METABOLIC REGULATION AND EPIGENETIC CONTROL: UNRAVELING THE COMPLEXITY OF SKELETAL STEM CELL FATE AND BONE HEALTH

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ABSTRACT

Skeletal stem cells (SSCs) are essential for bone formation and tissue regeneration within the skeletal system. These self-regenerating cells differentiate into various skeletal cell types, maintaining skeletal health. However, aging diminishes SSC capacity, impacting skeletal integrity. Epigenetics, the study of heritable changes in gene expression, plays a crucial role in stem cell regulation. Mechanisms like DNA methylation and histone modifications control gene expression without altering the DNA sequence. Dysregulation of epigenetic processes in transplanted cells may lead to immunological rejection or functional impairment. Understanding epigenetic regulation in stem cells is vital for tissue regeneration strategies. This narrative review focuses on summarizing existing scientific literature on epigenetic regulation within stem cells, particularly skeletal stem cells. The study utilized Google Scholar to search for relevant articles using keywords like "epigenetic", "stem cell", and "skeletal stem cell". Selection criteria included publication year, article title, abstract, Scopus ranking, and accessibility. Four articles were chosen as reference sources for the review. Recent research emphasizes cellular metabolism's role in regulating skeletal functions through skeletal stem cells (SSCs), crucial for skeletal health and potential regenerative therapies. Transcriptomic and epigenetic analysis of human SSCs reveal species-specific pathways. Metabolic pathways are vital for SSC self-renewal and multipotency, with glycolysis being the primary energy source for human bone marrow stem cells. Aging affects bone cells and inherited epigenetic changes significantly influence cell fate. Recent studies identify Ptip as a key epigenetic regulator of glycolysis in SSCs, impacting growth plate activity.

Keywords : Skeletal stem cells; epigenetic; regulation

INTRODUCTION

Skeletal stem cells (SSCs) refer to stem cells found in various parts of the tissue within the skeletal system, such as the periosteum, skull, and vertebrae. This discovery was made by Greenblatt and team. SSCs, or self-regenerating stem cells, produce various types of cells that form adult bone, which significantly explains how the physiology and specific disease processes in that area occur (Debnath et al., 2018; Sun et al., 2023; Cheng et al., 2024). Stem cells of the skeleton (SSC), which reside in the tissue, have regenerative properties and can differentiate into various types of cells, such as chondrocytes, bone cells, bone marrow adipocytes, and stromal cells, which are important for the growth and balance of the skeletal system (Li et al., 2022). The natural aging process leads to a decline in the capacity of adult stem cells to maintain the condition of the system to remain fresh and strong (Ambrosi et al., 2019; Butler et al., 2022).

Epigenetics is the scientific field that examines alterations in gene expression that are heritable and enduring, happening via adjustments to chromosomes rather than the DNA sequence per se. Despite not directly

impacting the DNA sequence, epigenetic mechanisms can control gene expression by means of chemical modifications to DNA bases and changes in the higher-order structures of chromosomes where DNA is packaged (Al Aboud et al., 2023). Epigenetics refers to changes in genetic activity that can be inherited, as well as long-term modifications in the cell's capacity to perform gene transcription at the chromosome structure level (Zhang et al., 2020; Walewska et al., 2023). The epigenetic control of gene expression can occur through processes such as DNA methylation, histone modifications, and chromatin remodeling, which occur without altering the DNA sequence itself (Walewska et al., 2023). Chromatin remodeling, DNA methylation, and post-translational histone modifications are among the primary epigenetic mechanisms observed to collaborate within stem cells. Epigenetic alterations in chromatin state do not impact the DNA sequence. Collectively, transcription factors, signaling transduction pathways, and epigenetics govern cell destiny and uphold the cellular capacity for differentiation (Zhang et al., 2021). Gene expression in transplanted cells has the potential to influence the quantity or configuration of abnormal methylation or histone modifications, potentially causing immunological disparity with the host tissue, resulting in rejection or immune tolerance. Irregular chromatin conditions might interfere with the genome stability or integrity of transplanted cells, heightening the risk of infection or functional impairment. Moreover, aberrant levels or patterns of methylation or histone modifications could modify gene expression levels within transplanted cells, consequently impacting synthesis (Nori et al., 2011, Kobayashi et al., 2012; Ramotowski et al., 2019; DeBrot, 2019; Yang et al., 2024). In this article, we will discuss the epigenetic regulation that occurs in stem cells and the implications for tissue regeneration.

