

Bone Disease and Regeneration: A Single-Cell Technique Termed Detects Vertebral Cellular Dynamics

Abstract

Bone is a vital organ that performs a variety of functions, and the bone marrow within the skeleton consists of a complex mixture of hematopoietic, vascular, and spinal cells. Current single-cell RNA-sequencing (scRNA-seq) techniques reveal heterogeneity and broadly distinct hierarchical structures in spinal cells. Spinal stem and progenitor cells (SSPCs) are located upstream in the hierarchy and differentiate into chondrocytes, osteoblasts, osteocytes, and bone marrow adipocytes. In the bone marrow, several types of bone marrow stromal cells (BMSCs) with SSPC potential are localized in distinct spatial and temporal regions, and BMSCs may be replaced by SSPCs during aging. In vivo lineage tracing techniques show that different types of vertebral cells accumulate simultaneously and contribute to bone regeneration. In contrast, with aging these cells differentiate into adipocytes, causing senile osteoporosis. scRNA-seq analysis revealed that changes in cell-type composition are the main cause of tissue senescence. In this review, we discuss the cellular dynamics of vertebral cell populations involved in bone homeostasis, regeneration, and osteoporosis.

Keywords: Aging • Bone marrow adipocytes • Bone regeneration • Single-cell RNA-sequencing (scRNA-seq)

Introduction

Progressive aging has a significant negative impact on the spinal system. Age-related diseases of the spine, especially those caused by loss of bone homeostasis and imbalance in bone metabolism, such as osteoporosis and associated fractures, significantly shorten healthy life expectancy [1]. Cellular senescence is a major cause of bone homeostasis imbalance. As we age, senescent cells accumulate within tissues, resulting in an overall decline in the tissue's ability to regenerate, leading to degenerative diseases. Removal of senescent cells prevents age-related bone loss in mice. Therefore, dynamic changes in vertebral cells are strongly associated with vertebral aging [2].

A thorough understanding of spinal cord cell biology is essential to addressing these bone-related adverse events. Spinal cells are composed of several cell types, including spinal stem cells (SSCs), spinal progenitor cells, differentiated chondrocytes, osteoblasts, and bone marrow adipocytes. SSCs are bone tissue-specific stem cells and are at the top of the skeletal formation hierarchy. More than 50 years have passed since bone marrow SSC was first established. SSCs are defined as mesenchymal cells with potential for self-renewal and tri-lineage differentiation into chondrocytes, osteoblasts, and adipocytes [3]. They have been experimentally demonstrated by ex vivo cell culture and/or subsequent in vivo heterotopic transplantation. Although ex vivo experiments using primary cell cultures are the gold standard for demonstrating SSC properties, it is controversial whether these cell culture results alone define cultured cells as stem cells. Target cells do not always behave in the same way as they do in their natural biological environment, because culture conditions differ greatly from those in the body. In addition, one of the criteria for SSCs, chondrocyte, osteoblast, and adipocyte differentiation potential, is evaluated under artificial conditions using different differentiation-inducing media. Therefore, SSCs and

Anshika Singh*

Department of Stem Cell and Research, India

*Author for correspondence:

anshikauvari@gmail.com

Received: 01-June-2023, Manuscript No. srrm-23-101884; **Editor assigned:** 05-June-2023, Pre-QC No. srrm-23-101884 (PQ); **Reviewed:** 19-June-2023, QC No. srrm-23-101884; **Revised:** 24-June-2023, Manuscript No. srrm-23-101884 (R); **Published:** 30-June-2023, DOI: 10.37532/srrm.2023.6(3).61-64

their progeny should be carefully defined using a variety of well-established methods in the research field of stem cell biology [4].

Bone marrow contains several types of SSCs and their progenitor cells (SSPCs:

spinal stem and progenitor cells) and their progenitor cells. Among the vertebral cells in the bone marrow, bone marrow stromal cells (BMSCs) are defined as a mesenchymal population located between the outer surface of bone marrow vessels and the bone surface, and several unexplained vertebral cell types have been identified. It has been suggested to be contained in BMSC. Although BMSCs are distinct from SSPCs, a subpopulation of BMSCs has been reported to contribute downstream vertebral cells as his SSPCs. These seemingly conflicting roles of BMSCs are complex. This is because BMSCs themselves, including their spatial location, are not yet fully understood. Therefore, there is a need to clearly define different tissue-specific BMSCs through basic research. Now, with the use of new techniques, BMSCs are unraveling to be a heterogeneous population, which will lead us to a new era of spinal stem cell biology [5].

