotypic stability and enhanced PGE2 secretion, supporting their potential as reliable candidates for cell-free therapeutic applications in inflammatory conditions. The data also highlight the use of white rate as model to understand health and production in animals.

Keywords | CD105, CD45, immunophenotype, prostaglandin E2, Rat white adipose-derived MSCs, regenerative medicine

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INTRODUCTION

The field of regenerative medicine has witnessed growing interest in mesenchymal stem cells (MSCs) over recent decades. These remarkable cells have captured researchers' attention primarily because they can develop into various cell types and possess powerful abilities to modulate immune responses (Ullah *et al*., 2015; Suciadi *et al*., 2019; Hendarto *et al*., 2013). When considering sources for these valuable cells, adipose tissue emerges as particularly promising for several compelling reasons.

Unlike other MSC sources, adipose tissue is readily accessible through simple liposuction procedures that cause minimal patient discomfort (Sridhar *et al*., 2025; Sumarwoto *et al*., 2021). The tissue itself is extraordinarily rich in stem cells – containing up to ~500 times more MSCs per gram than bone marrow aspirate (Zhou *et al*., 2020). When cultured in laboratory settings, these adipose-derived cells multiply more rapidly than their counterparts from other tissues (Mykuliak *et al*., 2022). While maintaining genetic stability across multiple passages (Wang *et al*., 2024). Perhaps most importantly, they demonstrate enhanced capacity to promote blood vessel formation compared to MSCs from other sources (Mykuliak *et al*., 2022).

For preclinical research purposes, rat white adipose tissue-derived MSCs (RWA-MSCs) represent an invaluable model that shares these beneficial properties while offering excellent translational relevance to regenerative medicine applications. Despite their potential, however, we still lack comprehensive understanding of their defining characteristics and secretory functions.

Proper identification of MSCs relies on immunocytochemistry to confirm they express specific surface markers including CD105, CD90, and CD73, while lacking hematopoietic markers such as CD45 (Han *et al*., 2019; Aswin *et al*., 2024; Kuncorojakti *et al*., 2025). Beyond these identifying features, the therapeutic benefits of MSCs largely stem from their secretion of bioactive molecules. Among these, prostaglandin E2 (PGE2) stands out for its crucial role in dampening inflammation and supporting tissue repair processes (Vasandan *et al*., 2016). Measuring PGE2 production through ELISA techniques provides valuable insight into the therapeutic potential of RWA-MSCs.

Despite considerable research on MSCs broadly, significant knowledge gaps persist regarding rat adipose-derived MSCs specifically. While researchers have thoroughly documented marker expression patterns in human and mouse MSCs, questions remain about whether RWA-MSCs maintain consistent phenotypic profiles during extended culture periods (Banu *et al*., 2025). Additionally, although scientists have characterized the immunomodulatory effects of PGE2 secretion in other MSC types (Zhang *et al*., 2018), we know surprisingly little about how culture conditions affect the secretory behavior of RWA-MSCs (Rasouli *et al*., 2024).

Further complicating matters, comparative studies between different MSC sources frequently exclude RWA-MSCs from analysis, creating a substantial gap in our understanding of their relative therapeutic value. Finally, the field suffers from a lack of standardized protocols for isolating and characterizing these cells, resulting in troubling inconsistencies across research studies. These knowledge gaps significantly limit our ability to utilize RWA-MSCs reliably in preclinical research and potential clinical applications, highlighting the urgent need for systematic investigation of their phenotypic stability and secretory capabilities.

MATERIALS AND METHODS

Isolation of rat white adipose tissue

White Adipose Tissue obtained from seven rats (*Rattus norvegicus*) strain Sprague-Dawley. Ketamine (30 mg/kg BW) and xylazine (5 mg/kg BW) as anaesthesia, were administered into the quadriceps muscle of the hind limb of *Rattus norvegicus*. Anaesthesia depth was confirmed by monitoring pedal withdrawal, palpebral reflex and respiratory rate (40–60 breaths/min). The rat was positioned dorsoventral on a sterile under pad, and the abdominal area was shaved and disinfected with povidone-iodine and 70% ethanol wipes. A midline incision (2–3 cm) was made using a sterile scalpel, and approximately 2–3 grams of abdominal white adipose tissue was carefully excised using forceps and scissors. The tissue was immediately rinsed three times in PBS supplemented with 1% Penicillin Streptomycin to remove blood contaminants, then transferred to a 15 mL conical tube containing MEM transport medium (Gibco). Post-procedure, euthanasia was performed via cervical dislocation following institutional animal ethics guidelines.