MATERIALS AND METHODS

This study falls under the category of a narrative review. A narrative review selectively identifies what researchers have written about a specific subject or topic. Its goal is to summarize the existing scientific literature and provide a comprehensive report on the current state of knowledge concerning that topic.

This study is inspired by the latest discoveries in the field of stem cells, discussing epigenetic regulation within stem cells. The process of searching for articles as reference sources for researchers in making reviews is through Google Scholar by typing keywords "epigenetic", "stem cell", and "skeletal stem cell". In the article collection process, the authors conducted selection by setting inclusion criteria for reference source articles. Article selection is based on the year of publication of the reference source article, the title of the reference source article, the abstract of the reference source article, the ranking of the reference source article in Scopus, and articles that are freely accessible.

Based on the author's selection results of the reference source articles, there are 4 articles that have been successfully chosen as reference source articles for review.

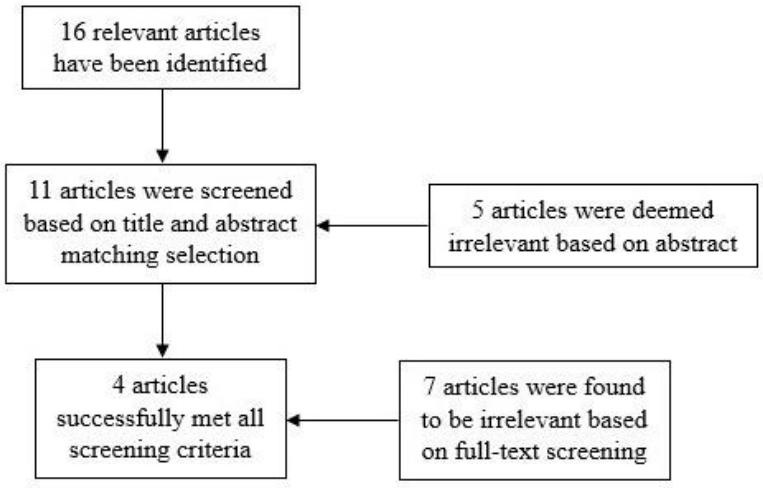

Figure 1. A graphical representation illustrating the process of conducting a literature search

RESULT AND DISCUSSION

The skeletal system performs numerous roles, including offering mechanical support, controlling motion, generating blood cells, storing minerals, and managing endocrine activities. This intricate function is accomplished through the interplay among different types of cells—osteoblasts, chondrocytes, bone marrow adipocytes, and stromal cells—all derived from skeletal stem cells. Fresh evidence suggests the significance of cellular metabolism in molecularly controlling the skeletal system (van Gastel & Carmeliet, 2021).

Skeletal Stem Cell Types

Skeletal stem cells, located at the top of the skeletal system hierarchy, provide the origin for various types of mature skeletal cells. Stromal cells that support blood formation (or some of them) also exhibit characteristics of stem cells or progenitor cells and participate in the formation of osteoblasts and adipocytes in the bone marrow. Common markers used to identify and/or isolate each of these cell types (Capulli et al., 2014; Hallet et al., 2019). Recent research evidence suggests that conserved pathways specific to certain species in skeletal formation and responses to injuries will guide regenerative approaches in the future (Chan et al., 2018). Recent research evidence can be demonstrated in Figure 2, adapted from the research report by Chan et al., 2018.

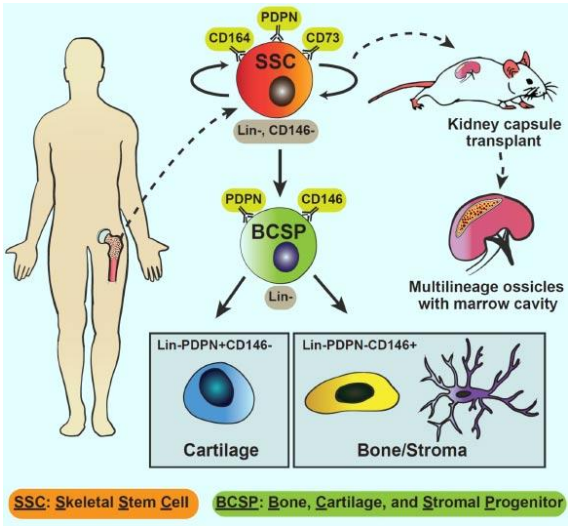

Figure 2. Discoveries regarding human skeletal stem cells

Stem cells, possessing self-renewal and multipotent capabilities, exist in fetal and adult bone marrow, with potential derivation from induced pluripotent stem cells (iPSCs). Researchers have mapped the lineage of skeletal tissue formation in humans by understanding the relationship between human skeletal stem cells and younger skeletal progenitors. Comparative analysis of transcriptomic and epigenetic data between human and mouse skeletal stem cells uncovers both shared evolutionary pathways regulating skeletal tissue formation and unique molecular pathways potentially responsible for species-specific differences in bone development and structure (Chan et al., 2018).

