

The role of catecholamines in mesenchymal stem cell fate

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Received: 17 March 2014 / Accepted: 28 July 2014
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Abstract Mesenchymal stem cells (MSCs) are multipotent stem cells found in many adult tissues, especially bone marrow (BM) and are capable of differentiation into various lineage cells such as osteoblasts, adipocytes, chondrocytes and myocytes. Moreover, MSCs can be mobilized from connective tissue into circulation and from there to damaged sites to contribute to regeneration processes. MSCs commitment and differentiation are controlled by complex activities involving signal transduction through cytokines and catecholamines. There has been an increasing interest in recent years in the neural system, functioning in the support of stem cells like MSCs. Recent efforts have indicated that the catecholamine released from neural and not neural cells could be affected characteristics of MSCs. However, there have not been review studies of most aspects involved in catecholamines-mediated functions of MSCs. Thus, in this review paper, we will try to describe the current state of catecholamines in MSCs destination and discuss

strategies being used for catecholamines for migration of these cells to damaged tissues. Then, the role of the nervous system in the induction of osteogenesis, adipogenesis, chondrogenesis and myogenesis from MSCs is discussed. Recent progress in studies of signaling transduction of catecholamines in determination of the final fate of MSCs is highlighted. Hence, the knowledge of interaction between MSCs with the neural system could be applied towards the development of new diagnostic and treatment alternatives for human diseases.

Keywords Mesenchymal stem cell · Differentiation · Catecholamines · Adrenergic signaling · Migration

Abbreviations

ATF4	Activating transcription factor 4
BARK	β-Adr kinase
BM	Bone marrow
BMSCs	Bone marrow stem cells
BMP4	Bone morphogenetic proteins
C/EBP	CCAAT/enhancer-binding protein
DBH	Dopamine-β-Hydroxylase
DEHP	Bis (2-Ethylhexyl) phthalate
Ebfl	Early B-cell factor 1
EPAC	Exchange protein activated by adenylyl cyclase
EPO	Erythropoietin
FGF	Fibroblast growth factor
GPC	Growth plate chondrocytes
GPCRs	G-protein-coupled receptors
GCs	Glucocorticoids
HGF	Hepatocyte growth factor
HSCs	Hematopoietic stem cells
IGF-1	Insulin-like growth factor-1
IRFs	Interferon regulatory factors
MAFbx	Muscle atrophy F-box protein
MKP-1	Mitogen-activated protein kinase phosphatase

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MSCs	Mesenchymal stem cells
MuRF1	Muscle ring finger1
OGP	Osteogenic growth peptide
PB	Peripheral blood
PDEs	Phosphodiesterase proteins
PGE2	Prostaglandin E2
pRb	Retinoblastoma cell cycle-related proteins
PKA	Protein kinase A
ROS	Reactive oxygen species
SDF-1	Stromal-derived factor-1
SHH	Sonic Hedgehog protein
SNS	Sympathetic nervous system
SREBPs	Sterol regulatory element binding proteins
S1P	Sphingosine1-phosphate
TBT	Tributyltin
TB4	Thymosin β
TF	Transcription factors
TH	Tyrosine hydroxylase
TGF- β	Transforming growth factor- β
TLR-9	Toll-like receptor 9
4EBP1	eIF4E binding protein1

Introduction

The isolation of mesenchymal stem cells (MSCs) from bone marrow (BM) compartments was originally reported in 1988 by Owen and Friedenstein (1998). Further studies have indicated the presence of multipotent cells known as adult stem cells in other tissues, including adipose tissue, muscle, cord blood, umbilical cord tissue, liver, spleen, BM and peripheral blood (PB) (Caplan and Bruder 2001). Phenotypically, these cells have no expression of the specific surface markers of hematopoietic lineage, including CD34, CD45, CD14, CD19 and CD3 (Haynesworth et al. 1992). In addition, MSCs have reported to be CD80[−], CD86[−], CD18[−] and CD31[−] but positive for CD29, CD44, CD71, CD73, CD90, CD105, CD106, CD166 and Stro-1 surface markers (Pittenger et al. 1999; Zuk et al. 2002). MSCs of various tissues share some common characteristics; however, these cells represent specific differences in their specialized markers. For example, adipocyte tissue MSCs are CD49d⁺CD106[−] cells, while CD markers of circulating MSCs share most of their immunophenotype with BM-derived MSCs (Zuk et al. 2002). Indeed, despite the lack of tissue-specific characteristics in MSCs, these cells are phenotypically heterogeneous with varying differentiation potentials. Therefore, it is important to identify special characteristics and better definitions of various tissues-derived MSCs.

The most characteristic feature of MSCs is their capability of self-renewal and multi-lineage differentiation into osteoblasts, adipocytes and chondrocytes (Farshdousti Hagh et al.

2012). Additionally, under defined conditions, these cells can differentiate into neurons, skeletal myocytes and endothelial cells (Nadri et al. 2008; Pittenger et al. 1999; Soleimani et al. 2010). Among conditions, plastic adherence, expression of surface markers and differentiation capacity are considered as criteria of human MSCs (Dominici et al. 2006). The ability of differentiation and easy isolation have made MSCs cells suitable sources for studies linked to cell therapy for tissue regeneration and engineering (Khajeniazi et al. 2013; Yazdani et al. 2013). In this regard, one of the most important functions of these cells is supporting hematopoiesis by creating a suitable scaffold in BM through the expression of adhesion molecules, including stromal cell-derived factor-1 (SDF-1) and CXCR4 and secretion of useful soluble mediators (Ahmadbeigi et al. 2013; Saki et al. 2011). Moreover, MSCs can adopt HSCs in various situations, caused by different amounts of oxygen in BM compartments (Grayson et al. 2007). Hypoxia conditions in BM can mediate MSCs proliferation by hypoxia-inducible factor (HIF)-1 and, recently, the role of some miRNAs involved in the hypoxia pathway, known as hypoxamirs, has been determined in regulating proliferation of MSCs (Grayson et al. 2007; Minayi et al. 2014).

Several mechanisms are involved in regulating MSCs functions such as the nervous system (Havasi et al. 2013). It has been reported that migration and differentiation of MSCs are under neuronal control. First, BM compartments are highly innervated, especially in proximity to endosteum and endothelial cells, which are rich in stem cells, implying indirect control over BM cells like MSCs (Mignini et al. 2003). Second, a variety of neural receptors have been found on MSCs (Silva et al. 2003). Third, catecholamines derived from noradrenergic endings in damaged tissues could result in MSCs recruitment (Mignini et al. 2003). Finally, it has been demonstrated that tyrosine hydroxylase (TH), a specific enzyme of synthesis catecholamines, is expressed through immune cells that in combination with released cytokines can affect MSCs-derived tissue (Stanojević et al. 2013). To our knowledge, the functional link between catecholamines and MSCs is not well determined. Thus, here, updated information from recent research on these topics, especially the central role of catecholamines in osteogenesis, adipogenesis, chondrogenesis, myogenesis and migration of MSCs, will be discussed. We describe adrenergic signaling, the effect of catecholamines on MSCs differentiation and the role of adrenergic signaling in the mobilization of MSCs.

Adrenergic signaling pathways in MSCs

Several subtypes of neural adrenergic receptor are named α and β , which are further subdivided into α 1, α 2, β 1, β 2 and β 3 (Cole and Sood 2012). There is an adrenaline ligand with

both α and β -adrenergic receptors (β -Adrs); however, catecholamine-mediated signaling is conducted more through subsets of β , due to α receptors being less sensitive to adrenalin (Cole and Sood 2012). The β -receptors belong to a large family of G-protein-coupled receptors (GPCRs). Ligation of β -receptors by catecholamines leads to $G_{\alpha s}$ -mediated stimulation of adenylyl cyclase and increases cAMP intracellular levels with conversion of ATP into cAMP (Cole and Sood 2012; Rosenbaum et al. 2009). Intracellular cAMP activates protein kinase A (PKA), a major effector system, to phosphorylate multiple target proteins such as transcription factors, kinases and cell-surface receptors either concurrently or sequentially (Fig. 1) (Cole and Sood 2012). Furthermore, β -Adrs can activate $G_{\alpha i}$, which differentially mediates adenylyl cyclase. Phosphodiesterase proteins (PDEs) specifically suppress cAMP second messenger levels (Rosenbaum et al. 2009). Phosphorylation of β -Adrs by PKA and β -Adr kinase (BARK) activated by PKA leads to the recruitment of β -arrestin, which subsequently induces the Src/Ras/MAPK

pathway (Fig. 1) (Cole and Sood 2012). Exchange protein activated by adenylyl cyclase (EPAC) is a second cAMP effector that activates other kinases such as P38 MAP and ERK1/2. Stimulation of ERK1/2 is limited through the concomitant activation of the mitogen-activated protein kinase phosphatase (MKP-1) pathways (Cole and Sood 2012). Although all three types of β adrenergic are associated with the same pathways, the timing and strength of the signaling can be different (Cole and Sood 2012). Generally, these signals can modulate the biological activity of catecholamines functions on the metabolism and mechanism involved in the proliferation and differentiation of MSCs (De Ugarte et al. 2003). Depending on the particular cell derived from MSCs, adrenergic signaling mediates different processes. Hence, a key question is how adrenergic signaling can perform different patterns with high specificity and reliability.

