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Mini Review

iPS cell technologies and their prospect for bone regeneration and disease modeling: A mini review

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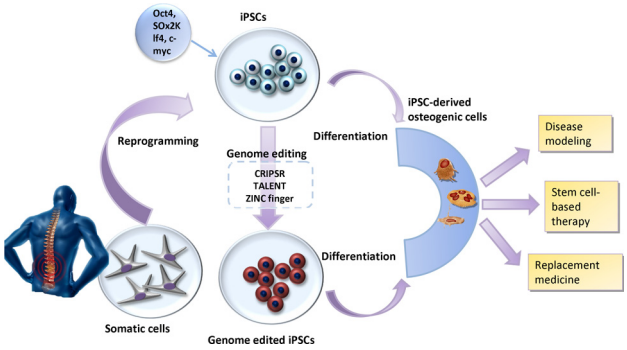
GRAPHICAL ABSTRACT



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ABSTRACT

Bone disorders are a group of varied acute and chronic traumatic, degenerative, malignant or congenital conditions affecting the musculoskeletal system. They are prevalent in society and, with an ageing population, the incidence and impact on the population's health is growing. Severe persisting pain and limited mobility are the major symptoms of the disorder that impair the quality of life in affected patients. Current therapies only partially treat the disorders, offering management of symptoms, or temporary replacement with inert materials. However, during the last few years, the options for the treatment of bone disorders have greatly expanded, thanks to the advent of regenerative medicine. Skeletal cell-based regeneration medicine offers promising reparative therapies for patients. Mesenchymal stem (stromal) cells from different tissues have been gradually translated into clinical practice; however, there are a number of limitations. The introduction of reprogramming methods and the subsequent production of induced pluripotent stem cells provides a possibility to create human-specific models of bone disorders. Furthermore, human-induced pluripotent stem cell-based autologous transplantation is considered to be future breakthrough in the field of regenerative medicine. The main goal of the present paper is to review recent applications of induced pluripotent stem cells in bone disease modeling and to discuss possible future therapy options. The present article contributes to the dissemination of scientific and pre-clinical results between physicians, mainly orthopedist and thus supports the translation to clinical practice.

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Introduction

Currently, stem cell-based therapies and research represent a significant advance in bone regeneration. Recent therapeutic options for bone disorders have included restricted or modified activity, immobilization of injured or diseased structures using splints and casts, non-steroidal anti-inflammatory drugs, corticosteroid administration, physical therapy, acupuncture, extracorporeal shock wave therapy, and surgical manipulation. However, attention is increasingly turning to the application of stem or progenitor cells as the basis for bone tissue regeneration. Several recently published animal studies show promising results for bone, tendon and cartilage regeneration. Bone marrow-derived mesenchymal stem cells (MSCs) were the first stem cell type investigated and remain the gold standard for many researchers [1]. However, MSCs must be isolated from various donors and are usually quite heterogeneous. Furthermore, therapy for skeletal disorders has various limitations, such as the age of pathologically related impairments regarding cell survival, proliferation activity and the potential of multilineage differentiation [2].

A major scientific breakthrough in biomedical research is related to the formation of induced pluripotent stem cells (iPSCs) by Takahashi and Yamanaka in 2006 [3]. By transferring a mixture of nuclear transcriptional factors (Oct4, Sox2, Klf4, and c-myc), terminally differentiated adult cells were successfully reprogrammed into iPSCs and closely resembled human embryonic stem cells [4,5]. So far, different human somatic cells have been reprogrammed into iPSCs. As the field grows, improved combinations of scaffolding biomaterials and bioreactors are creating a more suitable stem cell microenvironment for new tissue formation. Nevertheless, safety remains an important issue, especially with the potential of tumour formation [6].

The main purpose of the present review was to summarise the current state of IPSC technology and to discuss its prospects for regeneration and modeling bone disorders.

Methods for iPSC generation

The most used method for establishing iPSC lines had been insertion of a mixture of reprogramming factors (Sox2, Oct4, c-myc, Klf4 and Lin28) into the genome of somatic cells by using delivery vectors [7]. Substantial advances have been made in searching for new strategies to increase the effectiveness of reprogramming techniques, as well as new approaches for improving biosafety by reducing the number of genomic modifications required to complete the process [8]. Recently, methods used to transfer genes into target cells can be divided into: (a) integrative viral vectors (viral delivery system, transfection of linear DNA), (b) integrative free vectors (piggyBac transposon, plasmid/episomal plasmid vectors, minicircle vectors), and (c) non-integrating methods (direct protein/microRNA delivery, small molecules) (Fig. 1, Table 1) [4,5].

Integration methods apply viral vectors (e.g. retroviral and lentiviral) to transfer selected genes into the host genome. Their advantage is the undeniably high efficiency; however, these methods possess considerable risk of tumour formation. Because of this, different approaches have been also employed [9].

The most promising reprogramming approaches seem to be non-integrating techniques. For instance, the method of protein transduction can replace the use of transcription factors. The conjugation of proteins with short peptides responsible for cell penetration can be used for protein delivery into the cells. The majority of murine and human iPSCs were produced according to this method using purified polyarginine-tagged Oct4, Sox2, Klf4, and c-myc [10]. MicroRNAs (miRNAs) and small molecules have been also examined for their potential to enhance the reprogramming efficiency or replace reprogramming genes. miRNAs are an essential component of the gene network and are regulated by genes of pluripotency. Therefore, the expression of pluripotent stem cell-specific miRNAs, reprogramming gene-related miRNAs and the inhibition of tissue-specific miRNAs may support cell reprogramming in iPSCs [11].

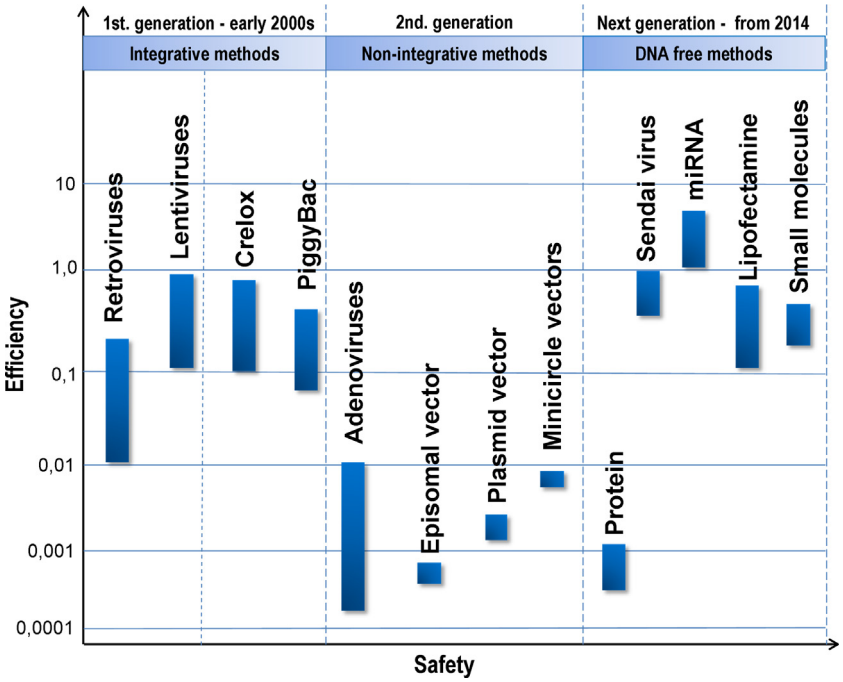

Fig. 1. Methods involved in the transfer of genes into the target cells.