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Small molecules and their controlled release that induce the osteogenic/chondrogenic commitment of stem cells

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ABSTRACT

Stem cell-based tissue engineering plays a significant role in skeletal system repair and regenerative therapies. However, stem cells must be differentiated into specific mature cells prior to implantation (direct implantation may lead to tumour formation). Natural or chemically synthesised small molecules provide an efficient, accurate, reversible, and cost-effective way to differentiate stem cells compared with bioactive growth factors and gene-related methods. Thus, investigating the influences of small molecules on the differentiation of stem cells is of great significance. Here, we review a series of small molecules that can induce or/and promote the osteogenic/chondrogenic commitment of stem cells. The controlled release of these small molecules from various vehicles for stem cell-based therapies and tissue engineering applications is also discussed. The extensive studies in this field represent significant contributions to stem cell-based tissue engineering research and regenerative medicine.

Contents

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1. Introduction

Millions of people suffer from skeletal system diseases, such as fractures, osteoporosis, imperfect osteogenesis, and osteoarthritis (OA), each year (Buckwalter and Mankin, 1998; Gitelis and Saiz, 2002; Mistry and Mikos, 2005). Cartilage, an avascular, aneural, and alymphatic tissue, lacks innate self-healing ability after injuries caused by disease or trauma (Cancedda et al., 2003; Chung and Burdick, 2008) and thus requires surgical intervention for restoration or replacement. In contrast, bone, which includes vascular networks, has the ability to regenerate in certain conditions, such as after slight fractures, with conventional treatment (Cancedda et al., 2003; Mistry and Mikos, 2005). However, self-healing is rarely sufficient for most bone defects, and therefore, surgery is often necessary. Among surgeries, autograft transplantation is the most suitable therapy for most defects. Unfortunately, autograft transplantations are inefficient due to limited tissue sources, low effectiveness for complete healing, and post-surgical complications. In addition, allografts and xenografts are associated with potential dangers, such as disease transmission and immunological rejection (Gitelis and Saiz, 2002; Mistry and Mikos, 2005; Yeatts and Fisher, 2011). Because of its high efficiency, tissue engineering is an excellent alternative therapy for skeletal defects or diseases, which can be applied to restore, reconstruct, maintain, or strengthen tissues and organs in various manners (Griffith and Naughton, 2002).

As one of the three key components (cells, cell growth/differentiation factors, and scaffolds) in tissue engineering (Langer and Vacanti, 1993),stem cells, known for their ability to maintain undifferentiated status via self-renewal and to differentiate into mature cell lines in response to instructive signals, hold great potential for the treatment of numerous diseases (Bianco and Robey, 2001; Chen et al., 2006; Tuan et al., 2003). Stem cells must be induced to form specific cell linages prior to use in tissue engineering therapies, as direct injection of stem cells into the host may lead to tumour formation (Lyssiotis et al., 2011; Reya et al., 2001). As potential cell growth/differentiation factors, small molecules exhibit inherent advantages over bioactive growth factors and genetic methods for inducing the differentiation of stem cells. First, small molecules are easier to obtain. Synthetic chemistry provides a variety of methods to prepare sufficient amounts of purified small molecule agents for tissue engineering applications. In the light of the simple structure of small molecules, a series of small molecules can be synthesized only by modifying their chemical structures. Hence, small molecules cost substantially less than growth factors and gene-related methods. Second, small molecules can induce cell differentiation in a rapid, revisable and accurate manner. Specific agonists or antagonists can be used to abrogate the influences exerted by small molecules. Therefore, the effects of small molecules can be well controlled, which is critical for effective therapy (Lyssiotis et al., 2011; Zaret, 2009; Zhang et al., 2012). Finally, small molecules strongly affect various cell behaviours. For instance, they can lead to self-renewal; cause dedifferentiation of mature stromal cells, driving them into induced pluripotent stem cells (iPS); and most importantly, play vital roles in the commitment of stem cells (Chen et al., 2004; Li et al., 2012; W. Li et al. 2013; Schugar et al., 2008; Thatava et al., 2011; Wu et al., 2004a). Therefore, small molecules can provide an accurate, efficient, revisable, cost-effective and reliable way to induce the differentiation of stem cells into mature cell lines, which will likely lead to large-scale applications of stem cell-based tissue engineering therapies.

