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Encapsulated Mesenchymal Stem Cell as Regenerative Alternative for MDR-TB: A Gene Expression Analysis of ABCG2 Efflux

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Abstract: Multidrug-resistant tuberculosis (MDR-TB) poses a significant global health challenge due to poor treatment outcomes. Encapsulated mesenchymal stem cells (MSCs) have emerged as a potential alternative therapy; however, their role in modulating bacterial drug sensitivity remains unclear. This study aimed to evaluate the expression of the ABCG2 efflux pump gene in encapsulated MSCs co-cultured with MDR-TB, and to explore its implications for bacterial sensitivity to anti-tuberculosis drugs. An in vitro experimental design was employed using encapsulated MSCs cultured with MDR-TB. Total RNA was isolated, converted into complementary DNA (cDNA), and analyzed using quantitative real-time PCR (RT-PCR). Gene expression levels were quantified using the Livak (ΔΔCt) method. Results demonstrated a progressive increase in ABCG2 gene expression on days 2, 7, and 14. Although this increase may reduce the direct antibacterial capacity of MSCs, previous studies have shown that their preserved paracrine function remains beneficial for immunomodulation. These findings support the continued investigation of encapsulated MSCs as an adjunctive therapy for MDR-TB, particularly through immunoregulatory mechanisms despite increased ABCG2 expression.

Keywords: ABCG2; Encapsulated; MDR-TB; MSCs

Introduction

Multidrug-resistant tuberculosis (MDR-TB) continues to rise globally, with 437.000 cases reported in 2020 and increasing to 450.000 in 2022, Indonesia remains one of the countries with the highest MDR-TB burdens, with cases increasing from an estimated 25.000 in 2018 to 27.000 in 2021. The treatment success rate remains low at only 48%, primarily due to the long treatment duration, narrow therapeutic index, and high drug toxicity, all of which contribute to increased mortality (Soeroto et al., 2021); (Chen et al., 2024). These challenges highlight a critical imperative for the development of novel therapeutic strategies that not only enhance treatment efficacy but also support tissue regeneration and functional recovery. Among various alternatives, cellular therapy using stem cells has emerged as a potential solution. However, stem cell therapy alone has yet to fully address the limitations of MDR-TB treatment, as treatment failure still occurs in 21.49% of cases, with similarly prolonged durations (Devi et al., 2023); (Soedarsono et al., 2023).

A major limitation is the low persistence of stem cells during therapy, leading to reduced migration to

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target organs and insufficient bacterial clearance and tissue repair (Wu et al., 2024); (Zhang et al., 2021). Encapsulation of stem cells offers a promising strategy to overcome these limitations. A product developed under the Indonesian Applied Research Grant Scheme (2022–2024) has led to two patents: ID S000006938 (dual stem cell ratio encapsulation) and ID S000006937 (dual stem cell encapsulation coated with platelet lysate). Mesenchymal stem cells (MSCs), known for their proliferative, differentiative, paracrine, and immunomodulatory properties, are encapsulated to preserve their viability and function within hostile microenvironments during treatment. Encapsulation preserves IL-10 paracrine secretion and further enhances TNF-α expression when coated with platelet lysate (Sibuea et al., 2020); (L. Yang et al., 2025).

Recent studies have supported the application of encapsulated MSCs in various inflammatory and infectious conditions (Kumar et al., 2022); (Huang et al., 2022). Encapsulated MSCs improved cell survival and reduced inflammation in lung injury models (Liang et al, 2020). Alginate-based MSC delivery systems enhanced tissue repair and maintained MSC viability in ischemic environments (Bolinas et al., 2025); (Guan et al., 2025). These findings reinforce the potential of encapsulation strategies to preserve MSC function and improve therapeutic outcomes. To justify the use of encapsulated MSCs as an alternative therapy for MDR-TB, it is crucial to assess their impact on bacterial drug sensitivity through the expression of ABCG2 efflux pump genes (Battah, 2022). Some studies indicate that MSCs may serve as reservoirs for dormant Mycobacterium tuberculosis, characterized by increased ABCG2 expression, resulting in decreased sensitivity to anti-tuberculosis drugs (Singh et al., 2020). This phenomenon can hinder bacterial clearance and reduce therapeutic efficacy. Conversely, MSCs are also known to secrete cytokines and chemokines such as IL-6, IL-8, and TGF-β1, which contribute to immune modulation and bacterial elimination (Trigo et al., 2025); (Sarhadi et al., 2021).

