eISSN 2005-5447
International Journal of Stem Cells Vol. 18, No. 2, 2025 https://doi.org/10.15283/ijsc24121

REVIEW ARTICLE

Mammalian Blastema: Possibility and Potentials

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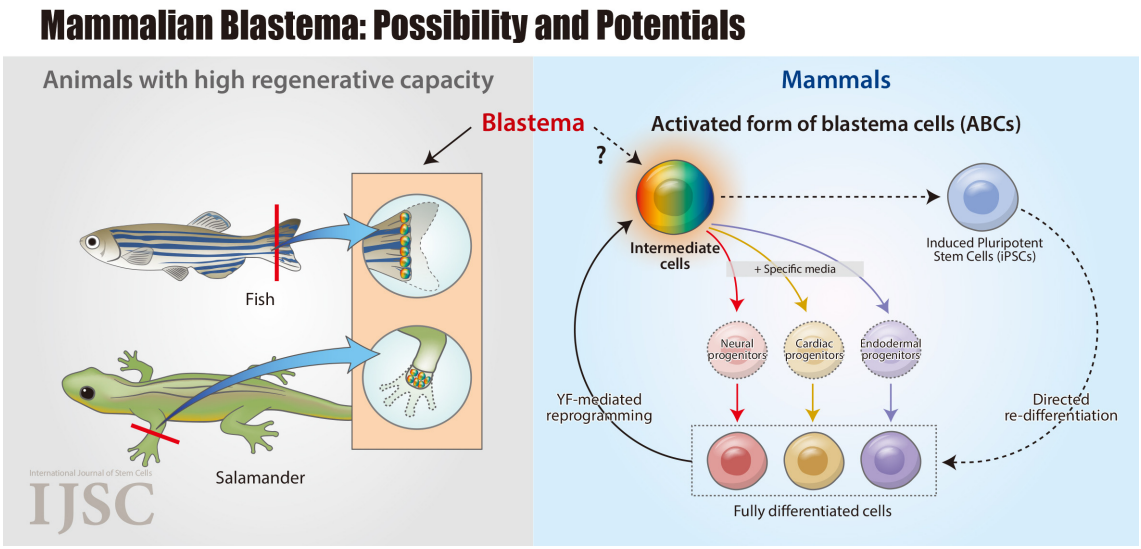

Received: November 14, 2024, Revised: November 26, 2024, Accepted: November 26, 2024, Published online: March 10, 2025
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Regeneration is a process that restores the structure and function of injured tissues or organs. Regenerative capacities vary significantly across species, with amphibians and fish demonstrating a high regenerative capacity even after severe injuries. This capacity is largely attributed to the formation of a blastema, a mass of multipotent cells reprogrammed from differentiated cells at the injury site. In contrast, mammals exhibit limited regenerative capacities, with blastema-like cells forming only in specific contexts, such as antler or digit tip regeneration. An interesting aspect of blastema formation in highly regenerative organisms is the temporary expression of pluripotency factors as known as the Yamanaka factors (YFs), which is a key requirement for reprogramming somatic cells into induced pluripotent stem cells (iPSCs). While iPSCs hold pros and cons, direct or partial reprogramming with YF has been proposed as a safer alternative. Since blastema formation and partial reprogramming are similar in terms of YF expressions, we found blastema-like cells in mammalian reprogramming with YF. This review outlines the characteristics of blastema across various organisms, emphasizing interspecies differences. We also explore studies on partial reprogramming and the possibility of inducing blastema-like cells via the temporary expression of YF in mammals.

Keywords: Regeneration, Blastema, Pluripotency factor, Cellular reprogramming, Intermediate cells

Introduction

Regeneration is the ability of living organisms to recover from damage and restore both the structure and function of damaged tissues. This process is often thought to simply recapitulate mechanisms from embryonic development, but recent studies suggest it involves more complex processes (1). While amphibians and fish can regenerate tissues even after severe injury, most mammals exhibit limited regenerative capacities, with the liver being one of the few exceptions (2).

These differences in the regenerative capacity of various species arise from variations in how cells respond to injury. In organisms with a high regenerative capacity, such as amphibians and fish, differentiated cells in damaged tissues temporarily revert to a more primitive, stem cell-like state, forming a cell mass known as the blastema (3). The blastema consists of reprogrammed stem-like cells that proliferate and contribute to tissue regeneration (4, 5). Interestingly, blastema-like cells are observed in mammals—such as the deer antler (6) and the mouse digit tip during regeneration (7, 8)—but their differentiation potential remains more restricted than in amphibians and fish (6).

