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Review Article

The Need to Update Quality Control Standards in Good Manufacturing Practices for Mesenchymal Stem Cells: Inclusion of Apoptosis and Senescence Assessment

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ABSTRACT

Mesenchymal stem/stromal cells (MSCs) are gaining increasing attention for potential clinical applications due to their regenerative and immunomodulatory properties. However, quality control checks under contemporary good manufacturing practices, which typically adhere to the minimal criteria proposed by the International Society for Cellular Therapy, are insufficient because they assess MSC identity rather than functional competency. Accumulating evidence indicates that apoptosis and senescence significantly impact MSC potency, viability, and immunomodulation potential following infusion. Notably, apoptotic or senescent MSCs can alter secretome profiles, disrupt therapeutic efficacy, and pose safety concerns. Herein, we propose adding apoptosis and senescence assessments to the standard quality control checks for MSCs by incorporating methods such as annexin A5 (ANXA5/annexin V) and propidium iodide staining, caspase activity assessment, senescence-associated β-galactosidase staining, and quantification of senescence-related gene expression (cyclin-dependent kinase inhibitors 1A (*CDKN1A/p21*) and 2A (*CDKN2A/p16*), and tumor protein p53 [*TP53*]). Such changes will enable the incorporation of functional markers and enhance the consistency, predictability, and clinical utility of MSC-based products. Harmonizing quality control strategies with new biological knowledge is crucial for creating next-generation cell therapeutics.

Key words: Mesenchymal stem cells, Apoptosis, Senescence, Cell therapy, Quality control

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INTRODUCTION

Mesenchymal stem/stromal cells (MSCs) are gaining increasing attention for potential clinical applications due to their regenerative and immunomodulatory properties. However, quality control checks under contemporary good manufacturing practices, which typically adhere to the minimal criteria proposed by the International Society for Cellular Therapy, are insufficient because they assess MSC identity rather than functional competency. Accumulating evidence indicates that apoptosis and senescence significantly impact MSC potency, viability, and immunomodulation potential following infusion. Notably, apoptotic or senescent MSCs can alter secretome profiles, disrupt therapeutic efficacy, and pose safety concerns. Herein, we propose adding apoptosis and senescence assessments to the standard quality control checks for MSCs by incorporating methods such as annexin A5 (ANXA5/annexin V) and propidium iodide staining, caspase activity assessment, senescence-associated β-galactosidase staining, and quantification of senescence-related gene expression (cyclin-dependent kinase inhibitors 1A (*CDKN1A/p21*) and 2A (*CDKN2A/p16*), and tumor protein p53 [*TP53*]). Such changes will enable the incorporation of functional markers and enhance the consistency, predictability, and clinical utility of MSC-based products. Harmonizing quality control strategies with new biological knowledge is crucial for creating next-generation cell therapeutics.

METHODS

Mesenchymal stem/stromal cells (MSCs) have become a cornerstone in regenerative medicine and immune modulation due to their capacity for multilineage differentiation, secretion of various factors, and immunosuppressive properties. Over the past two decades, clinical trials have been conducted to assess MSC-based therapies targeting diverse conditions, including graft-versus-host disease[1], osteoarthritis[2], rheumatoid arthritis[3], myocardial infarction[4], and autoimmune disorders[5,6]. Increasing interest in the clinical use of MSCs has highlighted the need for standard benchmarks to define, characterize, and produce MSCs of reproducible quality and function.

To meet this requirement, in 2006, the International Society for Cellular Therapy (ISCT) proposed the fol-

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lowing minimum criteria for MSC characterization: (i) plastic adherence under standard culture conditions, (ii) MSC-specific marker expression, and (iii) *in vitro* trilineage capacity for differentiation into osteoblasts, adipocytes, and chondroblasts[7]. Although these criteria are well developed and form the basis for characterizing MSCs, they essentially establish phenotypic identity but not functional viability or therapeutic potency. However, recent research has highlighted important discrepancies between the surface marker phenotype and actual biological activity[8]. MSCs that meet the ISCT standards can exhibit compromised immunomodulatory activity, reduced survival post-transplantation, or limited regenerative activity[9], most commonly due to functional compromise caused by cellular stress, senescence, or suboptimal handling during expansion[10]. Indeed, cell-fate processes, such as apoptosis and senescence, represent two important but often neglected biological states that compromise MSC quality. Apoptotic MSCs can rapidly lose function or trigger host immune responses, whereas senescent MSCs can exhibit altered secretory profiles and a loss of regenerative function[11].

