Emerging role of statins in tissue engineering and therapeutics —A review

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ABSTRACT

Statins are a group of secondary metabolites secreted by several microorganisms as a defense mechanism. They inhibit hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase enzyme in the cholesterol synthesis pathway and are an acceptable therapy for hyperlipidemia in human. More recently, however, statins have been shown to have multiple effects, called pleotropic effects, which are independent of their cholesterol-inhibiting action. In somatic and stem cells, statins influences the cellular proliferation, survival, differentiation, regeneration and repair which can be harnessed in ex vivo systems for cell expansion and/or differentiation of somatic and stem cells. Incorporation of statins in the biomaterials for scaffold production has improved the cell attachment and directed differentiation of stem cells into target cells to enhance the functionality of the tissue engineered construct. Thus, statins have generated a fresh impetus in its use in tissue engineering, regenerative medicine and therapeutics. This review discusses the sources, mode of action and emerging roles of statins in tissue engineering and therapeutics.

Keywords: Statins, tissue engineering, regenerative medicine, stem cells

INTRODUCTION

Tissue engineering (TE) is an emerging field of biotechnology that has created a new hope for treatment of several diseases in which regular chemotherapy or surgical interventions have failed. It allows in vitro generation of engineered tissue constructs by incorporating the patient-specific somatic cells and/or stem cells into natural or synthetic matrix created from biomaterials, decellularized tissues or synthetic chemicals. The TE construct can then be transplanted into the body for replacing the dead or damaged non-functional tissue in vivo. Several TE technologies and products are now commercially available which includes, serifilm for bioactive wound dressing, bovine pericardium, porcine pulmonary artery, human amniotic

membrane, saphenous vein, corneal repair etc. (Schneider *et al.*, 2009; Ortega *et al.*, 2012). Recent development in stem cell research has shown the possibility of isolating patient-specific stem cells and their directed differentiation into specific cell type for subsequent use in TE. However, such newer technologies are met with major challenges of efficacy and safety which must be overcome prior to their effective application in clinics. A particular challenge has been the ex vivo expansion of these cells which require an optimal culture milieu to promote proliferation and self-renewal, inhibit senescence and apoptosis and targeted differentiation into a specific cell type of choice.

Statins are a group of secondary metabolites which share structural homology with hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase enzyme in the cholesterol formation pathway and thereby, have found medical applications in reducing the blood cholesterol level (Figure 1). Lovastatin, the first statin to be used commercially in human, is produced by *Aspergillus terreus* and was approved by the Food and Drug Administration (FDA) in 1987. Currently, several members of statins including lovastatin, pravastatin, simvastatin, compactin, rosuvastatin, atorvastatin, rluvastatin, cerivastatin and pitavastatin are commercially available and are being commonly used for the treatment of hyperlipidemia, atherosclerosis and cardiovascular diseases (CVDs) such as coronary blockage and myocardial infarction (MI). More recently, statins have also been shown to influence the cellular

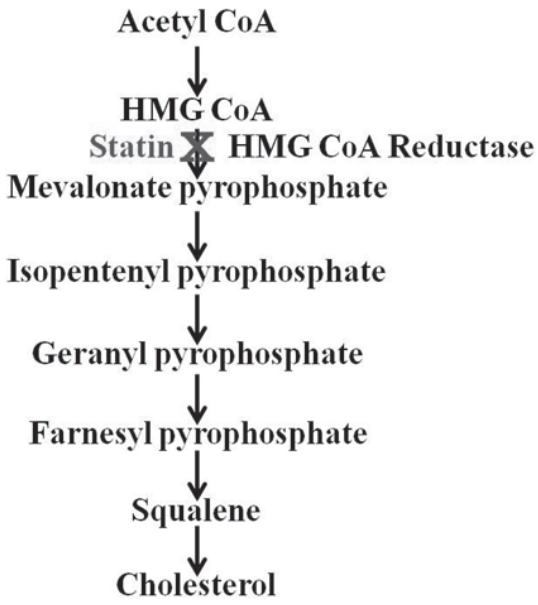

Fig. 1: Mechanism of action of statins in the cholesterol synthesis pathway**.**

proliferation, differentiation, regeneration and repair and therefore, have generated a fresh impetus in its use in TE and regenerative medicine (Esenkaya *et al.*, 2010; Steinmetz *et al.*, 2010; Abe *et al.*, 2012). This review discusses the sources, mode of action and emerging role of statins in TE, regenerative medicine and therapeutics.