Controlling the Metabolic Activity of Skeletal Stem Cells

Stem cells can self-renew and have the potential to generate various types of adult cells. This process is regulated by strict molecular controls, with metabolic pathways recognized as key in cellular decision-making (Chandel et al., 2016).

Human bone marrow stem cells (BMSCs) predominantly rely on glycolysis for energy and biomass production, with glucose also supporting biosynthesis and oxidative stress management (Lunt & Heiden, 2011; Salazar-Noratto et al., 2020). Hypoxic conditions in the bone marrow prompt a glycolytic shift in BMSCs regulated by HIF-1α, crucial for their survival and bone tissue generation. Studies suggest that BMSCs in their natural environment depend on glycolysis and HIF-1α (Shum et al., 2016; Stegen et al., 2016; Ambrosi et al., 2019; Matsushita et al., 2020; Serowoky et al., 2020; Tournaire et al., 2020). While glucose is the primary fuel for glycolysis, the tricarboxylic acid (TCA) cycle can utilize other nutrients. Although human BMSCs can perform fatty acid oxidation (FAO) in culture, the role of FAO in skeletal stem cells remains unclear, with limited impact on their survival. Additionally, BMSCs can efficiently oxidize acetoacetate, a ketone body, in the TCA cycle, producing ATP with lower reactive oxygen species levels than glucose oxidation (Board et al., 2017; Newman & Verdin, 2017). Amino acid metabolism, particularly glutamine, is vital for BMSC function, with its depletion impairing BMSC proliferation. Glutamine is utilized by BMSCs for amino acid and glutathione formation. However, the impact of glutaminase deletion on BMSCs varies depending on the method of deletion (Stegen et al., 2016; Chen et al., 2019; Kurmi & Haigis, 2020; Hu et al., 2020; Stegen et al., 2020; Yu et al., 2019).