Primary culture of RWA-MSCs

The adipose tissue was minced into ± 1 mm^3 fragments in a sterile petri dish and digested in 0.05% Trypsin-EDTA (Gibco) at 37°C for 60 minutes with constant stirring (70 rpm). Digestion was neutralized with two times volume of α-MEM supplemented with 15% FBS (Gibco) at 37°C for 5 minutes with constant stirring (70 rpm). Digested adipose tissue was filtered, followed by centrifugation for 10 min (2000 rpm). The filtered fragment was cultured as explant culture. The pellet was resuspended in complete growth medium (α-MEM + 15% FBS + 1% penicillin/streptomycin) and seeded in T25 flasks. Cultures were

maintained at 37°C in a humidified 5% CO_2 incubator (Thermo Scientific), medium was changed periodically.

Subculture and passaging

Cells at 80–90% confluency (day 2-7) were passaged by rinsing with PBS, followed by 3 min incubation with 0.05% trypsin-EDTA (Gibco) at 37 °C. Enzymatic activity was stopped with α-MEM + 10% FBS (1:1 ratio). The cell suspension was centrifuged (2000 rpm, 5 min), and the pellet was resuspended in fresh medium at a 1:2 split ratio. The cell suspension were devided and cultured in new flask.

Immunophenotypic characterization

Cells at third passage were fixed with 4% paraformaldehyde (15 min) for immunocytochemistry. Positive MSC markers (CD105, CD90, CD73) were detected using Endoglin/CD105 Antibody (Santa Cruz Buotechnlogy), CD90 antibody (BioLegend) and CD73 antibody (BioLegend) and negative marker CD45 were detected using CD45 Antibody (Santa Cruz Buotechnlogy). Acceptance criteria: >95% positivity for CD105/CD90/CD73 and <2% for CD45, based on International Society for Cellular Therapy ISCT guidelines (Davies *et al*., 2025).

PGE2 secretion analysis

Secretome was collected from cell culture (80% confluency) and centrifuged (2000 rpm, 20 min) to remove debris. PGE2 levels (ng/mL) were quantified using a commercial ELISA kit (Bioenzy) manufacturer's protocol. Samples were run, with absorbance measured at 450 nm (Elisa reader).

Data analysis

The immunophenotypic characterization of cells, RWA-MSCs were evaluated base on the International Society for Cellular Therapy (ISCT) criteria for mesenchymal stem cells: Cells were required to demonstrate >95% positivity for CD105, CD73, and CD90 surface markers, while maintaining <2% expression of the hematopoietic marker CD45, as quantified through upright microscope (Nikon Eclipse CI) and the image analysed using ImmunoRatio (ImageJ v1.53 software). Quantitative analysis of PGE2 secretion levels was performed using T Test, with data presented as mean ± SEM. The statistical analysis were conducted using SPSS v23 (IBM), with significance thresholds set at $p < 0.05$.

RESULTS AND DISCUSSION

Results and Discussion should be written as a series of connecting sentences, however, for manuscript with long discussion should be divided into subtitles. Results should be clear and concise.

Explant culture of adipose tissue and primary culture of RWA-MSCs

The isolation and expansion of mesenchymal stem cells from rat white adipose tissue (RWA-MSCs) has been optimized to yield robust cell populations with remarkable proliferative capacity (Banu *et al*., 2025). The explant culture method demonstrated exceptional efficiency, with cells were migrated from the tissue fragments within seven days of plating and rapidly adhered to the culture surface. Cells with characteristic fibroblast-like morphology typical of MSCs were observed, the cells were seen to be elongated (Figure 1).

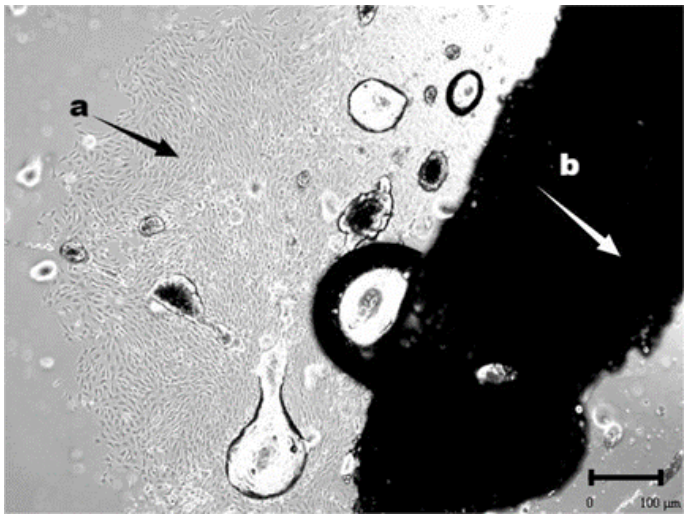

Figure 1: The explant culture: a: Cells adhesion and migration, b: Rat white adipose tissue fragment (magnification 100X).