In this review, we discuss small molecules used for osteogenic and chondrogenic commitment of stem cells. The stimulatory effect of various small molecules on the differentiation of stem cells, the mechanism involved during the differentiated process, and the controlled release of these small molecules for bone/cartilage tissue engineering applications are reviewed systematically. Tables 1 and 2 are abbreviations and cell lines mentioned in the text, respectively.

Table 1
Abbreviations used in this article.

Abbreviations	Meaning
OA	Osteoarthritis
iPS	Induced pluripotent stem cells
Cbfa1	Core-binding factor subunit alpha-1
Runx2	Runt-related transcription factor 2
ALP	Alkaline phosphatase
Hh	Hedgehog
hMSCs	Human mesenchymal stem cells
OCN	Osteocalcin
Dkk-1	Dickkopf-related protein 1
PKC	Protein kinase C
PKA	Protein kinase A
PLGA	Poly(lactic-co-glycolic acid)
ESCs	Embryonic stem cells
Colla I	Type I collagen
OSX	Osterix
BMP-2	Bone morphogenetic protein-2
OPG	Osteoprotegerin
VEGF	Vascular endothelial growth factor
PEG	Poly(ethylene glycol)
DEX	Dexamethasone
Ser125	Serine residue
HA	Hydroxyapatite
PCL	Polycaprolactone
ASC	Ascorbic acid-2-phosphate
ERK	Extracellular signal-regulated kinase
JNK	Jun N-terminal kinase
RANKL	Receptor activator of nuclear factor kappa-B ligand
PHBV	Polyhydroxylbutyratevalerate
TCP	Tertiary calcium phosphate
BSP	Bone sialoprotein
PPARγ	Peroxisome proliferator-activated receptor γ
AMPK	Adenosine 5′-monophosphate (AMP)-activated protein kinase
eNOS	Endothelial nitric oxide synthase
BP	Bisphosphonate
MAPK	Mitogen-activated protein kinase
MS	Mesoporous silica
SMSCs	Synovium mesenchymal stem cells
TGF-β	Transforming growth factor β
RA	Retinoic acid
ADAS	Adipose-derived adult stromal cells
KGN	Kartogenin
Colla II	Type II collagen
Cbfa	Core-binding factor subunit alpha
Runx1	Runt-related transcription factor 1
shRNAs	Short-hairpin RNAs
GAG	Glycosaminoglycan
Col2a1	Collagen type II, alpha 1
siRNA	Small interfering RNA
PGE2	Prostaglandin E2
cAMP	Cyclic AMP
GlcN	Glucosamine
MMP-13	Matrix metalloproteinase 13
GCs	Glucocorticoids
GRs	Glucocorticoids receptors
dbcAMP	Dibutyryl cyclic AMP

2. Small molecules and their controlled release that induce the osteogenic commitment of stem cells

A number of small molecules that can induce stem cells into osteoblastic cells have been reported to date (Table 3).

2.1. Purmorphamine

Purmorphamine, a 2,6,9-trisubstituted purine, has been reported as a cell-differentiation factor for bone repair (Chen et al., 2006; Faghihi et al., 2014; Rosa et al., 2009; Wu et al., 2002) .Mouse embryonic mesoderm fibroblasts C3H10T1/2 treated with purmorphamine exhibited a 50-fold increase in alkaline phosphatase(ALP, a glycoprotein found on the surface of osteoblasts) activity compared with untreated controls. The gene assay indicated that the Cbfa1/Runx2 gene, a reporter gene

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