Technological advances have provided new insights into spine biology. lineage studies based on cell surface markers are essential methods for studying cell populations. These approaches allow us to define cell populations and track their progeny. To adequately characterize heterogeneous vortex cell populations, single-cell RNA-sequencing (scRNA-seq) analysis is an important technique that complements previous approaches. scRNA-seq reveals the molecular signatures of individual cells, identifies new cell types, and provides insight into cell dynamics within tissues. Recent advances in scRNA-seq technology have confirmed the reliability of scRNA-seq technology in identifying cell types and analyzing gene expression patterns [6].

Spatiotemporal-specific vertebral stem cells

SSCs play an important role in the development, maintenance and regeneration of bone tissue. SSCs can self-renew and differentiate into osteoblasts, chondrocytes, adipocytes, and stromal cells required for bone growth and repair. The concept of SSC arose from studies that found that

autologous fragments of bone marrow or its cell suspension generate vertebral tissue after heterotopic transplantation. Currently, SSCs have been identified in mouse long bones by two different approaches [7].

In vivo lineage tracing approach. These approaches have the advantage of being able to select target cells while excluding hematopoietic and endothelial cells. In the first case, mouse SSC (mSSC) are defined as having multiple markers including CD51+CD90-CD105-CD200+PDGFR α +Sca1+CD45-TER119- and CD73+CD31-. The latter approach of *in vivo* lineage tracing using mouse genetic models uncovered several types of His SSCs at different locations in long bones. B. Parathyroid hormone-related protein (PTHrP) stem cells and growth plates located in the zone of growth arrest Early postnatal plate, cathepsin K+ periosteal stem cells [8]. CXCL12 + LepR + reticular stromal cells in adult-to-senile bone marrow and fibroblast growth factor receptor 3 (FGFR3) + endosteal stromal cells in young bone marrow. In particular, populations targeted by specific cre or creER lineages are said to include the SSC populations described above. These Cre driver lines mark not only SSC but also other cell types. These lineage-tracing-based SSC identification processes are often performed in combination with FACS-based approaches to isolate cell surface markers. This combined approach allows us to identify true SSCs with their distinct spatial mapping and cellular dynamics. These small populations of highly clonogenic SSCs, present in every bone compartment, play an important role in bone maintenance and regeneration [9].

Taken together, these scRNA-seq approaches demonstrate the heterogeneity of BMSCs. They fall into various specific types such as: B. Osteogenic and chondrogenic bipotent mesenchymal progenitor cells, osteogenic and adipogenic progenitor cells, and progenitor cells determined by osteogenic or adipose lineages. Importantly, a subset of BMSCs contains multiple possible spatiotemporal SSPCs. Note, however, that scRNA-seq analysis can only provide approximate representations of the various cell populations within BMSCs. Interactions with peripheral vascular cells and hematopoietic cells cannot be accurately represented. Moreover, spatial information

is lost in recently published scRNA-seq analyzes. Therefore, it is imperative to develop strategies for high-dimensional integrated and spatial transcriptome analysis that enable a more comprehensive understanding of the complex cellular interactions and dynamics within the bone marrow stromal microenvironment. Furthermore, we strongly believe that the accuracy of single-cell sequencing analysis can be improved by effectively integrating the biological information obtained from *in vivo* cell profiling into single-cell sequencing analysis. This synergistic effect has great potential to advance our understanding of the complex cellular landscape and increase the confidence of single-cell sequencing data [10].