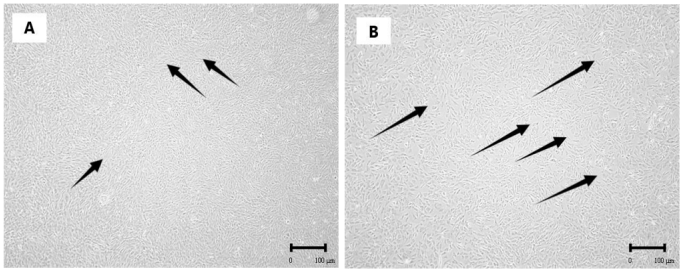

Figure 2: Rat White Adipose Tissue-Derived Mesenchymal Stem Cells (RWA-MSCs) at different passages demonstrated consistent growth characteristics. (A) First passage on the fourth day. (B) Third passage on the second day. The arrow indicated empty space (magnification).

The fourth day of the 1st passage cells culture in T25 flasks, fibroblast-like cells had already established a monolayer approximately 70-80% confluence (Figure 2A). The characteristics that supported this estimation were most of the surface area was already covered by cells and some empty spaces were still observed between cells. Cells were not yet fully confluent (100%). The robust growth characteristics were consistently maintained through subsequent passages.

The 3rd passage, cells were distributed approximately 60-70% confluence by second day of culture (Figure 2B). Cells were distributed throughout the culture area. Empty spaces were still observed between the cells. The surface of cells culture had not been completely covered.

This study successfully demonstrated consistent growth characteristics of fibroblast cells through multiple culture passages. The main findings showed that fibroblast cells reached 70-80% confluence on the fourth day of first passage culture in T25 flasks, with robust growth characteristics that were maintained through the third passage. This growth pattern aligns with literature showing that cells were passaged after reaching 60-70% confluency around the explants (Pathak *et al*., 2023), indicating that optimal culture conditions had been achieved. Culture maintenance at suboptimal confluence was important to prevent premature differentiation and maintain proliferative phenotype, as demonstrated by research indicating that cells are typically passaged before becoming fully confluent in order to maintain their proliferation phenotype (Wu *et al*., 2021; Wang *et al*., 2021).

Growth characteristic consistency from first to third passage indicated good culture stability. This phenomenon was supported by findings that secondary cultures reached 70-80% confluence faster (within 4-5 days) compared to primary cultures which required 8-10 days, demonstrating improved cell adaptation to in vitro conditions (Pathak *et al*., 2023). This growth acceleration in later passages was likely caused by selection of more homogeneous and adaptive cell populations to the culture environment (Syddall *et al*., 2024).

The remarkable stability of growth kinetics between early and later passages suggests that RWA-MSCs represent (Maldonado *et al*., 2025) an ideal candidate for applications requiring substantial cell expansion without compromising cellular characteristics, offering significant advantages over bone marrow-derived MSCs which typically show reduced proliferation rates in later passages.

Rat white adipose mesenchimal stem cells immunophenotypic characterization

Immunocytochemical staining of critical surface markers, used to characterize RWA-MSCs isolated from abdominal adipose tissue (Figure 3). (A) CD105 expression showed strong positive staining (brown/golden color) in 96.2% of cells, exceeding the minimum threshold of 95% required for MSC classification. (B) CD90 expression with prominent positive staining in 99.3% of cells, well above the 95% threshold. (C) CD73 expression demonstrated positive staining in 95.7% of cells, meeting the MSC characterization criteria. (D) CD45 expression demonstrated appropriate negative expression with only 1.7% of cells showing positive staining, well below the maximum 2% threshold for this hematopoietic marker. The immunophenotypic profile observed confirms these cells met the International Society for Cellular Therapy's minimal criteria for MSC identification, with strong expression of mesenchymal markers (CD105, CD90, CD73) and negligible presence of the hematopoietic marker CD45. The predominantly brown/gold staining in panels A-C indicates positive expression, while the predominantly purple counterstain in panel D confirms the absence of CD45 expression, as expected for MSCs. This distinct immunophenotype confirms the successful isolation of RWA-MSCs with characteristic mesenchymal properties suitable for regenerative applications.