Notably, the minimal criteria proposed by the ISCT underlie a widely accepted framework for characterizing MSCs. However, they may not fully encompass the diverse functional properties of MSCs described in more recent studies[12,13], and they do not adequately reflect other critical biological functions, such as immunomodulation, stress response, or *in vivo* persistence[12]. For example, MSCs are known to secrete various bioactive factors, including vascular endothelial growth factor (VEGF), indoleamine 2,3-dioxygenase 1 (IDO1/IDO), and transforming growth factor–beta (TGF-β), which contribute to their therapeutic effects on inflammation and tissue repair[12].

Earlier studies proposed functional assays to assess MSC immunosuppressive capacity. For instance, induction with IDO or prostaglandin E_2 (PGE_2) following stimulation with interferon gamma (IFNG/IFN-γ) was considered a more relevant quality control check for inflammation- and immune-related applications[12,14,15]. These biomarkers are tightly correlated with MSCs' ability to suppress T-cell growth and regulate immune responses, enabling a more functional assessment than analysis of surface antigens alone. In contrast, quantifying growth factors secreted by MSCs, such as TGF-β, VEGF, and hepatocyte growth factor (HGF), using singleplex or multiplex enzyme-linked immunosorbent assays (ELISAs) is a more appropriate indicator of therapeutic activity in regenerative settings, such as tissue repair[12,16]. Recognizing this dichotomy highlights the growing consensus that potency testing of MSCs should be tailored to specific clinical settings rather than adopting a one-size-fits-all approach. The integration of indication-related functional testing into existing good manufacturing practice (GMP) guidelines is expected to significantly enhance the relevance of individual MSC batches and avert *in vivo* inefficacy.

Thus, deficiencies in current quality control checks during MSC production under GMP guidelines, especially for MSCs intended for clinical use, highlight the need to shift from exclusive phenotypic characterization to a more integrated approach based on functional markers. In this commentary, we argue that apoptosis and cellular senescence should be routinely screened for during MSC quality control testing. These checks would improve the consistency, safety, and efficacy of MSC-based therapies and close the gap between laboratory characterization and clinical translation. We recommend routine screening of these cell-fate processes as part of MSC quality control workflows.

The ISCT's surface marker criteria for MSCs have a major limitation: MSCs may meet these requirements but be functionally compromised by senescence or processing-induced damage[17,18]. Several groups have reported that extended *in vitro* culture leads to replicative senescence in MSCs, even under idealized conditions[19–21]. Susumu Yamaguchi demonstrated that MSCs derived from young donors exhibit superior paracrine activity, including elevated secretion of factors such as brain-derived neurotrophic factor (BDNF), C-C motif chemokine ligand 2 (CCL2/MCP-1), and VEGF, as well as enhanced immunomodulatory capabilities compared to those derived from older donors[22]. These senescent MSCs maintain canonical markers (5'-nucleotidase ecto [NT5E/CD73], Thy-1 cell surface antigen [THY1/CD90], and endoglin [ENG/CD105]) and exhibit no major morphological abnormalities. Therefore, they can evade detection by standard quality control checks[22,23]. Nevertheless, they exhibit diminished proliferative and differentiation potential, compromised migratory capacity, and an altered secretory profile with a pro-inflammatory senescence-associated secretory phenotype (SASP), which can compromise their regenerative efficacy and even worsen disease pathology upon administration *in vivo*[20,24].

Similarly, MSCs in the early stages of apoptosis may still retain a normal morphology, making them difficult to detect without specific molecular markers. Recent research has demonstrated that MSCs may undergo early apoptosis after administration but still

exert curative functions[25,26], mediated by the release of apoptotic vesicles, such as apoptotic bodies, that are abundant in diverse cellular contents and promote intercellular communication. Such MSC-derived apoptotic vesicles are also promising candidates for drug delivery, tissue engineering, and immunomodulation[26]. The therapeutic effect is achieved through host phagocytic reprogrammed anti-inflammatory monocytes/macrophages efferocytosing apoptotic MSCs[27]. However, other biological functions of apoptotic MSCs, such as secreting growth factors and extracellular matrix components, as well as supporting tissue regeneration, can be severely compromised or even lost in the presence of apoptotic signaling cascades[25,27,28]. During apoptosis, the cellular machinery associated with active secretion and interaction with the cellular microenvironment is shut down[27], potentially compromising the long-term effectiveness of MSC-based therapies, especially in scenarios involving long-term support or integration into host tissues[25]. It may also introduce unpredictability into therapeutic outcomes, depending on the host's immune status or the inflammatory microenvironment.