SOURCE OF STATINS

In nature, statins are produced by microorganisms to inhibit the growth of competing microorganisms. They are reversible competitive inhibitor for HMG-CoA reductase and inhibit the synthesis of mevalonate from HMG-CoA which is required for the synthesis of ergosterol and isoprenoids – the essential components of cell wall in several microorganisms (Figure 1). Thus, statins contributes to the defense mechanism of the microorganisms.

Statins were first discovered in 1970s in a fermentation broth of *Penicillium citrinum* and was named mevastatin (ML-236B) due to their ability to inhibit the formation of mevalonate in the cholesterol synthesis pathway. In year 1976, the pharmaceutical company Merck & Co. showed an interest in its medicinal property of statins and isolated the lovastatin (Mevinolin, MK803) from the fungus *A. terreus*. The lovastatin was shown to have dramatic effect on lowering the low-density lipoprotein (LDL) cholesterol with no apparent adverse effects in healthy volunteers. Consequently, after pre-clinical trials in animals and clinical trials in human, it was approved by FDA for human use on 31 August 1987. Later lovastatin was isolated from a number of other microorganisms including *A. flavus, A. umbrosus, A. parasiticus, A. niger, A. flavipes, P. funiculosom, P. purpurogenum, Monascus purpureus, M. ruber, M. pilosus, Pleurotus ostreatus, Trichoderma viride, and Laetiporus spp.* In addition, several other statins such as simvastatin, pravastatin, cerivastatin etc. came into existence in 1990s, many of which were later withdrawn from the market due to certain side effects and associated health risks. Furthermore, several synthetic statins such as atorvastatin, fluvastatins, pitavastatin, rosuvastatin etc. were synthesized by modifying the structure-function relationship of the statin molecules to increase the safety and efficacy of the drugs.

Most statins are derivatives of acetate via a polyketide pathway (Fig. 2). The enzyme called lovastatin nonaketide synthase (LNKS) contains seven active sites (KS = ketosynthase; MAT = malonyl-CoA:ACP acyltransferase; DH = dehydratase; MT = methyltransferase; KR = ketoreductase; ACP = acyl carrier protein; CON = condensation domain) that catalyzes the reaction to form dihydromonacolin L from acetate and malonate molecules. The dihydromonacolin L is converted to monacolin L which in turn is converted to monacolin J by hydroxylation. The monacolin J is converted to lovastatin in the presence of LovD transesterase enzyme that catalyzes the attachment of the 2-methylbutyric acid to monacolin J. At the same time, the monacolin J can be converted to Simvastatin in the presence of LOV D after forming an intermediate á-dimethylbutyryl-S-methyl-3-mercaptopropionate (DMB-SMMP). The methyl group present in some Statins is derived from methionine and the oxygen atoms present in the main chain are inserted by aerobic oxidation.

