Biomedicine & Pharmacotherapy 89 (2017) 719–731

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Review

Dynamic changes of epigenetic signatures during chondrogenic and adipogenic differentiation of mesenchymal stem cells

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ARTICLE INFO

Article history:
Received 25 December 2016
Received in revised form 6 February 2017
Accepted 24 February 2017

Keywords:
Epigenetics
MSCs
Chondrogenic and adipogenic differentiation

ABSTRACT

Extensive studies have been performed to clarify the processes during which mesenchymal stem cells (MSCs) differentiate into their lineage fates. In vitro differentiation of MSCs into distinct lineages have attracted the focus of a large number of clinical investigations. Although the gene expression profiling during differentiation of MSC toward bone, cartilage, and adipocytes is well established, the master regulators by which MSC fate can be controlled are not entirely determined. During differentiation of MSCs into a special cell fate, epigenetic mechanisms considered as the primary mediators that suppress the irrelevant genes and activate the genes required for a specific cell lineage. This review dedicated to addressing the changes of various epigenetic mechanisms, including DNA methylation, histone modifications, and micro-RNAs during chondrogenic and adipogenic differentiation of MSC.

Contents

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http://dx.doi.org/10.1016/j.biopha.2017.02.093
0753-3322/

1. Introduction

In the last decades, increasing efforts have been made to present efficient methods for tissue regeneration purposes. Many cell-based treatments for an extensive variety of tissue disorders, including critical bone size defects, bone metabolic disorders, degeneration of cartilage tissue and cerebral and heart ischemia, have been presented so far. Among these, using the mesenchymal stem cell (MSC) as a multipotent stem cell capable of differentiating into cartilage, bone, and adipose tissues has gained an excellent popularity among the scientists and clinicians [1].

Because of its avascular nature, Cartilage tissue minimally regenerates by the body's healing mechanisms. Current therapeutic procedures do not sufficiently restore the long–term function of damaged cartilage tissue. Numerous challenges have presented by many reviewers regarding the use of cartilage engineering. As the MSCs are present in large quantities in cartilage, synovium, bone marrow, and adipose tissue, they are potential to be a proper cell source [2]. They are also capable of being expanded without losing their ability to differentiate into chondrogenic lineage. Recently, in vitro manipulation of cultured MSCs such as using growth factors, specific transcription factors, and epigenetic alterations has brought promising results for targeted differentiation of MSCs into specific cell lineages to be used for regenerative purposes.

Many environmental, biomaterial, molecular, and epigenetic factors are actively involved in the regulatory pathways of chondrogenic differentiation of MSCs. Detailed molecular mechanisms of MSC chondrogenic differentiation must be known for a safe medical application of engineered cartilage originated from MSCs. During the last years, many aspects of gene expression and extracellular matrix formation have been vastly investigated, but the epigenetic modifications remained minimally understood, under shadowing these mechanisms. This review highlights the major epigenetic mechanisms which are reported to be undergoing various changes during differentiation of MSCs into chondrocyte lineage.

2. Chondrogenic differentiation of mesenchymal stem cells

Chondrogenesis in MSCs is induced by the coordination of two basic parameters: density of the cells and presence of essential growth factors [3]. Proteins of TGF-β superfamily (e.g. BMP) have confirmed to act as the inducers of chondrogenic differentiation. The members of this superfamily can promote the deposition of proteoglycans. It is approved that in the absence of TGF-β, the differentiated cells contain minimal amounts of proteoglycan [4]. TGF-β1 as a conventional medium additive is used in cultures to activate the chondrogenesis. It has also been demonstrated that TGF-β3 has a more effective capacity to induce chondrogenic differentiation in the culture mediums. Sox9 is the primary transcription factor crucial for MSC chondrogenic differentiation. Interestingly, the expression of chondrocyte-specific genes, such as collagen I and aggrecan, are activated upon Sox9 expression. A mutation in the Sox9 gene results in a congenital dwarfism syndrome [5].

3. The role of epigenetic modifications in the stem cell fate determination

Various shreds of evidence support the involvement of epigenetic mechanisms through evolutionary stages of vertebrates, gene expression control, stem cell self-renewal, lineage fate determination, and some cell intrinsic molecular pathways. In a monolayer cell culture, MSC differentiation toward their specialized lineage fates is extensively coordinated by a network of transcription factors working together, which in turn are largely regulated by epigenetic signatures [6,7]. During differentiation into a particular lineage, many genes responsible for MSCs self-renewal and pluripotency endure repression, and the genes specific for distinct cell lineages undergo active transcription [8]. This on-off mechanism is strongly associated with the levels of post-translational modifications of histones and promoter DNA methylation. Recently, the micro-RNAs (miRNAs) have been introduced as another potential layer of gene expression regulators during stem cell differentiation [9].

DNA methylation is defined as covalent binding of a methyl group to the cytosine of CpG dinucleotides, which mainly occurs in promoter regions of genes and finally contributes to genes down-regulation [10]. During chondrogenic differentiation, many transcription factors specific for chondrocyte lineage become hypomethylated, which allows these genes to be transcribed at high levels. Among various histone modifications, methylation and acetylation of histones are the most studied post-translational changes and the other modifications are less clarified. A highly-coordinated interaction between these mechanisms would eventually determine whether the genes become active or repressed. While H3K4 acetylation is correlated with active genes, H3K9 and H3K27 trimethylation are the marks of down-regulated genes [11]. Along with DNA methylation, the histone modifications are supposed to be variably altered during MSC differentiation [12]. This review mainly focused on DNA methylation, histone modifications, and miRNA function during chondrogenic differentiation of MSCs. We also discuss the possible application of epigenetic machinery as a novel strategy to in vitro differentiation of MSCs into the chondrogenic lineage for regenerative purposes.

3.1. The role of epigenetic changes in induced pluripotent cells (iPS)

Three groups of stem cells are embryonic, postnatal, and induced pluripotent stem cell (iPS). iPS cells have been recently considered as cell models for epigenetic studies. As the somatic cells differentiate, their pluripotency reduces to lower levels by silencing of various genes via the expression of specific transcription factors (TFs), histone modifications, chromatin modifications, and DNA methylation [13]. The most significant TFs involved in pluripotency are Sox-2, Oct-4, Nanog, and other factors like Tbx3, Stat3, Myc, FoxD3, and p53 that are repressors of genes responsible for differentiation [14]. Several networks of proteins that are interrelated through physical and functional interactions are combined via epigenetic mechanisms to organize chromatin information and regulation of chromatin status as well as gene expression. a constant state of chromatin is one of the most significant characteristics of adult somatic cells, which is related to silencing of genes that are not specific for a certain cell lineage. Pluripotent stem cells in comparison with cells that are committed to a particular lineage display a unique epigenetic profile developed for active modifications of chromatin, including H3K36me3, H3K4me3, hypomethylated DNA, and histone acetylation [15]. These marks are commonly present in the pluripotency genes areas. Yet, dense heterochromatin is characterized with H3K9me3H, 3K27me3, and hypermethylated DNA and limits to various tissue-specific genes and repetitive sequences. Also, bivalent domains in these stem cells have augmented levels that may be characterized with H3K27me3 and H3K4me3 at the differentiation-linked genes. bivalent domain-marked genes are in a whole controlled condition, which means that their expression can be constantly silenced or rapidly turned on thru removal of H3K4me3 or H3K27me3, respectively. Disrupting of this precise balance can cause a reduce in self-renewal, an increase in pluripotent cells differentiation, and/or a block in somatic cells reprogramming to iPSCs [16–18]. It is clear that the cellular differentiation is critically dependent on epigenetic mechanisms,