We propose a practical approach to address these limitations: incorporating apoptosis and senescence assessments into routine GMP workflows with internally developed thresholds. Although there are currently no international standards, many research groups and manufacturers have successfully developed in-house acceptance criteria using trend analysis and historical product data. One recommended strategy involves collecting data from 20–30 GMP-grade MSC batches—preferably those that have passed preclinical or clinical testing—and quantifying relevant parameters such as senescence rate (e.g., senescence-associated β-galactosidase [SA-β-gal] positivity), apoptosis (e.g., annexin A5 [ANXA5/annexin V] and/or propidium iodide [PI] staining), and population doubling time (PDT). Statistical analysis (mean $\pm$ two standard deviations) can then be used to establish internal thresholds for each marker. Tests such as SA-β-gal staining, annexin V/PI-based flow cytometry, or PDT assessments are cost-effective and do not require high-end instrumentation, making them suitable even for medium-scale GMP facilities. Compared to the potential financial and ethical costs of failed clinical trials or adverse patient outcomes, the marginal cost of these assays is justified and essential. Subsequently, implementing run or control charts enables ongoing monitoring of process stability and early detection of drift. This practice aligns with key GMP principles and supports lot-to-lot consistency. Moreover, the importance of functional quality control is underscored by regulatory approvals of MSC-based therapies, such as darvadstrocel (Alofisel®, Takeda) for perianal fistulas[29] and TEMCELL® (JCR Pharmaceuticals) for graft-versus-host disease in Japan[30]. These products incorporated extensive product characterization, including functional assays, into their regulatory dossiers, strengthening the rationale for expanded quality control practices. Where possible, preference should be given to low-cost, easy-to-implement assays such as SA-β-gal staining, PDT measurement, or simple flow cytometry panels, which do not require complex equipment or high technical expertise.

The lack of appropriate metrics in contemporary GMP workflows also contributes to batch-to-batch inconsistency, a chronic problem in MSC manufacturing. Even when derived from the same donor and expanded under the same conditions, MSC lots may exhibit widely varying immunomodulatory capacity, angiogenic potential, or tissue regenerative capacity, potentially due to minor variation in passage number, confluency, oxygen exposure, cryopreservation procedures, or cellular stress. In the absence of regular analysis of functional quality attributes, such as apoptosis rates or senescence markers, achieving consistency and predictability from clinical-grade batch to batch is extremely challenging. The consequences of such limitations are immense. MSC trials have yielded inconsistent results, with some showing therapeutic benefits while others show no discernible or minimal effects[31–33]. While the disease model, delivery route, and dosing regimens are obvious variables, product integrity and the functional quality of the MSC product itself will also be determining factors in the therapeutic effect. As the field approaches regulatory approval and commercialization of MSC-based products, ensuring consistent and reproducible cell function is essential. To close this gap, there is increasing agreement that MSC characterization should include functional tests in addition to phenotypic profiling. Inclusion of these markers in standard quality control workflows could greatly increase the reliability of MSC-based therapies, reduce batch-to-batch variability, and improve clinical outcomes.

Therefore, we propose incorporating two additional quality control checks, senescence and apoptosis, into GMP guidelines for MSC-based products[34]. The GMP requirements and our proposed additions are presented in Figure 1.

The MSCs should pass the ISCT's quality criteria: fibroblast-like morphology; differentiation into