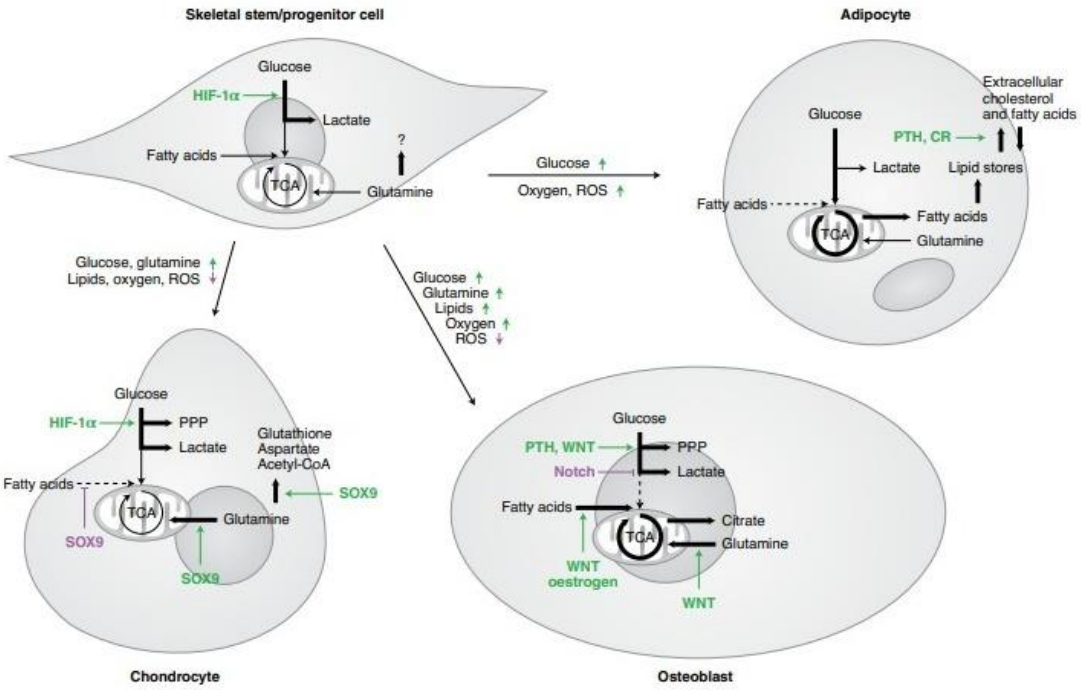

Figure 3. Skeletal stem cells metabolism

Cell Metabolism during the Process of Aging and Bone Degeneration

The aging process significantly impacts the function of skeletal cells and is a key risk factor in the development of degenerative bone diseases such as osteoporosis and osteoarthritis. Conversely, supporting specific metabolic pathways can enhance cell health and prevent bone damage or provide benefits in regenerative efforts (van Gastel & Carmeliet, 2021).

The aging process affects bone marrow stem cells (BMSCs), diminishing their frequency and osteogenic potential while triggering mitochondrial dysfunction, decreasing oxygen consumption, and elevating levels of reactive oxygen species (ROS) (Bellantuono et al., 2009; Yu et al., 2018). This dysfunction may involve declining NAD+ levels, leading to reduced sirtuin activity (Neri & Borzì, 2020). The administration of nicotinamide mononucleotide, an NAD+ precursor, enhances BMSC expansion, osteogenesis, and safeguards bone from aging and radiation-induced damage in mice (Song et al., 2019). Moreover, in aged BMSCs, reduced mitochondrial activity is influenced by diminished PGC-1α activity via p53 signaling and decreased GLS activity due to decreased estrogen-related receptor alpha signaling, resulting in impaired osteogenic differentiation and disturbances in bone-fat balance (Sui et al., 2016). Elevated kynurenine levels, an oxidized tryptophan metabolite, further impact mitochondrial metabolism in BMSCs and osteoblasts, contributing to reduced osteoblast numbers and increased bone loss and osteoporosis (Kondrikov et al., 2020).

Aging leads to reduced mitochondrial metabolism and increased oxidative stress in bone marrow stem cells (BMSCs), impacting bone formation and osteoblast function. Age-related changes affect the number and osteogenic capacity of periosteal skeletal stem cells (SSCs), influencing bone fracture healing. In joint cartilage, aging is a significant risk factor for osteoarthritis (OA), with mitochondrial dysfunction and metabolic

alterations playing crucial roles in OA pathogenesis. Therapeutic approaches targeting mitochondria, such as trehalose or pharmacological stabilization of HIF-1α, hold promise in preventing OA development (Hu et al., 2020). Additionally, alterations in fatty acid and cholesterol metabolism contribute to OA progression, emphasizing the significance of metabolic changes in this disease (Ashraf et al., 2011).

Metabolic Regulation of Epigenetic Modifications

Epigenetic changes inherited from stem cells play a crucial role in determining cell fate and maintaining identity. Nutritional conditions and metabolic health affect these changes, with metabolites from the TCA cycle serving as coenzymes. Insufficient nutrients during development can lead to lasting epigenetic modifications across generations. While there is no specific research on stem cell metabolism in aging, metabolic shifts during aging are believed to influence epigenetic changes, and vice versa, alterations in metabolism can exacerbate age-related epigenetic modifications.

The processes of DNA methylation and histone modification play a role in stem cell regeneration, while demethylation triggers activation and differentiation (Beerman & Rossi, 2015; Chandel et al., 2016). Hypoxia alters the balance of α-KG and succinate metabolites, affecting histone demethylase enzyme (HDMs) activity and influencing hematopoietic stem cell (HSC) regulation. Increased oxidative phosphorylation (OXPHOS) activity in activated HSCs accelerates cell differentiation. Serial proliferation challenges may result in decreased DNA methylation with age, contributing to excessive differentiation of aging HSCs (Chambers et al., 2007; Sun et al., 2014; Chandel et al., 2016). Mutations in epigenetic enzymes, such as DNMT3a, are often associated with leukemia and found in elderly individuals (Beerman & Rossi, 2015; Chandel et al., 2016).