A brief overview of adrenergic signaling related to differentiation and mobilization of MSCs indicates that, downstream of these, signaling would involve genes allocation of each lineage

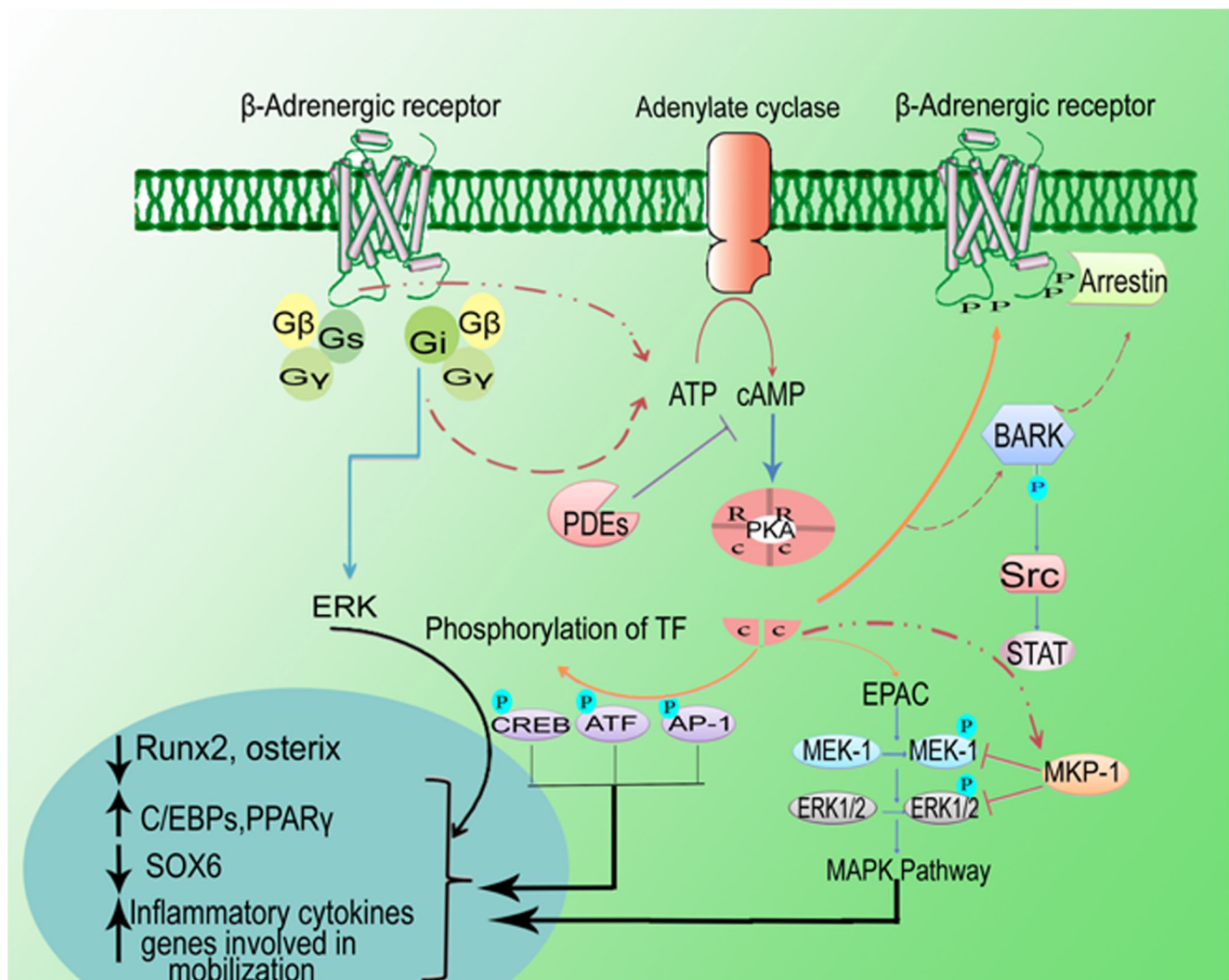


Fig. 1 Signaling of β -adrenergic receptors-coupled G-protein in MSCs. These receptors stimulate cAMP/PKA and MAP kinases

through the effect on regulatory transcription factors (TF) that can modify histones and methylation patterns. Recent findings on the MAPK pathway have shown that ERKs can regulate important enzymes of epigenetics, including DNA methyltransferase and acetyltransferase (Tsang and Cheng 2011). Furthermore, PKA-activated CREB mediate transcription via regulating methylation patterns (Lee et al. 2013). In addition, adrenergic signals could serve different miRNAs of each cell derived from MSCs (Collino et al. 2011). The control of TF and epigenetics including miRNA by adrenergic signaling seem to regulate MSCs fate (Collino et al. 2011). Despite important epigenetic and various aspects of this process in MSCs fate, this mechanism is beyond the scope of this paper and we focus on the interaction between downstream adrenergic signals with genes involved in MSCs fate.

Effect of catecholamines on mesenchyme-derived osteoblasts

Nervous system involvement in the regulation of bone mass is in agreement with the significant variations of bone formation through neural agonists (Soleimani et al. 2012). Catecholamine-producing nerves in the vicinity of osteoblasts can regulate bone remodeling, so suppressing nervous system activity leads to increased bone formation (Mignini et al. 2003). The administration of isoproterenol, a non-selective β -Adrs agonist, reduces osteoblasts number and bone mineral density without affecting body weight (Elefteriou et al. 2005). Conversely, deficiency or blockade of β -Adrs in mice will increase bone mass and prevent bone loss followed by ovariectomy (Minkowitz et al. 1991). One of the most convincing pieces of evidence for the involvement of catecholamines in regulating bone formation is the interaction between the nervous system and leptin. Leptin inhibits osteoblasts through up-regulation of the catecholamines releases/activity affecting the hypothalamus. So, infusion of β -Adrs antagonists suppresses the function of leptin on bone formation (Takeda et al. 2002). Moreover, it has been suggested that β -blockers could be considered as novel therapy for postmenopausal osteoporosis (Rejnmark et al. 2004).

Among all β -Adrs, β 2-Adr is the main, if not the only, adrenergic receptor expressed in osteoblasts (Li et al. 2010a, b). Thus, lack of β 2-Adr leads to a high bone mass phenotype (Li et al. 2010a, b). However, the role of β 1-Adr in bone formation is unknown. Recently, studies have shown that a lack of both β 1- and β 2-Adrs in osteoblasts results in decreased rather than increased bone formation. Indeed, β 1-Adr is required for high bone mass in β 2-/-Adr (Pierroz et al. 2006). The mechanism of the anti-osteogenic function of the nervous system seems to involve MSCs differentiation toward osteoblasts (Harada and Rodan 2003). Gene expression of adrenergic receptors has been detected in cell lines and primary osteoblasts, including α 1-Adr

in MC3T3-E1, β 1-Adr in SaOS-2, OHS-4 and TE-85 and β 2-Adr in primary osteoblasts, UMR106, MG63, ROS 17/2.8 and Saos2 (Suzuki et al. 1998). During MSC osteogenesis, the expression of the three β -Adrs is altered and β 2-Adr is markedly increased. The alteration extent of β 1-Adr is relatively low and expression of β 3-Adr is up-regulated but is much less than β 2-Adr (Li et al. 2010a, b). Generally, β 2-Adr seems to be the only adrenergic receptor presenting at significant levels in osteoblasts (Elefteriou 2008; Takeda 2005). Regarding the pathway of adrenergic signaling, shown in Fig. 1, cAMP-induced adrenergic agonists has been considered as the key pattern of transcriptional response-dependent catecholamines to signaling of osteoblast differentiation (Li et al. 2010a, b). β -Adr-induced AP-1 provides the condition for osteoblast proliferation and leads to increased levels of ATF4, a CREB-related transcription factor that seems critical in the differentiation and function of osteoblasts (Xiao et al. 2005).

The effects of the agonist and antagonist of β -Adr on osteogenic differentiation of MSCs is unclear and there are conflicting data in this respect. Li et al. (2010a, b) showed that the β -agonist suppresses osteogenesis with in a dose and time-dependent manner. Moreover, they proved that the inhibitory effect of isoproterenol on osteoblast differentiation from MSCs is through increased activity of cAMP and PKA in MSCs. So, propranolol, a potent PKA inhibitor, would abolish the effect of β adrenergic agonists on osteoblasts (Li et al. 2010a, b). In the same year, Uemura et al. (2010) insisted that neural agonists like epinephrine have anabolic effects on osteoblast differentiation on MSCs. In contrast to previous articles, they claimed that cAMP/PKA has an induced effect on the osteoblasts (Uemura et al. 2010). The CAMP pathway activated by G-proteins receptors such as β -Adrs can have a catabolic or anabolic role on bone formation in vitro. One of the possible explanations for this discrepancy may be due to using different doses of catecholamines and various in vitro conditions and methods. However, the effect of cAMP/PKA on osteogenesis should be clearly identified. This may suggest a role of several signaling TF and growth factors involved in differentiation of MSCs into osteoblasts by catecholamines, which could lead to down- or up-regulation of their expression (Table 1).