Cellular dynamics of BMSCs

Bone is a dynamic, unbroken tissue that is constantly remodeled throughout our lifetime. Several cell types play an important role in this process by controlling bone remodeling in a manner similar to osteocytes. Consistent with these scRNA-seq results, biological data using *in vivo* lineage tracing studies with tamoxifen-inducible creER or constitutively active Cre strains demonstrate BMSC heterogeneity and dynamics. Several studies have addressed the dynamics of large BMSC populations expressing CXCL12 and LepR. LepR-Cre labeled reticular stromal cells are the major source of osteoblasts and adipocytes in adult bone marrow. These cells reside in the bone marrow and are rarely found in bone by the first two months of life. However, the number of LepR-cre+ osteoblasts gradually increases from 6 to 14 months of age. Parentage studies using the tamoxifen-inducible LepR-creER lineage revealed that perinatal her LepR-creER+ medullary stromal cells decreased with age and did not differentiate into osteoblasts. In contrast, adult LepR-creER+ cells become the major source of osteoblasts.

Role of BMSCs on bone regeneration

An *in vivo* lineage tracing approach is a useful tool for visualizing cell dynamics during bone regeneration. Many types of vertebral cell-specific cre or creER mice have been used to elucidate the contribution of SSPCs to the bone regeneration process. However, many of these models contain 'constitutively active' Cre, such as: B. Prrx1-cre for periosteum and

LepR-cre, Adipoq-cre, and Mx1-cre for bone marrow. Tight control of the timing of Cre recombination is critical during the bone regeneration process, as various genes are positively and negatively expressed during the healing phase, resulting in dynamic changes in cellular state. The use of constitutively active Cre is useful for pre-bone regeneration of labeled cells because the expression of recombinase driver genes is upregulated during the bone regeneration process, which can lead to *de novo* recombination during bone regeneration. Dynamics may not be captured accurately. However, tamoxifen-inducible CreER strains can control the timing of recombination and are therefore immune to abrupt changes in gene expression at sites of bone regeneration. Therefore, the CreER system allows us to probe the lineage of spinal cells native to the tissue.

Conclusion

In this review, we focus specifically on the unique behavior of different subpopulations of BMSCs under physiological, injury, and aging conditions, and the heterogeneity associated with age-related osteoporosis, based on scRNA-seq data. We discussed phylogenetic heterogeneity.

Adipogenic BMSCs, a subpopulation of central reticular stromal cells, slowly differentiate into myeloid adipocytes during aging. These cells remain quiescent within the marrow cavity and do not migrate or differentiate into cortical osteoblasts. Upon injury, these cells are recruited to cortical defects and differentiate into osteoblasts during cortical bone repair in a canonical Wnt pathway-dependent manner. Senescent cells secrete pro-inflammatory factors and the formation of an abnormal microenvironment within the bone marrow exacerbates bone loss. A decrease in the number of osteoblasts and a marked increase in the number of adipocytes within the bone marrow are characteristic pathological hallmarks of osteoporosis.

References

1. Salinet ASM. Do acute stroke patients develop hypocapnia? A systematic review and meta-analysis. *J Neurol Sci.* 15, 1005-1010 (2019).
2. Jellish WS. General Anesthesia versus conscious sedation for the endovascular treatment of acute ischemic stroke. *J Stroke Cerebrovasc Dis.* 25, 338-341 (2015).

3. Rasmussen M. The influence of blood pressure management on neurological outcome in endovascular therapy for acute ischaemic stroke. *Br J Anaesth.* 25, 338-341 (2018).
4. Südfeld S. Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. *Br J Anaesth.* 81, 525-530 (2017).
5. Campbell BCV. Effect of general anesthesia on functional outcome in patients with anterior circulation ischemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient's data. *Lancet Neurol.* 41, 416-430 (2018).
6. Wu L. General anesthesia vs local anesthesia during mechanical thrombectomy in acute ischemic stroke. *J Neurol Sci.* 41, 754-765 (2019).
7. Goyal M. Endovascular thrombectomy after large vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 22, 416-430 (2016).
8. Headey D. Developmental drivers of nutritional change: a cross-country analysis. *World Dev.* 42, 76-88 (2013).
9. Deaton A, Dreze J. Food and nutrition in India: facts and interpretations. *Econ Polit Wkly.* 42- 65 (2008).
10. Headey DD, Chiu A, Kadiyala S. Agriculture's role in the Indian enigma: help or hindrance to the crisis of undernutrition? *Food security.* 4, 87-