This ongoing debate highlights the complexity of MSC-based therapy in MDR-TB (Yudintceva et al., 2024); (Musiał-Wysocka et al., 2019). Encapsulation may shield MSCs from the infectious microenvironment, preventing them from becoming a niche for dormant M. tuberculosis and preserving their therapeutic potential (Jain et al., 2020); (Li et al., 2021). However, its role in modulating bacterial drug sensitivity remains unclear. Assessing the expression of the ABCG2 efflux pump gene in encapsulated MSCs is critical to determine whether this approach can increase the susceptibility of Mycobacterium tuberculosis resistant strains to anti-tuberculosis drugs. A better understanding of this mechanism will support the use of encapsulated MSCs as a viable strategy to overcome the therapeutic failure often encountered in MDR-TB. In this study, we propose to analyze ABCG2 gene expression in encapsulated MSCs co-cultured with drug-resistant M. tuberculosis using real-time PCR (RT-PCR). The findings are expected to provide new insights into the role of encapsulation in enhancing MSC-based therapies for MDR-TB through improved bacterial drug sensitivity.

Method

This is a preclinical in vitro study and represents a continuation of previous research. In the previous research, mesenchymal stem cells (MSCs) were isolated, cultured, and characterized, followed by encapsulation and co-culture with drug-resistant MDR-TB (Sibuea et al., 2024). Total RNA was extracted and stored at −80°C. The current procedures include ethical approval, literature review, primer design for the ABCG2 efflux pump gene, cDNA synthesis from the stored RNA, and cDNA amplification using real-time polymerase chain reaction (RT-PCR). ABCG2 gene expression was quantified using the Livak method and analyzed using Microsoft Excel.

cDNA Synthesis

Stored RNA samples extracted from the co-culture was reverse transcribed into complementary DNA (cDNA) using ReadyScript™ cDNA Synthesis Mix (Sigma-Aldrich). The cDNA synthesis reaction included the ReadyScript™ mix, RNA template, and RNase/DNase-free water to a total volume of 20 µL. The mixture was incubated sequentially at 25°C for 5 minutes, 42°C for 30 minutes, and finally at 85°C for 5 minutes to complete the synthesis process. Subsequently, quantitative real-time PCR (qRT-PCR) was carried out to determine ABCG2 gene expression using the SensiFAST SYBR Lo-ROX Kit (Bioline). Each 20 µL reaction contained the SYBR mix, synthesized cDNA, RNase/DNase-free water, and specific primers targeting the ABCG2 gene (Forward primer: gctacaccacctccttctgt; Reverse primer: ggaagaagagaaccccagct). The qRT-PCR was performed with the following thermal profile: initial denaturation at 95°C for 3 minutes, followed by 40 cycles of denaturation at 95°C for 1–3 seconds, and annealing at 57°C for 20 seconds. Threshold cycle (Ct) values were used for analysis of gene expression using the Livak (ΔΔCt) method, with GAPDH as the reference gene.

Result and Discussion

The relative expression of ABCG2 mRNA normalized to GAPDH showed a progressive increase over the culture duration, specifically on days 2, 7, and 14 (Table 1, Figure 1). This result indicates that encapsulated mesenchymal stem cells exhibited an increased expression of the ABCG2 efflux pump gene over time. The upregulation of efflux pump genes such as ABCG2 has been associated with reduced bacterial sensitivity to anti-tuberculosis drugs.

Table 1. Relative Expression of ABCG2-GADPH mRNA

Duration of culture	Relative Expression of ABCG2-GADPH mRNA	SD
Day-2	0.02	0.08
Day-7	0.10	0.06
Day-14	0.19	0.02

These findings align with prior research suggesting that MSCs can serve as a niche for dormant Mycobacterium tuberculosis, particularly due to the upregulation of ABCG2, which contributes to efflux-mediated drug resistance. This mechanism may compromise the efficacy of MSCs in directly eliminating M. tuberculosis, resulting in limited therapeutic outcomes in MDR-TB.