An interesting aspect of blastema formation is the tran-

Received: November 14, 2024, Revised: November 26, 2024, Accepted: November 26, 2024, Published online: March 10, 2025
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sient expression of pluripotency factors. Studies have demonstrated that inhibiting these factors during the regeneration of fish fins or amphibian limbs suppresses the regeneration (9), indicating their critical role. These factors, often called Yamanaka factors (YFs) (10, 11), are well-known for their ability to reprogram somatic cells into induced pluripotent stem cells (iPSCs). While the expression of YF is activated during regeneration, the cells do not achieve full pluripotency *in vivo*. In contrast, iPSCs are fully reprogrammed and capable of differentiating into any cell type, offering great therapeutic potential, especially in mammals with low regenerative capacity, like humans (12). iPSCs also present reduced risks of immune rejection when derived from the patient's own somatic cells (13). Despite these advantages, iPSCs still have challenges, such as the risk of tumor formation due to residual undifferentiated cells, as well as genomic instability during reprogramming and culturing *in vitro*, which may increase the risk of tumorigenicity (14). Thus, direct or partial reprogramming has been proposed as a promising alternative, offering the advantage of generating target cells without transitioning through an iPSC state. This approach may help mitigate some of the risks associated with tumorigenicity and genomic instability (15-17). As we investigated the YF-mediated reprogrammings, we recently showed that the existence of blastema-like intermediate cells (ICs) during mammalian reprogramming *in vitro* (18).

This review summarizes the formation of blastema and the regeneration mechanisms in various animals. Additionally, we explore the possibility of identifying evolutionary remnants of blastema-like cells in mammals and discuss the induction of a mammalian version of blastema as well as potential applications in regenerative medicine.

What Is "Blastema"?

Regeneration refers to restoring new cells or tissues lost due to injury or disease. This complex process involves various cell types, including resident stem cells and immune cells in adult tissues, which are involved in the regeneration process (2). However, in certain types of injuries, such as the tail or limb amputation in amphibians, a process known as blastema-mediated regeneration is activated. Blastemas are mass of stem or progenitor cells that have differentiation potentials.

When an amputation occurs, the injured site is first covered by a layer of wound epidermis, beneath which blastemas are formed (5). The formation of blastemas involve several signaling pathways, including Fgf, Wnt, Bmp, and Hippo signaling. While these signaling pathways are known as essential, the exact mechanisms vary across different organisms (19-22). Once blastemas are formed, they undergo re-differentiation into cells of various lineages. This re-differentiation process leads to the completion of the regeneration, resulting in the recovery of both the structure and function of the damaged tissues (4). However, understanding the cellular and molecular basis of blastema formation still remain elusive.

Types of Blastemas

Historically, blastemas are defined as mass of pluripotent cells that can contribute to any regenerated structure (23, 24). Recently, however, the differentiation potential of blastemas has been found to vary across diverse organisms, reflecting changes through evolution. In invertebrates like planarians, a pluripotent cell mass called neoblasts accumulates at the wound site in response to injury, then form blastemas (25). In vertebrate organisms with high regenerative capacity, such as fishes and amphibians, blastemas contain a mixture of lineage-restricted progenitors (26-28). In mammals, digit tip blastemas are reported and considered to have limited regenerative capacity (7). Notably, blastema formation has not been reported in humans. Collectively, it seems that the differentiation potential of blastemas tends to decrease as organisms evolve.

Blastema-Mediated Regeneration in Animals

Planarians can regenerate whole organisms from tiny fragments of their bodies, including head, tail, or any other body parts. This amazing regenerative capacity is driven by a highly specialized and pluripotent cell population called neoblasts. Upon activation, neoblasts form a differentiated cell population that contributes to blastemas (29, 30). Recent advances in single-cell sequencing have revealed the heterogeneity within neoblasts, identifying various subtypes. Among the classified subtypes, it was confirmed that the subtype in which the surface protein *Smed-tspan-1* is expressed at a high level together with *Smed-piwi*, a marker of neoblasts, has significant regenerative potential. When a single cell of SMED-TSPAN-1+ neoblasts is transplanted into hosts devoid of stem cells, they can self-renew and differentiate into all cell types, thus proving functionally pluripotent (31). These neoblasts can be classified into several subtypes. Notably, gamma and sigma-neoblasts respond to injury by proliferating and have broad systemic capabilities, including the generation of zeta-neoblasts. However, zeta-neoblasts are not essential for regeneration; they primarily constitute a postmitotic

lineage, including epidermal cells (29). Unlike blastemas observed in other organisms, where somatic cells are reprogrammed in response to injury, the planarian blastema arises directly from neoblasts, which are already pluripotent (29, 32).