Effect of catecholamines on mesenchyme-derived myogenesis

Recently, Liu et al. (2011) found that myogenic progenitors are present in bone fractures (Liu et al. 2011). It has not yet been determined in this condition whether MSCs could differentiate to myogenic progenitors or would only provide appropriate stromals for myoblast cells. Furthermore, where do nervous systems stand in myogenic tissue? Very few studies on MSCs have been published showing that these cells could

Table 1 Transcriptions and signaling affecting on osteogenesis

Signaling and growth factors	Mechanisms of osteogenesis	Effect of catecholamine on factors	References
Wnt signaling	Activate the non-canonical Wnt/JNK pathway	Up-regulation of β -catenin	Qiu et al. 2011
TGF- β signaling	Increased expression of mRNA involved in osteogenesis	Catecholamines and TGF- β 1 have a positive feedback	Nogami et al. 1994; Zhao and Hantash 2011
SHH signaling	Interaction with Wnt and BMP signaling	Catecholamines and SHH have a positive feedback	Babashah et al. 2013; Charrier et al. 2001
FGF signaling	Phosphorylation of Runx2	Catecholamines and FGF have a positive feedback	Peng et al. 2002; Yu et al. 2003
Runx2	Regulation of genes involved in osteogenesis	Down-regulation of Runx2	Sato et al. 2007; Xiao et al. 2005
Osterix	Induction of preosteoblasts into fully functioning osteoblasts	Down-regulation of Osterix	Sato et al. 2007
TAZ	Induction of expression genes involved in osteogenesis	Not known	Xue et al. 2013
OGP	Stimulation of osteoblast-specific mRNA expression of core-binding factor 1 (cbfa1)	Not known	Chen et al. 2007
IGF-1	Increased expression of transcriptional co-activator with PDZ-binding motif (TAZ)	Catecholamines and IGF-1 have a positive feedback	Sun and Ng 1998; Xue et al. 2013
Insulin	Stimulation of Akt-dependent pathway	Down-regulation of insulin; insulin increases secretion of catecholamines	Sauter et al. 1983; Srivastava et al. 2012
PGE2	Induction of the expression of ALPase and Osterix	Catecholamines and PGE2 have a positive feedback	Negishi and Ito 1992; Ninomiya et al. 2011
Serotonin	Control osteogenesis positively and negatively.	Up-regulation of serotonin; serotonin leads to a down-regulation of catecholamine	Ducy and Karsenty 2010; Zweig and Axelrod 1969

TGF- β Transforming growth factor- β , *SHH* sonic Hedgehog protein, *FGF* fibroblast growth factor, *TAZ* transcriptional modulator, *OGP* osteogenic growth peptide, *IGF-1* insulin-like growth factor-1, *PGE2* prostaglandin E2

represent a myoblastic lineage phenotype (Shiota et al. 2007). However, under appropriated induction conditions, MSCs would acquire the phenotypic properties of skeletal myoblasts and cardiomyocytes (Shiota et al. 2007; Toma et al. 2002). In addition, studies have demonstrated that MSCs injection into patients with skeletal muscle dystrophy and myocardial infarction leads to improvement of muscle compliances that are associated with differentiation into muscle cells, myocardial thickness and myotubes growth (Gang et al. 2004). Important roles of catecholamines have been demonstrated in myogenesis, regulating skeletal muscle regeneration and cardiomyocyte formation (Lynch and Ryall 2008). New data suggest the important role of β -adrenoreceptors in myotoxic injury, including sarcopenia, muscular dystrophies and cancer cachexias (Beitzel et al. 2004; Koopman et al. 2009). Increasing muscle mass in neonatals followed by catecholamines injection has been found but it has not been identified whether or not differentiation of MSCs to muscle cells would be increased (Ryall et al. 2010). The direct effect of catecholamines has not yet been investigated on various stages of MSCs differentiation into myogenesis. However, it has been suggested that catecholamines play a pivotal role in the latter stages of myogenesis (Beitzel et al. 2004). For example,

expression of β -Adrs is increased significantly 2 days post-differentiation of muscle precursors, which subsequently use p21 as a stimulator, while terminal differentiation is upregulated (Ryall et al. 2010). All three isoforms of β -Adrs express in skeletal and cardiac muscle cells but the β 2 receptor contains the predominant population. In skeletal muscle, β agonists cause muscle mass through inducing PKA and PI3K rapamycin complex1 (mTORC1) and mediating phosphorylation of S6k and eIF4E binding protein1 (4EBP1) (Kline et al. 2007; Sneddon et al. 2001). Furthermore, decreasing key ubiquitin ligases of skeletal muscle, MAFbx (muscle atrophy F-box protein) and MuRF1 (muscle ring finger1), have been found followed by β -adrenoceptor treatment (Ryall et al. 2010). Furthermore, β -Adrs can accelerate skeletal muscle regeneration and improve the structure and function of these muscles (Ryall and Lynch 2008). Concerning cardiac muscle exposed by catecholamines, β -agonists inhibit the differentiation of these cells through β 1-Adr (Zaugg et al. 2000). Direct investigation of the effect of catecholamines on MSCs differentiation into muscle is necessary to determine the contribution of β -Adrs to myogenesis. In cardiac muscle based on receptor type, catecholamines have different effects and exhibit distinct outcomes on these cells (Shizukuda and

Buttrick 2002). Several observations emphasize neural-induced programmed cell death of cardiac muscle by $\beta 1$ Adr and antagonists of $\beta 2$ -ARs inhibit apoptosis (Xiao et al. 2006). Although it appears that catecholamines induce cardiac hypertrophy via α and $\beta 1$ -Adrs, selective overexpression of $\beta 2$ -Adr could restore ventricular function and hypertrophy (Morisco et al. 2001).

Effect of catecholamines on mesenchyme-derived adipocytes

The sympathetic nervous system (SNS) has a prominent role in differentiation and metabolism of adipocyte cells and SNS innervation has been found in adipocyte tissues (Path et al. 2001; Zhu et al. 2003). β -Adr agonists take their place as the predominant regulators in catecholamines-induced lipolysis of stored triglyceride in both white and brown adipocytes of brain. Thus, $\beta 3$ agonist may lead to increased energy expenditure and reduced fat stores (Grønning et al. 2006). Lack of the three known β -Adrs in mice decreases the metabolic rate and the extent of massive obesity due completely to the defeating of diet-induced thermogenesis (Li et al. 2010a, b). It has been suggested that 20–25 % of lipolysis is mediated through β -Adrs activation of ERK pathways (Collins 2011). Moreover, the catecholamine-induced pathway of p38 α MAPKs in adipocytes leads to the expression of transcription involved in the differentiation of brown adipocytes. However, the role of the p38 MAPK pathway in white adipocytes has not yet been reported (Collins 2011). The forkhead transcription factor FOXC2 affects genes involved in lipolysis via increased sensitivity of the β adrenergic-cAMP-PKA signaling pathways (Grønning et al. 2006). It has been well established that specific enzymes of neuronal cells such as dopamine- β -hydroxylase (DBH) and TH are expressed by adipocytes cells that are independent of nerve terminals, indicating the role of adipocyte tissue as a new source of catecholamine production (Barry and Murphy 2004). However, fat depots have different expression of neural enzymes and stress could stimulate the production of catecholamine in adipocytes (Barry and Murphy 2004; Vargovic et al. 2011). It can be suggested that there is an appropriate interaction between neural cells with adipocyte cells for the regulation of different effects on fat tissue.

Adrenergic receptors such as $\beta 1$, $\beta 2$ and $\beta 3$ and $\alpha 1$ and $\alpha 2$ receptors on adipocyte surfaces have been demonstrated (Bengtsson et al. 2000). As mentioned above, adrenergic agonists lead to the activation of the cAMP/PKA signaling pathway. Hence, it has been noted that catecholamines control adipocyte tissue functions in a large part through signaling mediated by β -Adrs (Collins 2011). The expression alterations of particular β -Adr subtypes during adipogenic differentiation from MSCs indicate that $\beta 2$ and $\beta 3$ are the main receptors of β -adrenergics and up-regulate upon adipogenic

induction (Bengtsson et al. 2000). $\beta 2$ - and $\beta 3$ -Adrs are expressed in early and late stages of differentiated adipocytes, respectively (Li et al. 2010a, b). $\beta 1$ -Adrs have a limited expression during the adipogenesis process of MSCs (Li et al. 2010a, b). In this line, studies on 3 T3-L1 fibroblasts demonstrated that, during the process of differentiation to the adipocyte, only up-regulated $\beta 2$ -Adr is observed and $\beta 1$ -Adr has an undetectable level (Guest et al. 1990). In other studies, in 3 T3-F442A cells, $\beta 1$ - and $\beta 3$ -Adr became detectable in early and late adipocytes, respectively (Feve et al. 1991). Nevertheless, it should be noted that different cell lines have exclusive characteristics. During brown adipocyte development, variations of the switch in the β -Adr subtypes have seen to be different from white adipocytes, so $\beta 1$ -Adr is expressed abundantly in preadipocytes, leading to increased proliferation, while $\beta 3$ -Adr is mainly detectable in later adipogenesis (Bronnikov et al. 1999). In human, most brown adipocytes are lost during the transition from newborn to adult. In vitro, the most frequent models of adipogenesis include using MSCs, preadipocytes and isolated adipocytes under suitable conditions (Hashemi et al. 2013; Yousefi et al. 2013). However, these cell populations have been reported to have the same differentiation potential into adipocytes (De Ugarte et al. 2003). Studies have shown that imipramine, a regulator of re-uptake of norepinephrine and serotonin, inhibits adipogenic differentiation in both 3 T3-L1 preadipocytes and mouse MSCs by stimulating $\beta 2$ - and $\beta 3$ -Adrs (Li et al. 2012). Moreover, β -Adr agonists, especially stimulators of $\beta 2$ and $\beta 3$, inhibit MSC adipogenesis with a trend of dose- and time-dependence, while antagonists have a positive effect on the development of adipocytes from MSCs (Li et al. 2010a, b). However, another study established that agonists adrenergics could lead to preadipocyte proliferation but inhibit its differentiation (Collins 2011). Finally, in brown-fat cells, a different behavior from catecholamines has been found, so that norepinephrine promotes the expression of factors involved in differentiation preadipocytes and also induces the proliferation of cultured brown-fat cells (Nedergaard et al. 1995; Rehnmark et al. 1990) (Table 2).