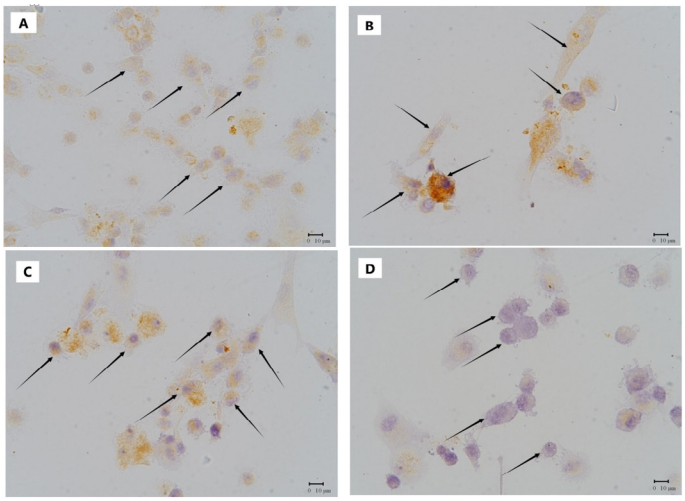

Figure 3: Immunocytochemical characterization of surface markers on Rat White Adipose-derived Mesenchymal Stem Cells (RWA-MSCs). (A) The arrow showed positive expression of CD105 (B) The arrow showed positive expression of CD90. (C) The arrow showed positive.

Based on the immunocytochemical staining results, this study successfully demonstrates the isolation and characterization of mesenchymal stem cells from abdominal adipose tissue with exceptional purity and phenotypic consistency. This immunophenotypic characterization strongly supports the current consensus regarding MSC marker expression established by the International Society for Cellular Therapy (ISCT). The expression patterns observed perfectly align with ISCT criteria, which specify >95% positivity for CD105, CD90, and CD73, and <2% positivity for CD45 (Xie *et al*., 2020; Wright *et al*., 2021). This alignment confirms that RWA-MSCs share fundamental phenotypic characteristics with MSCs from other species and sources.

This finding contributes several novel insights to the field of regenerative medicine and cellular therapy. The consistently high marker expression across all positive markers suggests that abdominal adipose tissue may offer

superior homogeneity compared to other adipose depots, addressing a critical concern in clinical translation where batch variability can compromise therapeutic efficacy (Chen *et al.*, 2024; Di Rocco *et al.*, 2024). The exceptionally high of CD90 expression in this study suggested these cells may possess potent immunomodulatory properties, an important consideration for therapeutic applications targeting inflammatory conditions. The higher CD105 expression in abdominal white adipose-derived cells may indicate enhanced angiogenic potential, as CD105 (endoglin) plays a crucial role in vascular development and repair. Furthermore, the minimal CD45 expression indicates that our protocol effectively eliminates hematopoietic contaminants without compromising MSC viability or phenotype, potentially reducing immunogenicity concerns in allogeneic applications (Li *et al.*, 2024).

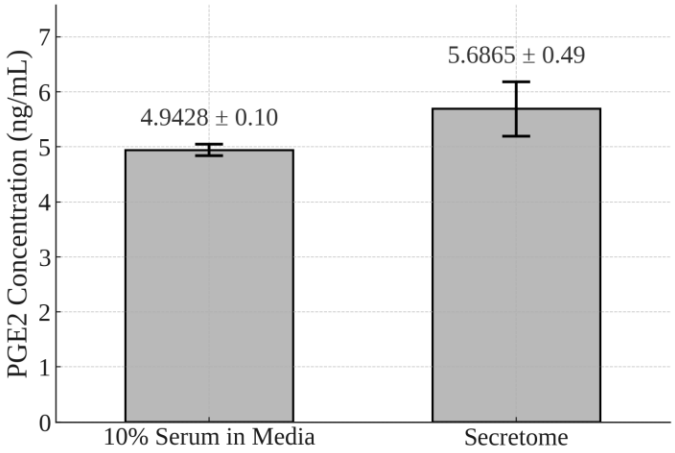

Figure 4: Rat white adipose-derived mesenchymal stem cells (RWA-MSCs) exhibit differential.

The stability of immunophenotypic profile through multiple passages suggests these cells maintain their defining characteristics during expansion, addressing a significant challenge in MSC research and therapeutics. This stability enhances both experimental reproducibility and therapeutic reliability.