Among vertebrates, fish and amphibians exhibit remarkable regenerative capabilities, which are initiated by blastema formation. For example, zebrafish can regenerate various tissues and organs, including fins, heart, spinal cord, and even brain. Fin regeneration serves as a representative model of regeneration, with the blastema consisting mainly of multipotent stem cells that can differentiate into fin rays, muscles, nerves, and blood vessels. Recent research utilizing single-cell transcriptomics has identified diverse cell types involved in fin regeneration, revealing a blastema comprised of highly proliferative and lineage-restricted progenitor cells (33, 34).

Amphibians such as salamanders are renowned for regenerating entire limbs, encompassing bones, muscles, nerves, and other tissues. Following limb amputation, dedifferentiated cells from the stump of the remaining limb aggregate to form blastemas. The limb blastemas are heterogeneous cell mass consisting of lineage-restricted progenitors. Additionally, the limb blastemas retain positional memory of the missing tissue's identity and spatial organization, establishing the pattern of the lost structures during regeneration (28, 35-38).

Intriguingly, blastema formation is also observed in *Drosophila*. Although *Drosophila* is not typically associated with extensive tissue regeneration, it displays unique regenerative phenomena in its imaginal discs. When an injury occurs in the imaginal discs, a cluster of S-phase-labeled cells forms at the injury site, similar to the process observed in amphibians. This cluster is referred to as a blastema. For instance, if a wing imaginal disc is damaged, the proliferating cells within the blastema differentiate into specific wing cell types, such as wing epidermal cells and wing veins (39, 40).

In animals with high regenerative capacity, damage induces the formation of a blastema composed of pluripotent or multipotent cell populations that respond to the damage and generate multiple cell types (Fig. 1).

Blastema in Mammals

Mammals generally exhibit limited regenerative capacity compared to animals like fish and amphibians, although some exceptions exist (41, 42). In contrast, examples such as the annual regrowth of deer antlers, the closure of ear hole punches in rabbits, and the regeneration of digit tips in rodents involve the formation of blastema-like cells (8, 43, 44). In these instances, all three animal models exhibit transient blastema formation, consisting of undifferentiated cell populations that later differentiate into the cell types necessary for regeneration. These regenerative responses are regulated by complex interac-

	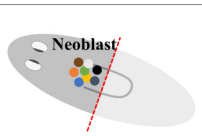			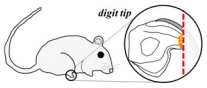	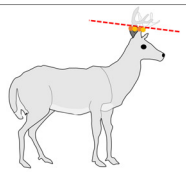
Formation process of blastema	Stem cell recruitment	Dedifferentiation & resident progenitor cell migration	Dedifferentiation & proliferative progenitor cells	Dedifferentiation	Resident progenitor cells
Differentiation potential of blastema	Pluripotent	Multipotent	Multipotent or lineage specific	Lineage specific	Lineage specific
Marker	*piwi-1*, *tspan-1*, *tgs-1*	*msxb*, *msxc*, *sly1*	*krt17*, *krt12*, *pax7*, *myf5*, *prrx1*	*Prrx1*, *Msx1*, *Pdgfra*	*PDGFRA*, *PRRX1*
References	*(30-32)*	*(21, 33,34)*	*(28, 37,38)*	*(19, 45-48)*	*(6, 49, 50)*

Fig. 1. Species-specific differences in blastema formation and regenerative potential. The characteristics of blastemas are summarized in terms of their formation process, differentiation potential, and specific markers. The dashed red lines indicate the site of injury or amputation where blastema formation begins. This figure illustrates that blastemas from different animals possess both unique and shared characteristics.

tions among various cell types, ultimately contributing to the formation of functional tissues.