Effect of catecholamines on mesenchyme-derived chondrocytes

Under specific conditions, MSCs differentiate into chondroprogenitor cells as a result from condensation and subsequently chondrocytes arise from these progenitors (Kadivar et al. 2006). Chondrocytes can undergo proliferation and convert to endochondral ossification, which induces bone formation (temporary cartilage) or remain as resting cells to form the complex tissue of articular cartilage (permanent cartilage) (Kadivar et al. 2006). Indeed, the formation of a

Table 2 Transcriptions and signaling affecting on adipogenesis

Factors	Mechanism	Effect of catecholamines on factors	References
C/EBPs	Binding to C/EBPs-response element of DNA	Down-regulation of C/EBPs	Li et al. 2010a, b
PPAR γ	Binding to PPAR γ -response element of DNA	Down-regulation of PPAR γ	Li et al. 2010a, b
E2F transcription factors	Induction of E2F pathway	Not known	Porse et al. 2001
KLF transcription factors	Induction of PPAR γ and C/EBP expression	Not known; while Klf has a positive effect on synthesis of TH	Caiazzo et al. 2011
SREBPs	Induction of PPAR γ expression	Up-regulation of SREBPs	Eberle et al. 2004; Swierczynski 2006
IRFs	Stimulation of promoters of key adipocyte genes	Not known	Eguchi et al. 2008
Ebfl	Stimulation of differentiation by activating PPAR γ and C/EBP α transcription	Up-regulation of Ebfl	Jimenez et al. 2007; Lecka-Czernik et al. 2012
pRb	Increased transcription of C/EBP β	Up-regulation of pRb	Fajas et al. 2002; Masur et al. 2001
BMP4	Stimulation of the HMGA2 expression	Not known; but BMP4 has a positive effect on catecholamine production	Markowski et al. 2011; Varley and Maxwell 1996
DEHP	Induction of the peroxisome proliferator-activated receptors α and γ (PPAR $\alpha\gamma$)	Not known	Biemann et al. 2012
GCs	Up-regulation of the C/EBPs by increase in PPAR γ 2 and aP2 expression	Catecholamines and GCs have a positive feedback	Ito et al. 2007; Udelsman et al. 1987
ROS	Induction of genes involved in early stage of adipogenesis	Not known	Tormos et al. 2011

C/EBP CCAAT/enhancer-binding protein, *PPAR γ* peroxisome proliferator-activated receptor gamma, *SREBPs* sterol regulatory element-binding proteins, *IRFs* interferon regulatory factors, *Ebfl* early B-cell factor 1, *pRb* retinoblastoma cell cycle related proteins, *BMP4* bone morphogenetic proteins, *DEHP* bis (2-ethylhexyl) phthalate, *GCs* glucocorticoids, *ROS* reactive oxygen species

cartilaginous model is well known as the physiological trigger for skeletal development.

As mentioned before, nerve endings of sympathetic origin innervate bone and could be involved in mediating endochondral ossification during skeletal growth (Grills et al. 1997; Harada and Rodan 2003). The effects of adrenergic activation on bone development could be regulated by the effects on chondrocytes (Lai and Mitchell 2008b). Expression of adrenergic receptors has been demonstrated in cell lines, for example in primary growth plate chondrocytes (GPC) and both proliferating and hypertrophic chondrocytes only the β 2-Adr was detected and α - and other β -Adr were abundantly found in primary costal chondrocytes (Takarada et al. 2009). Epinephrine can lead to the suppression of chondrogenesis by stimulation of β 2-Adr (Takarada et al. 2009). However, it has been found that epinephrine decreased apoptosis in chondrocytes (Takarada et al. 2009). Infrequent evidence has been found for the functional role of catecholamines signaling in the mechanisms underlying differentiation stages of chondrogenesis from MSCs (Lai and Mitchell 2008a). During the endochondral process, epinephrine inhibits SOX9, a transcription factor that is required in the early steps of chondrogenesis, through reducing SOX6 activation that is essential to form a functional heteromeric protein complex with Sox9 (Takarada et al. 2009). Furthermore, catecholamine

regulates the function between β -catenin and SOX9 during chondrocyte differentiation (Takarada et al. 2009). Administration of a β -Adr antagonist would optimize tissue repair by promoting MSCs-altered chondrocytes, preventing catecholamines-reduced formation of hypertrophic chondrocytes and recruitment of osteocytes (Rejnmark et al. 2004). Moreover, recent studies suggest that signal transduction of β -Adrs coupled to stimulation of both MAP kinase and ERK1/2 induces the growth of chondrocytes and inhibits their differentiation (Lai and Mitchell 2008a). Previously, the inhibitory effect of PKA and ERK1/2 has been investigated on the role of chondrogenesis in the interaction between FGF receptor3 activation and parathyroid hormone-related peptide (Mabvuure et al. 2012). In general, β -ARs would inhibit Col II and SOX6 through PKA and ERK1/2-up-regulated AP-1 factor Jun-B (Ikegami et al. 2011). The neural control of articular chondroblast and chondrocyte differentiation has not yet been characterized (see Table 3).

Effect of catecholamines on mobilization of MSCs

In steady-state conditions, isolation of MSCs from the PB with its phenotypic and functional criteria is difficult and controversial. However, studies have demonstrated that the numbers of MSCs

Table 3 Transcriptions and signaling affecting genes involved in mobilization

Factors	Mechanism of mobilization	Effect of catecholamines on the factors	References
SDF1	Recruitment of CXCR4 MSCs	Down-regulation of SDF1	Hu et al. 2013
CXCR4	Departure to sites of SDF1 rich	Up-regulation of CXCR4	Yu et al. 2012
CCL25(TECK)	The stimulation of CXCR2 ligands and LIF-receptor/gp130 ligand	Not known	
EPO	Induction of SDF-1 secretion in the microenvironments of injury	Up-regulation of EPO	Richter et al. 2013; Robertson et al. 1994
TB4	(1) Increased IL-8 secretion, (2) enhanced the proliferation of MSCs	Up-regulation of TB4	Hall et al. 1988; Jeon et al. 2013
S1P	Homing of MSCs into tissue via S1P receptor	Up-regulation of S1P	Jang et al. 2011
G-CSF	Increased bone resorption	Up-regulation of G-CSF; G-CSF also increases catecholamine expression	Brouard et al. 2010; Katayama et al. 2006
IGF1	Increased Akt/PI3K, MEK1/2-Erk1/2 and smad2/3	Not-known; while IGF-1 increases catecholamine expression	Hwang and Choi 1995; Kumar and Ponnazhagan 2012
HGF	Recruitment of MSCs into tissue via HGFR	Catecholamines and HGF have a positive feedback	Lindroos et al. 1991; Maina et al. 1998; Vogel et al. 2013
VEGF	Recruitment of MSCs into tissue via VEGFR	Up-regulation of VEGF	Yang et al. 2006; Zisa et al. 2009
PDGF-BB	Stimulation of MT1-MMP expression concert with ERK1/2 and PI3K/AKT activation	Up-regulation of PDGF	Sun et al. 2013; Vashisht et al. 1992
TLR-9	Stimulation of MMP-13 synthesis in the CpG-activated MSCs	Not known	Nurmemmiemi et al. 2010
MMP-2	Degradation of major constituent basement membrane	Up-regulation of MMP	Song and Li 2011; Yang et al. 2006

SDF1 Stromal-derived factor1, *EPO* erythropoietin, *TB4* thymosin β 4, *S1P* sphingosine1-phosphate, *HGF* hepatocyte growth factor, *TLR-9* toll-like receptor 9

would considerably increase in circulating blood after treatment with stimuli agents such as G-CSF, which augments mobilization and transmigration of MSCs (Cashen et al. 2007). G-CSF is a potent inducer of the mobilization of bone marrow stem cells (BMSCs) to the circulation and is the principal cytokine using current stimuli for BM transplant (Lapid et al. 2008). Studies have demonstrated that G-CSF receptors are expressed on MSCs surface. So, this could be suggested to be a direct and indirect mechanism of G-CSF-induced mobilization of MSCs (Kim et al. 2005). One of the mechanisms of G-CSF-induced mobilization of BMSCs is dependent on CXCR4–SDF1 interaction (Semerad et al. 2005). Interestingly, both CXCR4 and SDF1 are expressed in MSCs that provide an appropriate microenvironment for hematopoietic stem cells (HSCs) in BM (Gheisari et al. 2012; Nadri et al. 2007). The density gradient between CXCR4 and SDF1 could determine the recruitment of BMSCs such as MSCs to BM or into the circulation (Petit et al. 2002). Therefore, G-CSF-increased CXCR4 expression in these cells leads to their mobilization to PB containing high levels of SDF-1 released from BM (Lapid et al. 2008; Petit et al. 2002). Indeed, G-CSF increases the secretion of SDF from producing cells (Katayama et al. 2006). However, it has not yet been determined that circulating MSCs have a high expression of CXCR4 or SDF1. Growing evidence has shown that nervous systems are the main regulator of the G-CSF-induced mechanism of MSCs

mobilization (Saba et al. 2013). Severe neurological abnormalities lead to dramatically reduced mobilization of BMSCs into the circulation (Saba et al. 2013; Shome et al. 2012). Furthermore, a positive feedback between treatment of G-CSF and catecholamines has recently been described (Katayama et al. 2006). Catecholamines can induce the secretion of proteolytic enzymes in BM to cleave adhesion molecules, increasing bone absorption and the effect on expression genes involved in the mobilization of BMSCs (Dygai et al. 2012; Saba et al. 2013).