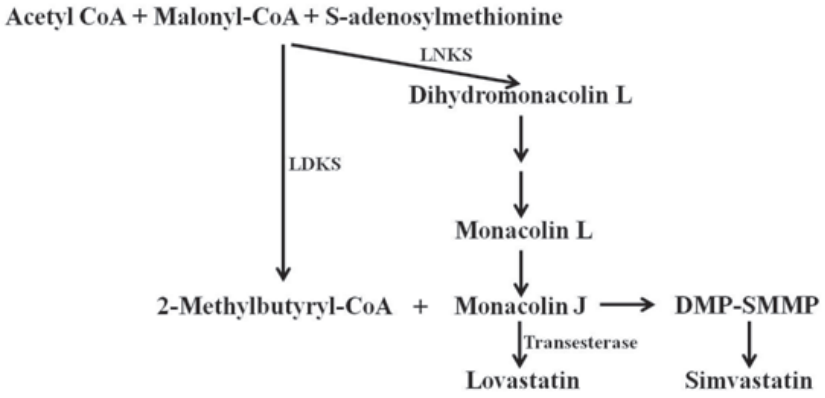

Fig. 2: Biosynthetic pathway of statins

PLEOTROPIC EFFECTS OF STATINS IN REGENERATIVE MEDICINE AND THERAPEUTICS

Statins have potent LDL cholesterol-lowering effects that provide cardiovascular protective action. They are accepted therapy for hyperlipidemia and, increases HDL cholesterol, urinary excretion of nitrite/nitrate, circulating levels of endothelial progenitor cells (EPC), and cell migration response to vascular endothelial growth factor (VEGF) in patients with low HDL cholesterol (Higashi *et al.*, 2010). In addition to lowering cholesterol levels, statins also exert a number of cholesterol-independent (pleiotropic) effects such as improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques (Bosel and Endres, 2006). Thus, they have found application in diseases such as fibrosclerotic aortic stenosis, arterial hypertension, alzheimer's dementia, rheumatic diseases (rheumatoid arthritis), multiple sclerosis, fibroproliferative disorders etc. The mechanisms of these pleiotopic effects are however, are not fully understood. For example, simvastatin exhibits anti-inflammatory and anti-fibrotic effects that work by decreasing the production of interleukin-6 and interleukin-8 (Park, 2009; Abe *et al.*, 2012). Similarly, many statins have neuroprotective effects on ischemic stroke (Bosel and Endres, 2006). They modify the endothelial function, increase blood flow, and inhibit thrombus formation, which are independent of lipid-lowering effects (Jung *et al.*, 2004). Since molecular mechanism occurring in the degenerate aortic valve resembles that of atherosclerosis, statins have also been tested for preventing the progression of native and bioprosthetic aortic valve degeneration (Hakuno *et al.*, 2009). Under in vitro situations, statins were shown to influence the proliferation and survival of various progenitor and stem cells such as EPC, dental pulp stem cells (DPSCs), mesenchymal stem cells (MSCs) etc. and hence, have found new application in TE and regenerative medicine for revascularization, bone formation and augmentation, lung injury, diabetic neuropathy, scar healing, tendon healing.

Effects of Statins in Nervous System

Statins have neuroprotective and neurogenic effects that may be beneficial in treating brain and spinal cord injuries, ischemic stroke of neural origin and neurologic diseases such as multiple sclerosis and Alzheimer's disease (Jung *et al.*, 2004; Bosel and Endres, 2006; Holmberg *et al.*, 2006). Several statins are also known to reduce the activity of neuronal glutamate receptors and protect neurons from excitotoxic insults. Simvastatin enabled neurite outgrowth by counteracting the myelin-associated neurite outgrowth inhibition signals from growth-inhibitory molecules commonly found at central nervous system (CNS) injury sites and thus, may be beneficial in promoting axon regeneration in brain and spinal cord injury (Holmberg *et al.*, 2006).

At higher doses, statins may also inhibit the neurite sprouting and may even induce neuronal apoptosis (Bosel and Endres, 2006). Thus, they may have application in the treatment of neuronal neoplasm. Cerezo-Guisado *et al.*, (2005) observed that lovastatin could suppress the cell growth and induced apoptosis in rat brain neuroblasts by inhibiting the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) pathway. It significantly decreased the PI3K activity, PKB/Akt phosphorylation, and their downstream effectors, p70S6K and the eukaryotic initiation factor 4E (eIF4E) regulatory protein 1, 4E-BP1 (Cerezo-Guisado *et al.*, 2005). Apoptosis was also accompanied by a decrease in both Bcl-2 and Bcl-xL protein levels and decreased prenylation of both Ras and RhoA proteins whereas Rac1 geranylgeranylation was not affected (Cerezo-Guisado *et al.*, 2005).