In particular, mice possess a certain degree of regenerative ability, albeit not as extensive as that observed in salamanders. Specifically, mice can regenerate digit tips under certain conditions, such as when only the distal parts of the skin, bones, and nails are amputated, leaving structures like tendons, glands, or joints intact. However, more proximal amputations result in wound healing without regrowth of the digit tips (45). The essential step in digit tip regeneration is the formation of transient proliferating cells called the digit tip blastema, which generates different cell types to replicate the original tissue structure (46). Recent advancements in defining blastema cell identities have been achieved through single-cell RNA sequencing. This technique revealed that the mouse digit tip blastemas are heterogeneous cell mass consisting of Schwann cells, immune cells, endothelial cells, vascular smooth muscle cells, and fibroblasts. Among these cell types, fibroblasts form the largest portion of the blastema and commonly express broad fibroblast markers such as *Prrx1*, *Msx1*, and *Pdgfra*. Moreover, regenerative genes like *Mest*, which are absent in unamputated digit tips but upregulated after amputation, have been identified. These genes may play a role in regulating blastema formation. However, further research is necessary to elucidate the specific roles of these cell types and genes in blastema formation and the overall regeneration process. The exact origin of these cells, whether they are stem cells or de-differentiated progenitors, remains to be further investigated (7, 24, 46-48).

As mentioned, blastema is not typically found in mammals except in the case of mouse digit tip regeneration. However, recent reports indicate the presence of blastema-like cells in the regeneration of deer antlers, which occurs annually and exhibits the highest rate of bone growth among animals (49). Antler regeneration involves elements such as wounding, nerve input, and the wound epidermis, which are traditionally considered essential for epimorphic regeneration. Nevertheless, this process requires more than just these three elements, indicating the need for additional factors for successful regeneration (6, 50). Researchers have identified mesenchymal cells expressing the *paired-related homeobox 1* gene (*PRRX1*) during the early stages of antler regeneration, naming them antler blastema progenitor cells (ABPCs). In lower-level organisms such as axolotls, the blastema is formed through a dedifferentiation process. In contrast, ABPCs in antlers are not generated by dedifferentiation but are instead permanently present in the antler-generating tissue. Through integrated single-cell analysis involving deer, mouse, axolotl, and zebrafish, it was found that ABPCs integrate well with the blastema of mouse digit tip regeneration but not with the blastemas of axolotl limb or zebrafish fin regeneration (6). Accordingly, antler blastemas are similar to those of mouse digit tip blastemas but differ from those in animals with high regenerative capacity.

In summary, mammalian blastema-like cells, such as those observed in mice during digit tip regeneration and in deer during antler regrowth, demonstrate a limited capacity for regeneration compared to non-mammalian vertebrates.

Adaptive Cellular Reprogramming during Mammalian Regeneration

The limited regenerative capacity of blastema in mammals raises intriguing questions about the underlying mechanisms of cellular reprogramming. Recent studies have shown that certain mammalian cells can achieve temporary plasticity through a process known as “adaptive cellular reprogramming” (51), particularly in response to damage that depletes tissue-specific stem cells. During the regeneration of mouse intestines (52-54) and lungs (55-58), terminally differentiated somatic cells regain the ability to replenish both lost stem cells and other cell types in the damaged regions by “reprogramming.”

Ayyaz et al. (54) depleted 90% of adult stem cells in mouse intestines through irradiation and discovered a new type of stem cells that rarely found under homeostatic conditions. These cells, known as revival stem cells (revSCs), transiently appear in the injured crypts of the intestine, particularly in the absence of Lgr5+ intestinal stem cells. Ultimately, revSCs differentiate into all cell types within the crypts to reconstruct the damaged intestine.

Similarly, transitional ICs important for tissue regeneration have been identified in the injured lungs of mice, known as damage-associated transient progenitors (DATPs), alveolar differentiating intermediates (ADIs), or proliferating alveolar type 2-like cells (PATS) (55-57). For example, when bleomycin was administered to mouse lungs to deplete alveolar type 1 (AT1) cells, this injury triggered AT2 cells to become more plastic cells, known as DATPs, through reprogramming, which then replaced the damaged AT1 cells and repaired the lungs (57). DATPs/ADIs/PATS were also found in other adverse conditions, such as idiopathic pulmonary fibrosis and in postmortem lungs of coronavirus disease 2019 patients (59).

Adaptive cellular reprogramming induced by damage generates stem cell-like cells in mammals. These stem cell-like cells seem to be the blastemas found in animals with high regenerative capacity, as damage-induced repro-

gramming results in the formation of blastemas. This similarity suggests an evolutionary conserved process shared by mammals and lower animals.