Stress has a positive effect on the migration of MSCs into PB or to damaged sites and tumor microenvironments (Kawada et al. 2004). Recently, epinephrine and norepinephrine-induced mobilization of MSCs to sites of tumors has been determined, which promote angiogenesis and protect tumor cells (Chakroborty et al. 2009). Dopamine as another catecholamine has been reported as remarkably reducing the migration of MSCs, acting through its D2 receptors (Saba et al. 2013; Shome et al. 2012). The release of various cytokines and growth factors in damaged tissue leads to increased mobilization of MSCs from BM to the circulation and finally from there to the wound bed (Hocking and Gibran 2010). It should be noted that the migration of MSCs is dependent upon the different cytokine/receptors and catecholamines having positive or negative effects in this scenario (Table 1). However, the signaling networks that orchestrate the processes of

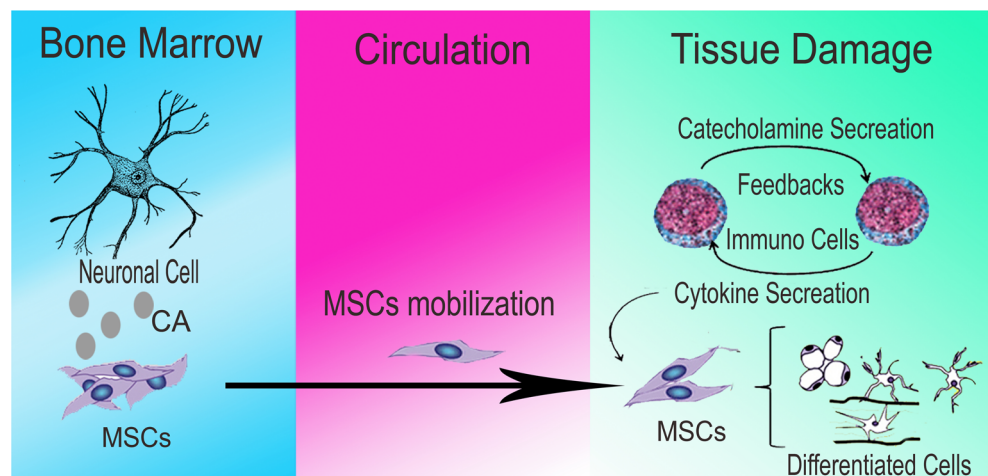
MSCs mobilizations are unknown and many questions remain unanswered. The stimulation of the sympathetic nervous system occurs in patients with severe injuries in whom plasma catecholamine levels are significantly higher than the steady-state condition (Jeschke 2013; Ostrowski et al. 2013). In addition, catecholamines secreted from immune system cells, such as lymphocytes, macrophages and neutrophils and epidermal keratinocytes in damaged tissue can subsequently lead to further release of inflammatory cytokines (Stanojević et al. 2013). Also, cytokines involved in damaged sites support catecholamine synthesis from immune cells. Such feedback between catecholamines and cytokines could increase the expression of SDF-1 tissue injury and recruit MSCs CXCR4+ to these environments (Pullar et al. 2008). Catecholamines can have complex behaviors for mobilization of MSCs to circulation and tissue injury. Agonists of adrenergic receptors in BM lead to mobilization of stem cells including MSCs into the circulation, suggesting high levels of migration of these cells to damaged microenvironments. Also, cytokines induced by catecholamines-derived tissues would differentiate MSCs to tissue lineage cells and promote tissue repair (see Fig. 2 for details) (Pullar et al. 2008). Moreover, injection of β blockers reduces MSCs migration to sites of damage, which could be having positive and negative effects on tissue repair (Baranski et al. 2011). These blockers would remain stem cells such as MSCs in BM compartments in patients with shock and severe damage tissue; therefore, MSCs recruitment to tissue repair would decrease (Baranski et al. 2011). It should more and more be considered that the neural system can be an effective factor for mobilization in both steady-state and trauma conditions.

From nervous system research to clinical application of neural drugs

The broad advances in nervous system research has promised to practitioners in the use of neural drugs in treating disease

such as bone fracture, obesity and myocardial infarction that catecholamines play pivotal roles in these disorders (Collins 2011; Eleftheriou 2005; Shizukuda and Buttrick 2002). In addition, catecholamines-induced appropriate and efficient MSCs mobilization could improve the conditions of tissue repair (Shome et al. 2012). Therapeutic modulation of the nervous system may involve more than tissue selectivity and leads to significant challenges in the whole body (Duncan et al. 1985). Expression of adrenergic receptors in most cells is another challenge, causing mechanism-based side effects and different effects. As an example, β agonists affect regeneration and formation of skeletal muscles but lead to cardiomyocyte failure (Ryall et al. 2010; Shizukuda and Buttrick 2002). Thus, exploiting the therapeutic purposes of these drugs, protein kinases, TF for example, could provide information to help face challenges that might be met. As mentioned above, the main objective of catecholamines is the stimulation of PKA and MAPK pathways through β - and α -Adrs, involving a variety of specific genes (Cole and Sood 2012). Hence, adrenergic drugs would involve these pathways and achieve their therapeutic approaches (Weiss et al. 2013). The adrenergic pathway is considered as a major pathway in this line and an attractive target for developing drugs to reduce skeletal, metabolism and cartilage diseases (Weiss et al. 2013). There are, however, examples in disorders of bone, muscle, adipocytes and chondrocytes where adrenergic drugs could be met (Collins 2011; Eleftheriou 2008; Lai and Mitchell 2008b). Much has been reported about using propranolol, a β -blocker, as promising new therapies for preventing bone loss in postmenopausal women with the risk of bone fractures, in astronauts exposed to long-term microgravity and in bedridden elderly patients whose bone mass may reduce (Mano et al. 2010). Moreover, β -blockers have been found that attenuate cardiac hypertrophy and improve cartilage damage (Morisco et al. 2001). Interestingly, propranolol injections to patients with solid tumors decreases MSCs migration into the tumor environment and inhibits the

Fig. 2 The effect of catecholamine on migration of MSCs to injury sites. BM catecholamines induce the mobilization of MSCs to peripheral blood through their effects on molecular adhesion and proteolytic enzymes. Positive feedback between catecholamines and cytokines leads to increased cytokines involved in MSCs differentiation to improve damaged tissues



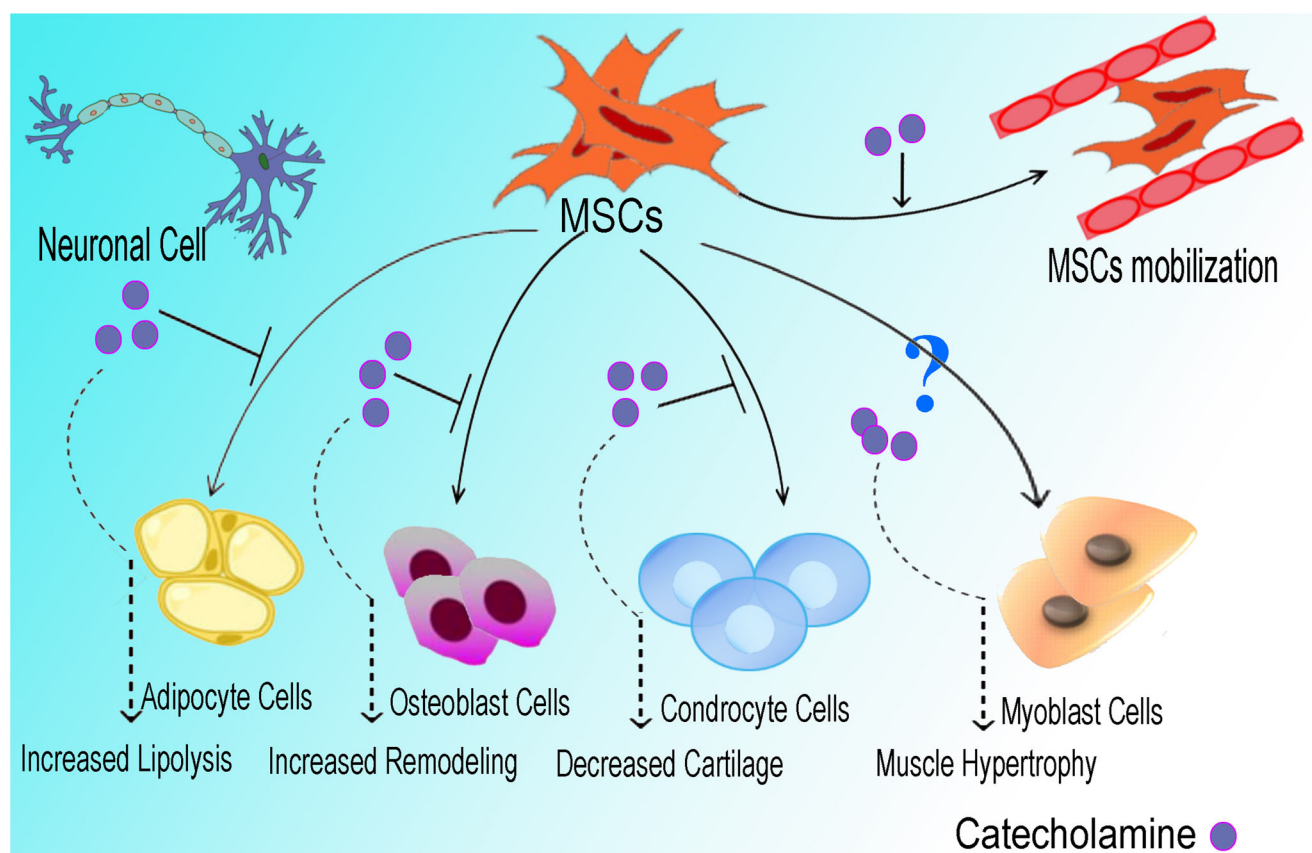


Fig. 3 Outline of catecholamines role in the final fate of MSCs. Catecholamines inhibit MSCs differentiation into adipocytes, osteoblasts and chondrocytes but increase MSCs mobilization into circulation and sites of injury. The direct effects of catecholamines on myogenic

differentiation from MSCs have not been identified. *Dotted lines* show the direct effects of catecholamine on differentiated cells from MSCs, causing increased lipolysis, remodeling of bone, decreased cartilage and hypertrophy of muscle

supportive role of MSCs in making appropriate stroma for cancer cells (Chakroborty et al. 2009). In addition, stimulating catecholamine release or blocking norepinephrine re-uptake through drugs such as phentermine and mazindol, respectively, have some inhibitor effects on adipocytes and increased lipolysis (Ranjit et al. 2011). Despite the supportive role of catecholamines in skeletal muscle injury, nervous excitation has some stimulant effects, including elevation of blood pressure and heart rate (Duncan et al. 1985). The central induction of MSCs mobilization via catecholamine stimulators has not been identified in patients and as with other therapies, exposing patients to neural drugs will be the main challenge.