Statins also augmented the survival and differentiation of oligodendrocyte progenitors in animal model of multiple sclerosis (Paintlia *et al.*, 2005). Administration of Lovastatin restored the impaired remyelination through enhanced survival and differentiation of oligodendrocyte progenitors in the spinal cord and thus, has the potential to augment remyelination in multiple sclerosis lesions and other neuroinflammatory diseases (Paintlia *et al.*, 2005). In another study, combination therapy of lovastatin and rolipram (phosphodiesterase-4 inhibitor) provided neuroprotection and promoted neurorepair in inflammatory demyelination model of multiple sclerosis (Paintlia *et al.*, 2009).

Effects of Statins in Skeletal System

Most of the signaling molecules involved in osteocyte differentiation, bone mineralizaion and bone remodeling are also involved in lipid and glucose metabolism. Thus, statins can also influence the bone formation, growth and remodeling. For example, statin can enhance the expression of bone morphogenetic proteins (BMP) and interact with the Rho/Rho-kinase pathway to promote the differentiation of MSCs into differentiated osteoblasts and subsequent bone formation (Ohnaka and Takayanagi, 2004). Several statins are therefore, under investigation as a safe and effective drug for managing skeletal injuries by stimulating the healing of fresh fractures, non-unions, and spinal fusions (Wang *et al.*, 2007; Hamada and Fukagawa, 2008; Park, 2009; Zou *et al.*, 2012).

Statins have also been reported to promote osteoblastic activity and inhibit osteoclastic activity and thereby, increase cancellous bone volume, bone formation rate, and cancellous bone compressive strength (Park, 2009). There are now ample animal studies that show metabolic effects of statins on bone metabolism mostly by reducing bone resorption rather than by stimulating bone formation (Tang *et al.*, 2008; Du *et al.*, 2009). Thus, statins can increase bone mass density and reduce fracture risk in osteoporosis cases, although the data are conflicting (Tang *et al.*, 2008).

Statins also have application in bone tissue engineering. Du *et al.*, (2009) showed that statins improves the implant osseointegration around titanium implants in osteoporotic rats (Du *et al.*, 2009). In another study, statin (naringin, a flavonoid available commonly in citrus fruits and having HMG-CoA reductase inhibitor activity) in collagen matrix have the effect of increasing new bone formation locally and can be used as a bone graft material (Wong and Rabie, 2006).

Effects of Statins in Vascular Disease

Statins are well known to reduce vascular diseases by decreasing cholesterol synthesis (Deschaseaux *et al.*, 2007) and inducing the differentiation and mobilization of EPCs from bone marrow (Dimmeler *et al.*, 2001; Deschaseaux *et al.*, 2007). They can also reduce the cellular levels of isoprenoid compounds (Vincent *et al.*, 2001), restore NO production by up-regulating eNOS mRNA and protein levels and preserve NO inactivation by reactive oxygen species (ROS) to protect against vascular diseases (Martinez-Gonzalez and Badimon, 2007). These effects are mediated, at least in a part, through mechanisms independent of their lipid lowering effect.

Statins can also inhibit angiogenesis by decreasing endothelial cell locomotion by delocalizing RhoA from cell membrane to cytoplasm, responsible for the disorganization of actin stress fibers. It also decreased MMP-2 secretion, involved in cell invasion, by Ras inhibition. Thus, anti-angiogenic activity of statins provides a beneficial effect on atherosclerosis and on cancer prevention as shown by clinical studies (Vincent *et al.*, 2001).