Prostaglandin E_2 (PGE_2) secretion

MSCs release numerous beneficial bioactive molecules and growth factors into the medium culture (Nugraha *et al.*, 2019; Wicaksono *et al.*, 2023). The present study demonstated Prostaglandin E2 (PGE_2) levels which measured in two different culture media: Standard culture medium supplemented with 10% serum (10% Serum in Media) and cell-free secretome (Secretome). Data are presented as mean ± standard error of the mean (SEM).

Prostaglandin E2 (PGE_2) secretion. Secretome media inducing significantly higher PGE_2 production (5.6865 ±0.492 ng/mL) compared to conventional 10% serum-supplemented media (4.9428±0.098 ng/mL). The secretome group showed a 15.1% increase in PGE_2 concentration. This finding provided crucial insights into the paracrine signaling capacity of adipose-derived MSCs and their potential therapeutic applications in regenerative medicine.

This finding supported the development of MSC-derived secretome products for inflammatory and autoimmune conditions. The PGE_2 concentrations achieved exceed the threshold required for immunomodulation reported by English (2013), who demonstrated that 2-3 ng/mL PGE_2 effectively suppresses T-cell responses. Additionally, PGE_2's role in tissue repair and regeneration, through promotion of angiogenesis and matrix remodeling (Huang *et al.*, 2022; Cheng *et al.*, 2021) suggested broad therapeutic potential. The use of secretome media could facilitate large-scale production of MSC-derived factors while maintaining batch consistency, addressing current manufacturing challenges in cell therapy (Trigo *et al.*, 2025; Pincela Lins *et al.*, 2023). The enhanced PGE_2 production in secretome media suggested that conditioned media preparations could offer an alternative therapeutic efficacy to support conventional cell therapy approaches. The consistent PGE_2 levels observed (evidenced by low standard deviations) indicate reproducible production, essential for standardized therapeutic applications.

This study demonstrated that RWA-MSCs represent a reliable source of PGE_2, with secretome culture conditions offering enhanced production suitable for therapeutic applications. These results contributed evidence to support MSC secretome-based therapies as promising alternatives to cellular transplantation, particularly for inflammatory and immune-mediated conditions requiring sustained immunomodulation.

CONCLUSIONS

This study successfully demonstrated the isolation and characterization of rat white adipose-derived mesenchymal stem cells (RWA-MSCs) with exceptional purity and phenotypic consistency. Cells exhibited stable growth characteristics, reaching 70-80% confluence on day four of first passage and maintaining consistent proliferation through third passage. The immunophenotypic profile perfectly aligned with ISCT minimal criteria, showing high expression of mesenchymal markers CD105 (96.2%), CD90 (99.3%), and CD73 (95.7%) with negligible hematopoietic marker CD45 (1.7%). Notably, secretome media induced 15.1% higher PGE_2 production compared to standard serum-supplemented media, exceeding therapeutic thresholds for immunomodulation. The stability of cellular characteristics across multiple passages positions RWA-MSCs as ideal candidates for large-scale expansion without compromising therapeutic properties.

These findings contribute significant evidence supporting adipose-derived MSC secretome as a promising cell-free therapeutic alternative, particularly for inflammatory and immune-mediated conditions.

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NOVELTY STATEMENT

This study is one of the first systematic studies to thoroughly characterize MSCs from white adipose tissue of rats (*Rattus norvegicus*), previous research focused more on human and mouse MSCs, so that RWA-MSCs data is still very limited. RWA-MSCs maintained a consistent immunophenotypic profile through the third passage, this stability has not been well documented for rat adipose MSCs before. The PGE2 concentration exceeded the therapeutic threshold for immunomodulation (2-3 ng/mL), this is the first data on the PGE2 secretion profile of RWA-MSCs under different culture conditions.

AUTHOR'S CONTRIBUTION

WP: Conceptualization, methodology, writing reviewing and editing, visualization, investigation. FAR and AA: Supervision, conceptualization, methodology. FSP: Visualization, investigation.

Ethical approval

This research was conducted in compliance with international standards for laboratory animal welfare as outlined in the Guide for the Care and Use of Laboratory Animals and was ethically approved by the Animal Care and Use Committee (ACUC), Veterinary Faculty, Airlangga University, Indonesia (No: 1.KEH.180.12.2023).

Generative AI and AI-assisted technology statement

During the preparation of this manuscript, the authors used AI-assisted tools solely to improve language clarity and grammar. The authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflict of interest

The authors have declared no conflict of interest.

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