Induced Blastema-Like Cells in Mammals

Given that both revSCs and blastemas are generated through reprogramming, we need to ask whether there are shared factors that induce this reprogramming. In terms of reprogramming, YFs are strong drivers for generating iPSCs. Long-term expression of YF is required until the establishment of induced pluripotency (10, 11). Interestingly, two phenomena are observed with the transient expression of YF during reprogramming. One phenomenon is pluripotency factor-mediated direct reprogramming (PDR) *in vitro* (15, 16, 60), while the other is induced rejuvenation *in vivo* (61-63). It is plausible that YF-induced rejuvenation is achievable because YF are key transcription factors expressed in "embryonic" stem cells. In PDR, cells of all three germ layers can be obtained through transient YF expression and lineage-specific culture medium (Fig. 2). Given that reprogramming factors are typically the transcription factors specific to the reprogramming target cells, it seems implausible that YF can generate cells of all three germ layers in PDR without generating iPSCs. It is particularly notable that YF are temporally expressed dur-

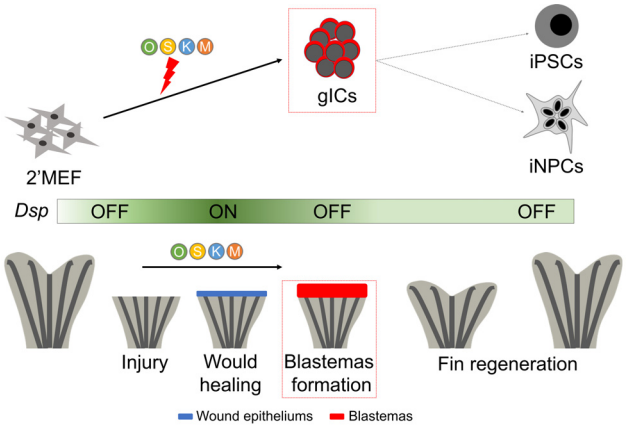

Fig. 3. A comparison between *in vitro* reprogramming and *in vivo* regeneration. This figure is the summary of our recent publication (18). In *in vitro* reprogramming, the transient expression of Yamanaka factors (OSKM; *Oct3/4, Sox2, Klf4,* and *c-Myc*) induces granular intermediate cells (gICs), which further generate either induced pluripotent stem cells (iPSCs) or induced neural progenitor cells (iNPCs). In *in vivo* regeneration, an injury to fish fin induces the formation of blastemas, which then further regenerate entire fin. Interestingly, OSKM also affect *in vivo* regeneration of fish fin. *Desmoplakin* (*Dsp*) expression is required for the formation of both gICs and blastemas. Collectively, it is notable that gICs and blastemas seem to be equivalent.