Effects of Statins in Fibrosis and Wound Healing

Statins have been shown to inhibit the expression of connective tissue growth factor (CTGF) that plays a significant role in wound healing and scarring. They have also been to induce apoptosis in fibroblast cells by inhibiting with Ras molecules (Tan *et al.*, 1999). Simvastatin, lovastatin, or pravastatin each demonstrated significant reductions in scar formation by means of CTGF inhibition and thus, may lead to innovative and effective antiscarring therapies (Abe *et al.*, 2012; Ko *et al.*, 2012). Since anti-fibrotic effects of statins are independent of their anti-inflammatory effects, they are particularly useful in preventing the neointima or scar formation in the innermost layer (intima) of blood vessels after a vascular surgery such

as angioplasty or stent placement (Abe *et al.*, 2012). Indeed, olmesartan and pravastatin each modestly attenuated the balloon injury-induced neointimal formation in rats without significant changes in blood pressure or serum lipid levels (Chen *et al.*, 2007). Statins have also been shown to inhibit vascular smooth muscle cell (VSMC) proliferation in vitro (Indolfi *et al.*, 2000) and stimulate the EPC recruitment in the bio-engineered EPC capture stent (den Dekker *et al.*, 2011) and thus, were helpful in reducing the neointimal area and the neointima-media ratio after balloon injury and stenting.

Statins can inhibit Rho-GTPase signaling to influence TGF-beta-mediated myofibroblast transdifferentiation and hence, has potential use in wound healing modulation. Lovastatin inhibited TGF-beta-induced CTGF transcription, alpha-SMA expression and p38 activation, whereas Smad-2/3 phosphorylation and nuclear translocation were preserved (Meyer-Ter-Vehn *et al.*, 2008). Thus, lovastatin inhibited myofibroblast transdifferentiation human tenon fibroblasts and therefore, may serve to inhibit scarring after filtering glaucoma surgery (Meyer-Ter-Vehn *et al.*, 2008).

STATINS IN SENESCENCE AND CELLULAR PROLIFERATION

In vitro expansion of several cell types have been difficult due to sub-optimal culture condition, senescence and limited in vitro proliferation potential. Recent reports suggest that statins may influence cellular senescence and proliferation. In particular, statins have been shown to reduce senescence and increase the proliferation of EPCs via regulation of cell cycle regulatory genes including the upregulation of cyclin proteins and downregulation of the cell cycle inhibitor p27Kip1(Assmus *et al.*, 2003). These effects of statins were independent of NO, ROS and Rho kinase activity and did not influence telomerase activity (Assmus *et al.*, 2003). Since EPCs play an important role in postnatal neovascularization of ischemic tissue, our ability to culture them in vitro would prove to be useful in clinical cell therapy of myocardial ischemia. Henrich *et al.* (2007) observed that simvastatin had protective effects on EPC survival and differentiation even in a hyperinflammatory situation. Simvastatin also inhibited the TNF-alpha- induced apoptosis in EPCs (Henrich *et al.*, 2007) and enhanced the regeneration of endothelial cells via secretion of VEGF in injured arteries (Matsuno *et al.*, 2004).

The effect of statins on cellular proliferation however, seem to vary with the cell type. While statins stimulated the proliferation of EPCs, they markedly inhibited the in vitro proliferation of VSMCs in a dose-depended manner. Thus, they have beneficial effect on reducing the neointima formation after stenting (Indolfi *et al.*, 2000). Dekker *et al.* (2011) observed that, statin stimulated the EPC recruitment in of the bio-engineered EPC capture stent and contributed to a reduction of in-stent re-stenosis formation. Statins such as simvastatin and lovastatin were also reported to inhibit the proliferation of acute myeloid leukemia (AML) progenitor cells (Newman *et al.*, 1997). The mechanism of inhibition of cell proliferation remains unknown but it is likely to be related to high requirement of cholesterol and its

derivatives by proliferating neoplastic cells for both DNA synthesis and cell growth. Thus, inhibition of cholesterol synthesis by statins could affect cell cycle progression and proliferation in cancerous cells (Lishner *et al.*, 2001). Indeed, statins are shown to have inhibitory effect on the proliferation and growth of several types of cancer cells including liver, colon, leukemia, malignant B, stomach, and breast cells (Otsuki *et al.*, 2003; Kamigaki *et al.*, 2011).