Conclusion

The formation of adipocytes, skeletal, chondrocyte and myocyte cells during embryogenesis and migration of MSCs involves a network of signaling that has a pivotal role in MSCs differentiation toward the diverse lineages (Guzzo et al. 2013; Linsley et al. 2013; Xinari et al. 2013). The functional interaction of catecholamines signals is the main method of regulating distinct sets of genes in MSCs. Catecholamines

have direct effects on MSCs differentiation and cells derived from MSCs (see Fig. 3). In general, we can conclude that bone, adipocyte and cartilage tissue are suppressed via the nervous system and the direct effect of catecholamines on osteoblasts, adipocyte cells and chondrocytes increases remodeling bone, lipolysis adipocytes and delay in cartilage tissue repair, respectively (Fig. 3). Catecholamines have different effects on myogenesis and MSCs mobilization and lead to muscle hypertrophy and increased MSCs migration (Sarkar et al. 2013). Thus, emerging evidence addresses all downstream involved adrenergic signals but some important questions remain to be answered. For example, is there a role for adrenergic agonists in the control of MSCs physiology? The catecholamines are definitely important for the regulation of bone formation but do all the catecholamines such as epinephrine, nor-epinephrine and dopamine play a role in MSCs differentiation into bone? Adrenergic signals appear to control adipogenesis through modulating the differentiation of MSCs toward adipocytes; however, the direct role of adrenergics on the pathogenesis of disease with high adipocytes such as aplasia in BM has not been well described. We know that most adrenergic receptors are expressed in cartilage but the precise role of catecholamines in the induction of endochondral ossification for bone formation remains unclear. Finally, there is

considerable evidence to show that stress can cooperate with other pathways that promote cancer development through targeting of MSCs migration to tumor environments that can be therapeutic alternatives but the effects of feedback of cytokines and catecholamines on tumor progression induced by migration of MSCs are not understood (Sarkar et al. 2013). These and other questions will probably be discovered in the coming years.

Acknowledgments We would like to acknowledge Thomas J. Kelly for his revisions and thank all our colleagues at the Department of Hematology in Tarbiat Modares University for assistance with the manuscript. This study was supported by Tarbiat Modares University.

References

- Ahmadbeigi N, Soleimani M, Vasei M, Gheisari Y, Mortazavi Y, Azadmanesh K, Omidkhoda A, Janzamin E, Nardi NB (2013) Isolation, characterization, and transplantation of bone marrow-derived cell components with hematopoietic stem cell niche properties. *Stem Cells Dev* 22:3052–3061
- Babashah S, Sadeghizadeh M, Hajifathali A, Tavirani MR, Zomorod MS, Ghadiani M, Soleimani M (2013) Targeting of the signal transducer Smo links microRNA-326 to the oncogenic hedgehog pathway in CD34+ CML stem/progenitor cells. *Int J Cancer* 133:579–589
- Baranski GM, Offin MD, Sifri ZC, Elhassan IO, Hannoush EJ, Alzate WD, Rameshwar P, Livingston DH, Mohr AM (2011) beta-blockade protection of bone marrow following trauma: the role of G-CSF. *J Surg Res* 170:325–331
- Barry FP, Murphy JM (2004) Mesenchymal stem cells: clinical applications and biological characterization. *Int J Biochem Cell Biol* 36:568–584
- Beitzel F, Gregorevic P, Ryall JG, Plant DR, Sillence M, Lynch GS (2004) β 2-Adrenoceptor agonist fenoterol enhances functional repair of regenerating rat skeletal muscle after injury. *J Appl Physiol* 96:1385–1392
- Bengtsson T, Cannon B, Nedergaard J (2000) Differential adrenergic regulation of the gene expression of the β -adrenoceptor subtypes β 1, β 2 and β 3 in brown adipocytes. *Biochem J* 347:643–651
- Biemann R, Navarrete Santos A, Navarrete Santos A, Riemann D, Knelangen J, Blüher M, Koch H, Fischer B (2012) Endocrine disrupting chemicals affect the adipogenic differentiation of mesenchymal stem cells in distinct ontogenetic windows. *Biochem Biophys Res Commun* 417:747–752
- Bronnikov G, Bengtsson T, Kramarova L, Golozubova V, Cannon B, Nedergaard J (1999) beta1 to beta3 switch in control of cyclic adenosine monophosphate during brown adipocyte development explains distinct beta-adrenoceptor subtype mediation of proliferation and differentiation. *Endocrinology* 140:4185–4197
- Brouard N, Driessen R, Short B, Simmons PJ (2010) G-CSF increases mesenchymal precursor cell numbers in the bone marrow via an indirect mechanism involving osteoclast-mediated bone resorption. *Stem Cell Res* 5:65–75
- Caiazzo M, Colucci-D'Amato L, Volpicelli F, Speranza L, Petrone C, Pastore L, Stifani S, Ramirez F, Bellenchi GC, di Porzio U (2011) Krüppel-like factor 7 is required for olfactory bulb dopaminergic neuron development. *Exp Cell Res* 317:464–473
- Caplan AI, Bruder SP (2001) Mesenchymal stem cells: building blocks for molecular medicine in the 21st century. *Trends Mol Med* 7:259–264
- Cashen AF, Lazarus HM, Devine SM (2007) Mobilizing stem cells from normal donors: is it possible to improve upon G-CSF? *Bone Marrow Transplant* 39:577–588
- Chakroborty D, Sarkar C, Basu B, Dasgupta PS, Basu S (2009) Catecholamines regulate tumor angiogenesis. *Cancer Res* 69:3727–3730
- Charrier J-B, Lapointe F, Le Douarin NM, Teillet M-A (2001) Anti-apoptotic role of sonic hedgehog protein at the early stages of nervous system organogenesis. *Development* 128:4011–4020
- Chen Z-x, Chang M, Y-I P, Zhao L, Y-r Z, L-j W, Wang R (2007) Osteogenic growth peptide C-terminal pentapeptide [OGP (10–14)] acts on rat bone marrow mesenchymal stem cells to promote differentiation to osteoblasts and to inhibit differentiation to adipocytes. *Regul Pept* 142:16–23
- Cole SW, Sood AK (2012) Molecular pathways: beta-adrenergic signaling in cancer. *Clin Cancer Res* 18:1201–1206
- Collino F, Bruno S, Deregibus MC, Tetta C, Camussi G (2011) MicroRNAs and mesenchymal stem cells. *Vitam Horm* 87:291–320
- Collins S (2011) Beta-adrenoceptor signaling networks in adipocytes for recruiting stored Fat and energy expenditure. *Front Endocrinol (Lausanne)* 2:102
- De Ugarte DA, Morizono K, Elbarbary A, Alfonso Z, Zuk PA, Zhu M, Dragoo JL, Ashjian P, Thomas B, Benhaim P, Chen I, Fraser J, Hedrick MH (2003) Comparison of multi-lineage cells from human adipose tissue and bone marrow. *Cells Tissues Organs* 174:101–109
- Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop D, Horwitz E (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The international society for cellular therapy position statement. *Cytotherapy* 8:315–317
- Ducy P, Karsenty G (2010) The two faces of serotonin in bone biology. *J Cell Biol* 191:7–13
- Duncan JJ, Farr JE, Upton SJ, Hagan RD, Oglesby M, Blair SN (1985) The effects of aerobic exercise on plasma catecholamines and blood pressure in patients with mild essential hypertension. *JAMA* 254:2609–2613
- Dygai AM, Khmelevskaya ES, Skurikhin EG, Pershina OV, Andreeva TV, Ermakova NN (2012) Catecholamine regulation of stromal precursors and hemopoietic stem cells in cytostatic myelosuppression. *Bull Exp Biol Med* 152:723–727
- Eberle D, Hegarty B, Bossard P, Ferré P, Foulfelle F (2004) SREBP transcription factors: master regulators of lipid homeostasis. *Biochimie* 86:839–848
- Eguchi J, Yan Q-W, Schones DE, Kamal M, Hsu C-H, Zhang MQ, Crawford GE, Rosen ED (2008) Interferon regulatory factors are transcriptional regulators of adipogenesis. *Cell Metab* 7:86–94
- Eleftheriou F (2005) Neuronal signaling and the regulation of bone remodeling. *Cell Mol Life Sci* 62:2339–2349
- Eleftheriou F (2008) Regulation of bone remodeling by the central and peripheral nervous system. *Arch Biochem Biophys* 473:231–236
- Eleftheriou FAJ, Takeda S, Starbuck M, Yang X, Liu X, Kondo H, Richards WG, Bannon TW, Noda M, Clement K, Vaisse C, Karsenty G (2005) Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature* 434(7032):514–520
- Fajas L, Egler V, Reiter R, Hansen J, Kristiansen K, Debril M-B, Miard S, Auwerx J (2002) The retinoblastoma-histone deacetylase 3 complex inhibits PPAR γ and adipocyte differentiation. *Dev Cell* 3:903–910
- Farshdousti Haghi M, Noruzinia M, Mortazavi Y, Soleimani M, Kaviani S, Mahmoodinia Maymand M (2012) Zoledronic acid induces Osteoblastic differentiation of mesenchymal stem cells without change in Hypomethylation status of OSTERIX promoter. *Cell J* 14:90–97
- Fève B, Emorine L, Lasnier F, Blin N, Baude B, Nahmias C, Strosberg A, Pairault J (1991) Atypical beta-adrenergic receptor in 3 T3-F442A adipocytes. Pharmacological and molecular relationship with the human beta 3-adrenergic receptor. *J Biol Chem* 266:20329–20336
- Gang EJ, Jeong JA, Hong SH, Hwang SH, Kim SW, Yang IH, Ahn C, Han H, Kim H (2004) Skeletal myogenic differentiation of mesenchymal stem cells isolated from human umbilical cord blood. *Stem Cells* 22:617–624