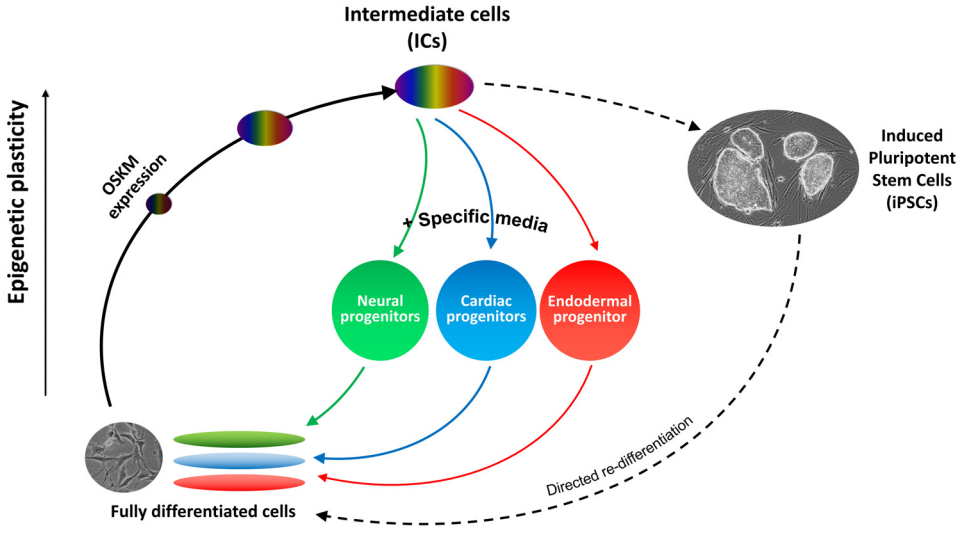

Fig. 2. Two Yamanaka factor (YF)-mediated reprogrammings. The YFs (OSKM; *Oct3/4, Sox2, Klf4,* and *c-Myc*) can induce two types of reprogramming: induced pluripotent stem cell reprogramming (iPSCR) and pluripotency factor-mediated direct reprogramming (PDR). In iPSCR, long-term expression of YF is required, while in PDR, transient expression is sufficient. Induced pluripotent stem cells (iPSCs) require re-differentiation to generate cells of all three germ layers (ectoderm, mesoderm, and endoderm). However, in PDR, cells of all three germ layers can be generated directly from intermediate cells (ICs). Considering that iPSCs are generated from ICs, these ICs seem to possess unique epigenetic plasticity. It is notable that the ICs and iPSCs are distinct.

ing the blastema-mediated fin regeneration in zebrafish, and knockdown of these YF has been shown to impair the fin regeneration (9). Additionally, recent report indicates that YF expression facilitates the generation of revSCs (64). Collectively, thus, the YF are involved in both *in vitro* reprogramming and *in vivo* regeneration.

We recently reported that *Desmoplakin* (*Dsp*) is a common factor between *in vitro* reprogramming and *in vivo* regeneration (18). In this study, we aimed to identify the ICs involved in YF-mediated reprogramming by comparing iPSC reprogramming and PDR. We successfully identified two types of ICs and found that *Dsp* is required during the intermediate stage, as confirmed by knockdown of *Dsp*. We then hypothesized that ICs might be analogous to blastemas, as YF are required for the generation of both ICs *in vitro* and blastemas *in vivo*. This hypothesis was further confirmed by knockdown of *dsp* during fin regeneration in zebrafish. When we compared our *in vitro* reprogramming results with published *in vivo* regeneration data using single-cell RNA sequencing, we found that granular ICs exhibited the highest similarity to blastema cells (Fig. 3). These results suggest that (1) blastema-like cells can be induced in mammalian cells, and (2) YF can induce these blastema-like cells in mammals. In summary, YF may induce blastema-like cells in mammals.

Perspectives

We reviewed animal regeneration from the perspectives of blastema formation and evolution context. Currently, regeneration in mammals is considered limited and distinct from that in amphibians, fish, and planarians. In this review, we propose that regeneration is evolutionarily conserved from the perspective of adaptive cellular reprogramming: when damage occurs, cells or tissues respond by generating "ICs" through this reprogramming process across all animals. Because these ICs may acquire stem cell-like potential, they can regenerate the damaged tissue. In lower animals, these ICs are known as blastema, whereas in mammals they are referred to as revSC, although the regenerative potential of these ICs varies depending on tissue type and animal species.

We observed that blastema-like ICs during YF-mediated reprogramming *in vitro*, as described in our recent publication (18). We expect that these blastema-like ICs have the potential to generate cells of all three germ layers, as ICs are formed during PDR, which can reprogram somatic cells into ectodermal, mesodermal, and endodermal cells (15, 16, 65). Although further characterization and elucidation are needed, we expect that our blastema-like ICs could be a more activated form of blastema cells (ABCs) in terms of their differentiation potential, as blastema is currently regarded as a mixture of multipotent cells. The concept of ABC is quite challenging but could open new pathways for advancing regenerative medicine.

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Funding

This research was supported by the Korean Fund for Regenerative Medicine grant (#23A0102L1) funded by the Korea government (the Ministry of Science and ICT [MSIT] and the Ministry of Health & Welfare); the ABC-based Regenerative BioTherapeutics (ABC project) grant (#RS-2024-00426031) funded by MSIT; the National Research Council of Science & Technology grant (#GTL24021-000) by MSIT; the Bio&Medical Technology Development Program (#RS-2024-00508575) of the National Research Foundation funded by MSIT; and the Korea Research Institute of Bioscience and Biotechnology Research Initiative Program (#KGM5362414).

Potential Conflict of Interest

There is no potential conflict of interest to declare.

Authors' Contribution

Conceptualization: JN, JK. Formal analysis: JN, BM, AB, SYL. Funding acquisition: JK. Investigation: JN, BM, AB, SYL, MJC, JK. Project administration: JK. Supervision: JK. Validation: JN, JH, JK. Writing – original draft: JN. Writing – review and editing: JK.

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