STATINS IN CELLULAR DEATH

Statins have also been shown to induce apoptosis and cell death. Lovastatin potently induced apoptosis in lung fibroblasts isolated from fibrotic lesions, fibroblast cells constitutively expressing growth-promoting genes such as Myc as well as in non-transformed lung fibroblasts by inhibiting the levels of mature Ras, a molecule directly implicated in fibroblast rescue from apoptosis (Tan *et al.*, 1999). Thus, statins provide a possible therapy for fibroproliferative disorders. Indeed, lovastatin reduced granulation tissue formation in the guinea pig wound chamber model, with associated ultrastructural evidence of fibroblast apoptosis (Tan *et al.*, 1999).

Statins also induce apoptosis in neoplastic cells and thus, may have anticancer property. Kamigaki *et al.*, (2011) observed that treatment of human cholangiocarcinoma cells with statins induced apoptosis by suppressing the classical MAPK pathway (Kamigaki *et al.*, 2011). Apoptotis inducing effects of statins have also been reported in EPCs, skeletal muscle cells and neuronal cells, as described above.

STATINS IN STEM CELL DIFFERENTIATION

Statins have also been shown to induce the differentiation of stem cells and progenitor cells (Park, 2012). They are well known to stimulate the expression of BMP and BMP receptor (BMPR) and hence, have recently emerged as a candidate for inducing osteogenic differentiation and bone formation in stem cells (Chen *et al.*, 2010; Nyan *et al.*, 2010; Pagkalos *et al.*, 2010). Phillips *et al.*, (2001) observed that, addition of compactin to the differentiation medium promoted an increase in BMP2 expression and thereby, greatly enhanced the osteoblastic differentiation and bone nodule formation in embryonic stem (ES) cells without modifying the expression of osteogenic markers. Similarly, simvastatin could be used as an osteogenic induction agent for ES cells (Pagkalos *et al.*, 2010) and MSCs such as DPSCs (Okamoto *et al.*, 2009) and amniotic fluid-derived MSCs [AFSMC; (de Lara Janz *et al.*, 2012)]. When AFSMCs were incubated with simvastatin, it caused morphological changes, calcium deposits formation and expression of typical osteogenic genes, osteopontin and osteocalcin (de Lara Janz *et al.*, 2012). Zhou *et al.*, (2010) reported that simvastatin at optimal concentrations can be used to promote osteogenesis in adipose-derived stromal cells and platelet-rich plasma to produce injectable tissue-engineered bone. Park *et al.*, (2012) further reported that combination of simvastatin and BMP-2 enhanced the differentiation of osteoprecursor cells by regulating the protein expression of phospho-Smad1/5/8.

Statins have also been shown to influence the Notch signaling pathway, which plays a key role in multiple cell functions such as differentiation, proliferation, and apoptosis (Xu *et al.*, 2009). Thus, simvastatin enhanced the differentiation of bone marrow stromal cells into endothelial cells via notch signaling pathway (Svejda, 2006; Xu *et al.*, 2009). Xu *et al.*, (2009) observed that simvastatin stimulation of rat MSCs resulted in significantly increased expression of endothelial-specific genes and proteins, including von Willebrand factor (vWF), CD31, vascular endothelial-cadherin (VE-cadherin), VEGF receptor-2 (VEGFR2, Flk-1), and VEGF receptor 1 (VEGFR-1, Flt-1). Simvastatin also significantly increased the capillary tube-like formation of the BMSCs. In addition, the intracellular cleavage of Notch (NICD) was markedly enhanced by simvastatin in BMSCs. Incubation of BMSCs with a gamma-secretase inhibitor, or Notch1 small interfering RNA (siRNA) that significantly inhibited the formation of NICD, blocked the expression of endothelial-specific markers in BMSCs and their differentiation into functional endothelial cells. These data suggest that simvastatin induces rat BMSCs differentiation into endothelial cells via a Notch signaling pathway (Xu *et al.*, 2009).