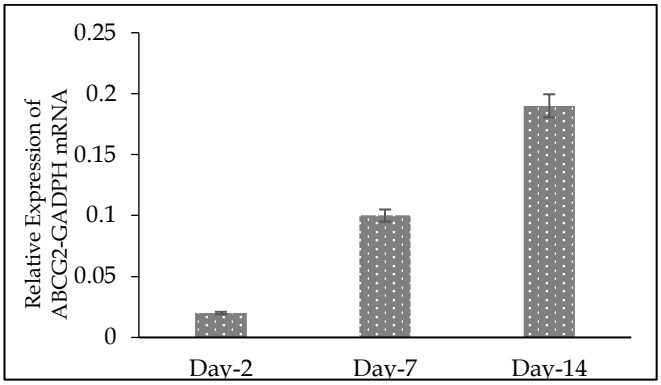

Figure 1. *Relative Expression of ABCG2-GADPH mRNA*

Recent studies have shown that ABCG2 efflux pumps of the BM-MSCs were upregulated in unresponsive to the anti-TB drugs rifampicin and isoniazid. (Zhong et al., 2024); (H. Lee et al., 2025), A recent study demonstrated that ABCG2 is a crucial determinant of stem cell plasticity and chemoresistance in hypoxic environments, suggesting that increased ABCG2 expression may serve as an adaptive response of MSCs to stress conditions induced by bacterial co-culture (Han et al., 2022); (Bogiel et al., 2025). Furthermore, ABCG2 overexpression can be a marker for stem cell dormancy and low differentiation potential (Frąszczak & Barczyński, 2023); (Nair et al., 2023). Interestingly, the progressive increase in ABCG2 expression observed in this study may also be related to extended exposure of encapsulated MSCs to a microenvironment simulating infection stress and nutrient limitation. Oxidative or hypoxic conditions upregulates ABCG2 via HIF-1α activation, as a cellular defense mechanism against accumulated xenobiotics and oxidative stress (Yun et al., 2021); (Ryoo et al., 2016). Previous study demonstrated that alginate-based encapsulation may prolong MSC metabolic activity, resulting in sustained ABC transporter expression under in vitro culture (Kuncorojakti et al., 2020).

However, contrary to concerns regarding ABCG2-induced dormancy, other studies have identified a dual role of MSCs, emphasizing their paracrine functions. Han et al. highlighted that MSCs secrete IL-6, TGF-β1, and VEGF in response to infectious stimuli, which modulate the immune system and enhance tissue repair (J.-H. Lee et al., 2024); (Cortes-Dericks & Galetta, 2025). In our study, although direct bacterial clearance may be hindered by efflux activity, the MSCs' preserved secretory function remains a therapeutic advantage. Thus, despite the increased ABCG2 gene expression, the therapeutic rationale for using encapsulated MSCs as an alternative therapy for MDR-TB remains valid. The retention of paracrine function, even under efflux pump upregulation, strengthens their role as immunomodulators capable of supporting host immune responses and tissue regeneration. Rather than being viewed as a therapeutic limitation, ABCG2 upregulation may reflect MSC adaptation and survival strategy, enabling sustained paracrine output under stress. The implications of our findings suggest that while encapsulated MSCs upregulate ABCG2 gene expression over time—which may attenuate their direct antimicrobial activity—their immunomodulatory potential through paracrine signaling remains intact. This supports the rationale for using encapsulated MSCs as an adjunctive rather than primary therapy for MDR-TB.

Limitation of The Study

One important limitation of this study is the exclusive reliance on in vitro data. The co-culture system may not fully replicate the complex in vivo microenvironment, including immune responses, tissue matrix interaction, and systemic circulation, which can influence both gene expression and therapeutic efficacy. Additionally, the study only measured mRNA levels of ABCG2 without confirming protein expression or functional activity of the efflux pump (Fanelli et al., 2020); (Ma et al., 2021). Future studies should include western blotting or flow cytometry to validate protein-level changes and explore whether ABCG2 expression correlates with actual efflux activity and reduced drug

accumulation in MSCs. Another limitation lies in the scope of genes analyzed. While ABCG2 is a key efflux pump, other drug resistance-associated genes (e.g., ABCB1, ABCC1) and dormancy-related transcription factors may also contribute to therapeutic outcomes and should be evaluated in subsequent research (S. Yang et al., 2025); (Uzuner et al., 2021). ; (Wang et al., 2024).

Lastly, the study did not assess the impact of encapsulation material properties (e.g., porosity, biodegradability) on gene expression, which could be an additional variable affecting MSC behavior. In conclusion, while encapsulated MSCs demonstrate increased ABCG2 expression over time—potentially limiting direct bactericidal activity—their preserved paracrine function underscores their utility in immunomodulation and tissue repair (Chandran et al., 2024); (Vohra & Arora, 2023). Further in vivo validation and expanded molecular profiling are essential to optimize MSC-based therapies for MDR-TB (Omoteso et al., 2025); (Rao et al., 2019).

Conclusions

Encapsulated mesenchymal stem cells cultured with drug-resistant MDR-TB demonstrated a progressive increase in ABCG2 gene expression. Although this efflux-related upregulation may limit the cells' direct bactericidal effect, their retained paracrine function presents a significant therapeutic advantage. These findings support the continued investigation of encapsulated MSCs as a promising adjunctive strategy in MDR-TB therapy.

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Conceptualization, C. V. S.; methodology, E. J. S.; validation, E. P. S; formal analysis, C. D. M; investigation, G. A. B. N. L. ; resources, O. A. V. T .; data curation, W. L. S.: writing—original draft preparation, C. K. S.; writing—review and editing, C. V. S.: visualization, and E. J. S. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest
The authors declare no conflict of interest related to the publication of this manuscript.

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