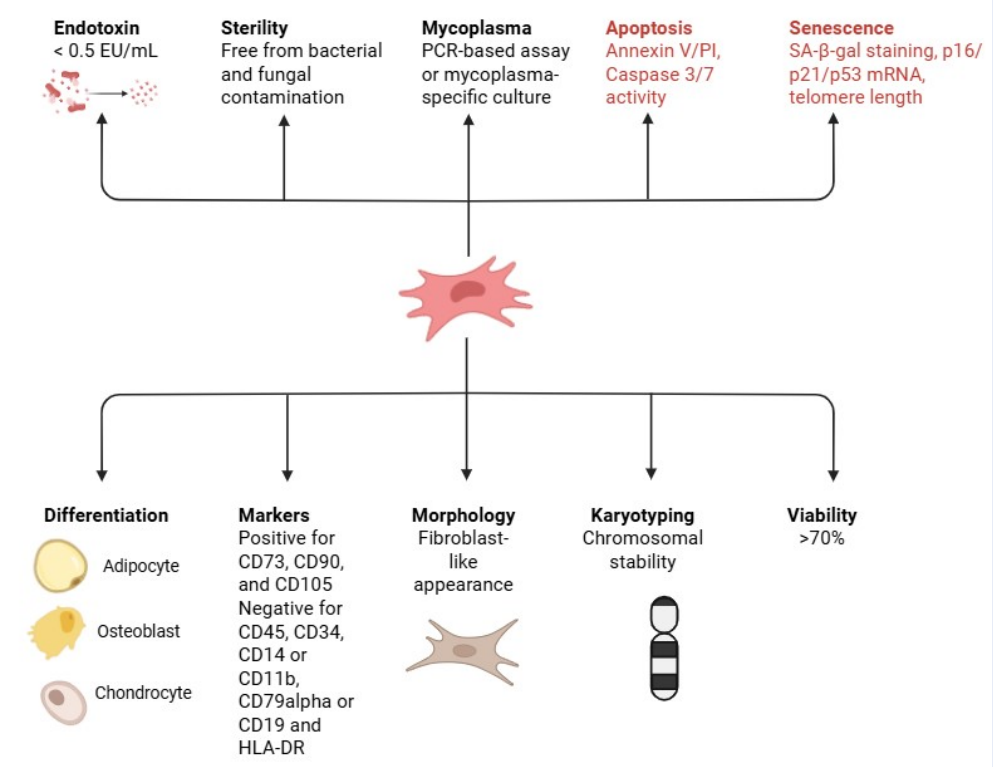

Figure 1: The key quality control checks for GMP-grade MSCs. The MSC-based products should be free of endotoxin (<0.5 EU/mL) and bacterial, fungal, and mycoplasma contamination. MSCs should exhibit viability greater than 70% and chromosomal stability, as assessed by karyotyping.

adipocytes, osteocytes, and chondrocytes; positivity for CD73, CD90, and CD105; and negativity for markers such as protein tyrosine phosphatase receptor type C (PTPRC/CD45), CD34 molecule (CD34), CD14 molecule (CD14), CD19 molecule (CD19), and human leukocyte antigen–DR isotype (HLA-DR). Assessments of apoptosis (annexin V/PI staining and caspase 3 [CASP3] and 7 [CASP7] activity) and senescence (SA-β-gal staining; mRNA levels of *p16*, *p21*, and *p53*; and telomere length) are gaining prominence in assessing the therapeutic efficacy and safety of MSC-based products. The use of these markers enables defective or senescent cells to be recognized early, thereby enhancing the consistency of the final MSC-based product and therapeutic outcomes. This figure was created using BioRender.

In the short term, defining thresholds in-house using prior lots of GMP-grade MSCs is a pragmatic solution to enhance the reproducibility of the final product. In the longer term, we urge international working groups and regulators to finalize guidelines by consensus and to incorporate validated functional markers, including these cell-fate measures, into MSC potency testing. Easy, cost-effective, and technically straightforward markers of quality must be prioritized to enhance reproducibility across manufacturing facilities and laboratories.

LIMITATIONS

The major limitation of our proposal is the current lack of internationally validated cutoffs for senescence and apoptosis in MSCs. Therefore, we do not propose specific cutoffs; instead, we simply recommend incorporating two additional assays, apoptosis detection and SA-β-gal staining, as supplementary quality control checks to better assess the functional state of MSCs. Moreover, while the suggested assays are low-cost and practical, their interpretation and thresholds may require product-specific optimization. Future clinical trials should aim to correlate these functional markers with therapeutic efficacy to support regulatory standardization of MSC-based products. Further consensus-building among international GMP bodies (e.g., the ISCT, European Medicines Agency [EMA], and U.S. Food and Drug Administration [FDA]) will be essential to translate these recommendations into

formal regulatory practice.

CONCLUSIONS

Apoptosis and cellular senescence are key determinants of MSC biological fitness. Failure to screen for these parameters increases the risk of clinical failure, batch-to-batch variation, and even adverse patient outcomes. Therefore, we recommend a framework for internal threshold setting using preclinical and clinical-grade batch data, along with trend analysis tools, to integrate monitoring of these functional states into GMP workflows. In the future, the field would benefit from a concerted effort to define a consistent panel of functional markers for MSC potency, preferably associated with specific clinical outcomes. They should become standard components of product characterization in regulatory approval dossiers for MSC-based advanced therapy medicinal products. By creating GMP workflows that are sensitive not only to cellular identity but also to biological function, we can ensure a safer, more predictable, and more efficacious future for MSC-based regenerative medicine.

ABBREVIATIONS

GMP: Good Manufacturing Practice
ATMPs: Advanced Therapy Medicinal Products
QC: Quality Control

AUTHORS' CONTRIBUTIONS

Phat Duc Huynh conceived and wrote the manuscript. Ngoc Bich Vu revised and finalized the content. Both authors approved the final version.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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