Histone acetyltransferase (HAT) requires acetyl-CoA from glycolysis, while histone deacetylase (HDAC) depends on the NAD+/NADH ratio (Imai & Guarente, 2014). Both influence metabolic pathways, such as insulin and glucose, as well as crucial protein regulation for mitochondrial biogenesis and metabolism, such as FOXOs and HIF-1α. Loss of HAT or HDAC can disrupt stem cell function, especially regeneration. In quiescent stem cells, a high ratio of acetyl-CoA to NAD+ may sustain regeneration activity, while in stem cells activated by oxidative phosphorylation, deacetylation may be more dominant for differentiation. Decreased NAD+ occurs in aging stem cells, which also leads to reduced histone acetylation. Obesity and high-fat diets also affect HDAC activity, resulting in HSC dysfunction resembling aging (Zhang et al., 2013; Tie et al., 2014; Chandel et al., 2016).

Regulation of Epigenetic in Skeletal Stem Cell

Epigenetic changes play a crucial role in regulating the capacity and activity of stem cells (Zhao et al., 2023). Liang et al. isolated bone precursor stem cells (SSC), pBCSP, and BCSP from neonatal mouse growth plates for RNA-seq and ChIP-seq analysis to identify distinct epigenetic features. Ptip plays a major role in controlling the activity and capacity of SSCs by regulating the glycolysis pathway (Liang et al., 2024).

Genes regulated in SSCs lacking Ptip associated with the glycolysis pathway show higher glycolytic activity. ChIP-seq analysis indicates increased H3K27ac marks, indicating a shift towards more active epigenetic changes. Pgk1 is a gene regulated in SSCs lacking Ptip and is believed to influence metabolic profiles. Increased Ptip suppresses Pgk1, while decreased Pgk1 restores glucose consumption and lactate production to normal levels (Liang et al., 2024).

There are dynamic epigenetic changes from SSCs to pBCSPs and BCSPs. Research by Liang et al. revealed that Ptip is a major epigenetic regulator of the glycolysis pathway in SSCs, which then affects the activity and structure of growth plates (Liang et al., 2024). The mechanism of epigenetic regulation in skeletal stem cells is explained through Figure 4, adapted from the research by Zhao et al, 2023.

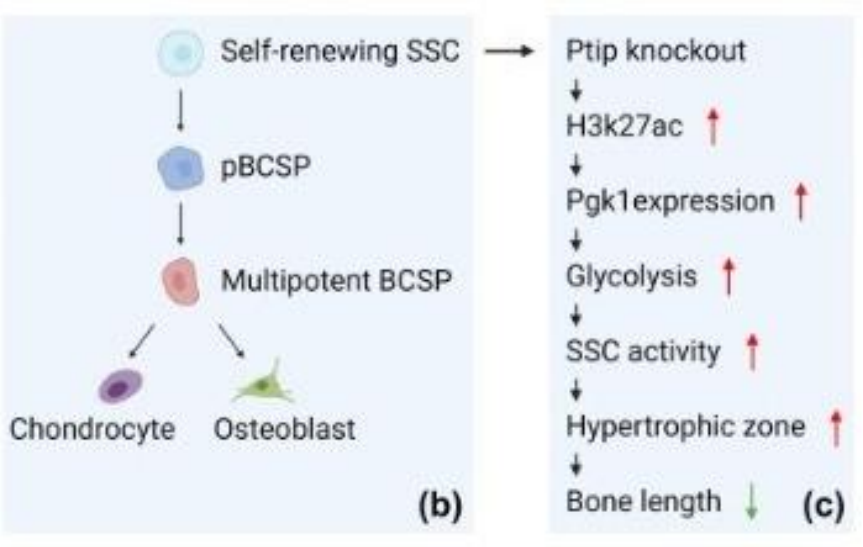

Figure 4. Epigenetic Regulation of Skeletal Stem Cell

SUMMARY

The skeletal system, crucial for mechanical support, blood cell generation, and more, relies on various cell types, including skeletal stem cells (SSCs), which give rise to osteoblasts, chondrocytes, and others. Recent studies highlight the role of cellular metabolism in skeletal regulation. SSCs, pivotal in skeletal hierarchy, originate diverse skeletal cells. Understanding human SSC lineage through transcriptomic and epigenetic analysis reveals species-specific pathways and potential regenerative strategies. Stem cells' self-renewal and multipotency, regulated by metabolic pathways, are pivotal in skeletal health. Human bone marrow stem cells predominantly utilize glycolysis, but can also perform fatty acid oxidation and efficiently use ketone bodies. Aging affects bone cells, impacting bone formation and osteoarthritis development. Epigenetic changes inherited from stem cells play a key role in cell fate determination. Recent research identifies Ptip as a major epigenetic regulator of glycolysis in SSCs, influencing growth plate activity and structure.

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