- Gheisari Y, Azadmanesh K, Ahmadbeigi N, Nassiri SM, Golestaneh AF, Naderi M, Vasei M, Arefian E, Mirab-Samiee S, Shafiee A, Soleimani M, Zeinali S (2012) Genetic modification of mesenchymal stem cells to overexpress CXCR4 and CXCR7 does not improve the homing and therapeutic potentials of these cells in experimental acute kidney injury. *Stem Cells Dev* 21:2969–2980
- Grayson WL, Zhao F, Bunnell B, Ma T (2007) Hypoxia enhances proliferation and tissue formation of human mesenchymal stem cells. *Biochem Biophys Res Commun* 358:948–953
- Grills BL, Schuijers JA, Ward AR (1997) Topical application of nerve growth factor improves fracture healing in rats. *J Orthop Res* 15:235–242
- Grønning LM, Baillie GS, Cederberg A, Lynch MJ, Houslay MD, Enerbäck S, Taskén K (2006) Reduced PDE4 expression and activity contributes to enhanced catecholamine-induced cAMP accumulation in adipocytes from FOXC2 transgenic mice. *FEBS Lett* 580:4126–4130
- Guest S, Hadcock J, Watkins D, Malbon C (1990) Beta 1-and beta 2-adrenergic receptor expression in differentiating 3 T3-L1 cells. Independent regulation at the level of mRNA. *J Biol Chem* 265:5370–5375
- Guzzo RM, Gibson J, Xu RH, Lee FY, Drissi H (2013) Efficient differentiation of human iPSC-derived mesenchymal stem cells to chondroprogenitor cells. *J Cell Biochem* 114:480–490
- Hall NS, O'Grady M, Steiner R, Goldstein A (1988) Interactions Between Thymosins and Neuroendocrine Circuits. In: Gorio A, Perez-Polo JR, Vellis J, Haber B (eds) *Neural Development and Regeneration*, vol 22, NATO ASI Series. Springer, Berlin, pp 571–582
- Harada SI, Rodan GA (2003) Control of osteoblast function and regulation of bone mass. *Nature* 423:349–355
- Hashemi SM, Hassan ZM, Pourfathollah AA, Soudi S, Shafiee A, Soleimani M (2013) In vitro immunomodulatory properties of osteogenic and adipogenic differentiated mesenchymal stem cells isolated from three inbred mouse strains. *Biotechnol Lett* 35:135–142
- Havasi P, Nabioni M, Soleimani M, Bakhshandeh B, Parivar K (2013) Mesenchymal stem cells as an appropriate feeder layer for prolonged in vitro culture of human induced pluripotent stem cells. *Mol Biol Rep* 40:3023–3031
- Haynesworth SE, Baber M, Caplan AI (1992) Cell surface antigens on human marrow-derived mesenchymal cells are detected by monoclonal antibodies. *Bone* 13:69–80
- Hocking AM, Gibran NS (2010) Mesenchymal stem cells: paracrine signaling and differentiation during cutaneous wound repair. *Exp Cell Res* 316:2213–2219
- Hu C, Yon X, Li C, Lü M, Liu D, Chen L, Hu J, Teng M, Zhang D, Fan Y (2013) CXCL12/CXCR4 axis promotes mesenchymal stem cell mobilization to burn wounds and contributes to wound repair. *J Surg Res* 183(1):427–434
- Hwang O, Choi HJ (1995) Induction of gene expression of the catecholamine-synthesizing enzymes by insulin-like growth factor-I. *J Neurochem* 65:1988–1996
- Ikegami D, Akiyama H, Suzuki A, Nakamura T, Nakano T, Yoshikawa H, Tsumaki N (2011) Sox9 sustains chondrocyte survival and hypertrophy in part through Pik3ca-Akt pathways. *Development* 138:1507–1519
- Ito S, Suzuki N, Kato S, Takahashi T, Takagi M (2007) Glucocorticoids induce the differentiation of a mesenchymal progenitor cell line, ROB-C26 into adipocytes and osteoblasts, but fail to induce terminal osteoblast differentiation. *Bone* 40:84–92
- Jang S, Kim D, Lee Y, Moon S, Oh S (2011) Modulation of sphingosine 1-phosphate and tyrosine hydroxylase in the stress-induced anxiety. *Neurochem Res* 36:258–267
- Jeon B-J, Yang Y, Kyung Shim S, Yang H-M, Cho D, Ik Bang S (2013) Thymosin beta-4 promotes mesenchymal stem cell proliferation via an interleukin-8-dependent mechanism. *Exp Cell Res* 319:2526–2534
- Jeschke M (2013) Pathophysiology of Burn Injury. In: Jeschke MG, Kamolz L-P, Shahrokhi S (eds) *Burn Care and Treatment*. Springer, Vienna, pp 13–29
- Jimenez MA, Åkerblad P, Sigvardsson M, Rosen ED (2007) Critical role for Ebf1 and Ebf2 in the adipogenic transcriptional cascade. *Mol Cell Biol* 27:743–757
- Kadivar M, Khatami S, Mortazavi Y, Shokrgozar MA, Taghikhani M, Soleimani M (2006) In vitro cardiomyogenic potential of human umbilical vein-derived mesenchymal stem cells. *Biochem Biophys Res Commun* 340:639–647
- Katayama Y, Battista M, Kao W-M, Hidalgo A, Peired AJ, Thomas SA, Frenette PS (2006) Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. *Cell* 124:407–421
- Kawada H, Fujita J, Kinjo K, Matsuzaki Y, Tsuma M, Miyatake H, Muguruma Y, Tsuboi K, Itabashi Y, Ikeda Y (2004) Nonhematopoietic mesenchymal stem cells can be mobilized and differentiate into cardiomyocytes after myocardial infarction. *Blood* 104:3581–3587
- Khajeni S, Allameh A, Soleimani M, Mortaz E (2013) Changes in COX-2 and oxidative damage factors during differentiation of human mesenchymal stem cells to hepatocyte-like cells is associated with downregulation of p53 gene. *Biol Chem* 394(9):1213–1222
- Kim DH, Yoo KH, Choi KS, Choi J, Choi S-Y, Yang S-E, Yang Y-S, Im HJ, Kim KH, Jung HL, Sung KW, Koo HH (2005) Gene expression profile of cytokine and growth factor during differentiation of bone marrow-derived mesenchymal stem cell. *Cytokine* 31:119–126
- Kline WO, Panaro FJ, Yang H, Bodine SC (2007) Rapamycin inhibits the growth and muscle-sparing effects of clenbuterol. *J Appl Physiol* 102:740–747
- Koopman R, Ryall JG, Church JE, Lynch GS (2009) The role of β -adrenoceptor signaling in skeletal muscle: therapeutic implications for muscle wasting disorders. *Curr Opin Clin Nutr Metab Care* 12:601–606
- Kumar S, Ponnazhagan S (2012) Mobilization of bone marrow mesenchymal stem cells *in vivo* augments bone healing in a mouse model of segmental bone defect. *Bone* 50:1012–1018
- Lai LP, Mitchell J (2008a) Beta2-adrenergic receptors expressed on murine chondrocytes stimulate cellular growth and inhibit the expression of Indian hedgehog and collagen type X. *J Cell Biochem* 104:545–553
- Lai LP, Mitchell J (2008b) β 2-adrenergic receptors expressed on murine chondrocytes stimulate cellular growth and inhibit the expression of Indian hedgehog and collagen type X. *J Cell Biochem* 104:545–553
- Lapid K, Vagima Y, Kollet O, Lapidot T (2008) Egress and mobilization of hematopoietic stem and progenitor cells. *StemBook*. Harvard Stem Cell Institute, Cambridge
- Lecka-Czernik B (2012) Marrow fat metabolism is linked to the systemic energy metabolism. *Bone* 50:534–539
- Lee Y, Moujalled D, Doerflinger M, Gangoda L, Weston R, Rahimi A, de Alboran I, Herold M, Bouillet P, Xu Q (2013) CREB-binding protein (CBP) regulates β -adrenoceptor (β -AR)-mediated apoptosis. *Cell Death Differ* 20:941–952
- Li H, Fong C, Chen Y, Cai G, Yang M (2010a) β 2- and β 3-, but not β 1-adrenergic receptors are involved in osteogenesis of mouse mesenchymal stem cells via cAMP/PKA signaling. *Royaume* 496:77–83
- Li H, Fong C, Chen Y, Cai G, Yang M (2010b) Beta-adrenergic signals regulate adipogenesis of mouse mesenchymal stem cells via cAMP/PKA pathway. *Mol Cell Endocrinol* 323:201–207
- Li H, Fong CC, Chen Y, Cai G, Yang M (2012) Imipramine inhibits adipogenic differentiation in both 3 T3-L1 preadipocytes and mouse marrow stromal cells. *J Genet Genomics* 39:173–180
- Lindroos PM, Zamegar R, Michalopoulos GK (1991) Hepatocyte growth factor (hepatopoietin A) rapidly increases in plasma before DNA