Statins also has promotive but differential effect on circulating bone marrow-derived vascular progenitor cells namely, EPCs and smooth muscle progenitor cells (SMPCs), which contribute to angiogenesis, atherosclerosis, and the response to vascular injury. Pravastatin promoted the differentiation of EPCs from MNCs but had to the differentiation of SMPC cells (Kusuyama *et al.*, 2006). Statins were also shown to augment the EPC differentiation from mononuclear cells and CD34-positive hematopoietic stem cells (HSC) isolated from peripheral blood (Dimmeler *et al.*, 2001). Treatment of mice with statins increased c-kit+/Sca-1+ positive HSCs in the bone marrow and elevated the number of differentiated EPCs via the PI3K/Akt pathway as demonstrated by the inhibitory effect of pharmacological PI3K blockers or overexpression of a dominant negative Akt construct (Dimmeler *et al.*, 2001).

Statins were also shown to stimulate cartilage nodule formation during embryoid body differentiation of mouse ES cells (Kramer *et al.*, 2012), muscular tissue differentiation (Martini *et al.*, 2009), VSMC differentiation (Wagner *et al.*, 2010) and periodontal ligament cells (Kim *et al.*, 2011) by unknown mechanism. Wagner *et al.*, (2010) reported that lovastatin may induce VSMC differentiation through inhibition of Rheb (Ras homologue enriched in brain- a upstream activator of mTORC1) and mammalian target of rapamycin complex 1 (mTOR). On the other hand, Wada *et al.*, (2008) observed that statins may active GATA6 to induce differentiation of VSMC. Similarly, Kim *et al.*, (2011) reported that, statins may also be useful for regenerating periodontal hard tissue by stimulating the osteoblastic differentiation of periodontal ligament cells via the ERK1/2 pathway.

STATINS IN CELL AND TISSUE-BASED THERAPY

Statins can act as a therapeutic agent while transplanting MSCs into damaged tissue for correcting the bone tissue disorder (Rojbani *et al.*, 2011). Statin-releasing, biodegradable, nano- to micro- scale fiber scaffolds not only provide better cell

attachment and enhanced osteoblastic differentiation of MSCs but also potentiate the functional neovascularization, angiogenesis and functional recovery (Wadagaki *et al.*, 2011; Zhang *et al.*, 2012). Thus, they have potential application in bone tissue engineering. Indeed, inclusion of statins into scaffolds of á-tricalcium phosphate (Nyan *et al.*, 2010), hyaluronic acid hydrogel (Bae *et al.*, 2011), polycaprolactone (Piskin *et al.*, 2009) and polyurethanes (Yoshii *et al.*, 2012) were found to trigger osteogenic differentiation of the MSCs and modulate their function for enhanced bone tissue repair .

Statins may also have application in cardiac tissue engineering through transplantation of MSC or cardiac stem cell (CSC) transplantation (Torella *et al.*, 2008). When statins were combined with MSC transplantation, they promoted cell survival and cardiovascular differentiation and improved the cardiac function in infracted hearts (Yang *et al.*, 2009; Cai *et al.*, 2011). Xu *et al.* (2011) observed that rosuvastatin activated the JAK-STAT pathway and thereby, increased the efficacy of allogeneic MSC transplantation in infarcted hearts.

SIDE EFFECTS OF STATINS

One of the major side-effects of statins is the development of myositis and, in some patients undergoing concomitant immunosuppressive treatment, the development of rhabdomyolysis (Gadbut *et al.*, 1995; Hong and Sequeira, 2000). These effects have been observed in 0.2% of patients and are due to a direct toxic effect of the statins on regeneration, growth and differentiation of skeletal muscle cell (Veerkamp *et al.*, 1996). The potency varies with the type of statin. In a comparative study, Gadbut *et al.* (1995) observed that simvastatin was more potent than Lovastatin which was several times potent than pravastatin. Atorvastatin was also shown to have an adverse effect on tendon although the data are inconclusive (Esenkaya *et al.*, 2010).

CONCLUSION

The pleotropic effects of statins may be harnessed to inhibit the cellular senescence and promote the cell survival and targeted differentiation of somatic and stem cells for their application in TE and regenerative medicine. However, mechanisms of action of these effects are largely unknown. Furthermore, the cellular response to statins seems to vary not only with the cell type but also with the source, dose and duration of treatment with statins.

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