- synthesis and liver regeneration stimulated by partial hepatectomy and carbon tetrachloride administration. *Hepatology* 13:743–750
- Linsley C, Wu B, Tawil B (2013) The effect of fibrinogen, collagen type I, and fibronectin on mesenchymal stem cell growth and differentiation into osteoblasts. *Tissue Eng A* 19:1416–1423
- Liu R, Birke O, Morse A, Peacock L, Mikulec K, Littele DG, Schindeler A (2011) Myogenic progenitors contribute to open but not closed fracture repair. *BMC Musculoskel Disord* 12:288
- Lynch GS, Ryall JG (2008) Role of β -adrenoceptor signaling in skeletal muscle: implications for muscle wasting and disease. *Physiol Rev* 88:729–767
- Mabvuure N, Hindocha S, Jordan D, Khan WS (2012) Chondrogenesis and developments in our understanding. *Curr Stem Cell Res Ther* 7: 243–259
- Maina F, Hilton MC, Andres R, Wyatt S, Klein R, Davies AM (1998) Multiple roles for hepatocyte growth factor in sympathetic neuron development. *Neuron* 20:835–846
- Mano T, Nishimura N, Iwase S (2010) Sympathetic neural influence on bone metabolism in microgravity (review). *Acta Physiol Hung* 97: 354–361
- Markowski DN, Helmke BM, Meyer F, von Ahsen I, Nimzyk R, Nolte I, Bullerdiek J (2011) BMP4 increases expression of HMGA2 in mesenchymal stem cells. *Cytokine* 56:811–816
- Masur K, Niggemann B, Zanker KS, Entschladen F (2001) Norepinephrine-induced migration of SW 480 colon carcinoma cells is inhibited by β -blockers. *Cancer Res* 61:2866–2869
- Mignini F, Streccioni V, Amenta F (2003) Autonomic innervation of immune organs and neuroimmune modulation. *Autonomic Autacoid Pharmacol* 23:1–25
- Minkowitz B, Boskey A, Lane JM, Pearlman HS, Vigorita VJ (1991) Effects of propranolol on bone metabolism in the rat. *J Orthop Res* 9: 869–875
- Morisico C, Zebrowski DC, Vatner DE, Vatner SF, Sadoshima J (2001) β -Adrenergic cardiac hypertrophy is mediated primarily by the β_1 subtype in the rat heart. *J Mol Cell Cardiol* 33:561–573
- Nadri S, Soleimani M, Hosseini RH, Massumi M, Atashi A, Izadpanah R (2007) An efficient method for isolation of murine bone marrow mesenchymal stem cells. *Int J Dev Biol* 51:723–729
- Nadri S, Soleimani M, Mobarrae Z, Aminia S (2008) Expression of dopamine-associated genes on conjunctiva stromal-derived human mesenchymal stem cells. *Biochem Biophys Res Commun* 377:423–428
- Nedergaard J, Herron D, Jacobsson A, Rehnmark S, Cannon B (1995) Norepinephrine as a morphogen?: its unique interaction with brown adipose tissue. *Int J Dev Biol* 39:827–837
- Negishi M, Ito S (1992) Prostaglandin E₂-induced arachidonic acid release and catecholamine secretion from cultured bovine adrenal chromaffin cells. *Biochem Pharmacol* 44:2315–2321
- Ninomiya T, Hosoya A, Hiraga T, Koide M, Yamaguchi K, Oida H, Arai Y, Sahara N, Nakamura H, Ozawa H (2011) Prostaglandin E₂ receptor EP4-selective agonist (ONO-4819) increases bone formation by modulating mesenchymal cell differentiation. *Eur J Pharmacol* 650:396–402
- Nogami M, Romberger DJ, Rennard SI, Toews ML (1994) TGF- β 1 modulates β -adrenergic receptor number and function in cultured human tracheal smooth muscle cells. *Am J Physiol Lung Cell Mol Physiol* 266:L187–L191
- Nurmenniemi S, Kuvaja P, Lehtonen S, Tiuraniemi S, Alahuhta I, Mattila RK, Risteli J, Salo T, Selander KS, Nyberg P, Lehenkari P (2010) Toll-like receptor 9 ligands enhance mesenchymal stem cell invasion and expression of matrix metalloprotease-13. *Exp Cell Res* 316: 2676–2682
- Ostrowski SR, Pedersen SH, Jensen JS, Mogelvang R, Johansson PI (2013) Acute myocardial infarction is associated with endothelial glycocalyx and cell damage and a parallel increase in circulating catecholamines. *Crit Care* 17:R32
- Owen M, Friedenstien AJ (1998) Stromal stem cells:marrow-derived osteogenic precursors. *Ciba Found Symp* 136:42–60
- Path G, Bornstein SR, Gurniak M, Chrousos GP, Scherbaum WA, Hauner H (2001) Human breast adipocytes express interleukin-6 (IL-6) and its receptor system: increased IL-6 production by β -adrenergic activation and effects of IL-6 on adipocyte function. *J Clin Endocrinol Metab* 86:2281–2288
- Peng H, Myers J, Fang X, Stachowiak EK, Maher PA, Martins GG, Popescu G, Berezney R, Stachowiak MK (2002) Integrative nuclear FGFR1 signaling (INFS) pathway mediates activation of the tyrosine hydroxylase gene by angiotensin II, depolarization and protein kinase C. *J Neurochem* 81:506–524
- Petit I, Szyper-Kravitz M, Nagler A, Lahav M, Peled A, Habler L, Ponomaryov T, Taichman RS, Arenzana-Seisdedos F, Fujii N, Sandbank J, Zipori D, Lapidot T (2002) G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. *Nat Immunol* 3:687–694
- Pierroz DD, BP, Boussein ML, Ferrari SL (2006) Low cortical bone mass in mice lacking β_1 and β_2 adrenergic receptors is associated with low bone formation and circulating IGF-1. *J Bone Miner Res* 21(Suppl.1):S277
- Pittenger MF, Mackay A, Beck SC et al (1999) Multilineage potential of adult human mesenchymal stem cells. *Science* 284:143–147
- Porse BT, Pedersen TÅ, Xu X, Lindberg B, Wewer UM, Friis-Hansen L, Nerlov C (2001) E2F repression by C/EBP α is required for adipogenesis and granulopoiesis in vivo. *Cell* 107:247–258
- Pullar CE, Manabat-Hidalgo CG, Bolaji RS, Isseroff RR (2008) β -Adrenergic receptor modulation of wound repair. *Pharmacol Res* 58:158–164
- Qiu W, Chen L, Kassem M (2011) Activation of non-canonical Wnt/JNK pathway by Wnt3a is associated with differentiation fate determination of human bone marrow stromal (mesenchymal) stem cells. *Biochem Biophys Res Commun* 413:98–104
- Ranjit S, Boutet E, Gandhi P, Prot M, Tamori Y, Chawla A, Greenberg AS, Puri V, Czech MP (2011) Regulation of fat specific protein 27 by isoproterenol and TNF- α to control lipolysis in murine adipocytes. *J Lipid Res* 52:221–236
- Rehnmark S, Nechad M, Herron D, Cannon B, Nedergaard J (1990) Alpha- and beta-adrenergic induction of the expression of the uncoupling protein thermogenin in brown adipocytes differentiated in culture. *J Biol Chem* 265:16464–16471
- Rejnmark L, Vestergaard P, Kassem M, Christoffersen BR, Kolthoff N, Brixen K, Mosekilde L (2004) Fracture risk in perimenopausal women treated with beta-blockers. *Calcif Tissue Int* 75:365–372
- Richter S, Qin N, Pacak K, Eisenhofer G (2013) Chapter Fourteen - Role of Hypoxia and HIF2 α in Development of the Sympathoadrenal Cell Lineage and Chromaffin Cell Tumors with Distinct Catecholamine Phenotypic Features. In: Lee EE (ed) *Advances in Pharmacology*, vol 68. Academic, New York, p 285–317
- Robertson D, Krantz SB, Biaggioni I (1994) The anemia of microgravity and recumbency: role of sympathetic neural control of erythropoietin production. *Acta Astronaut* 33:137–141
- Rosenbaum DM, Rasmussen SG, Kobilka BK (2009) The structure and function of G-protein-coupled receptors. *Nature* 459:356–363
- Ryall JG, Lynch GS (2008) The potential and the pitfalls of β -adrenoceptor agonists for the management of skeletal muscle wasting. *Pharmacol Ther* 120:219–232
- Ryall JG, Church JE, Lynch GS (2010) Novel role for β -adrenergic signalling in skeletal muscle growth, development and regeneration. *Clin Exp Pharmacol Physiol* 37:397–401
- Saba F, Soleimani M, Atashi A, Mortaz E, Shahjehani M, Roshandel E, Jaseb K, Saki N (2013) The role of the nervous system in hematopoietic stem cell mobilization. *Lab Hematol* 19:8–16
- Saki N, Abroun S, Farshdousti Hagh M, Asghareh F (2011) Neoplastic bone marrow niche: hematopoietic and mesenchymal stem cells. *Cell J (Yakhteh)* 13:131–136

- Sarkar C, Chakroborty D, Basu S (2013) Neurotransmitters as regulators of tumor angiogenesis and immunity: the role of catecholamines. *J Neuroimmune Pharmacol* 8:7–14
- Sato S, Hanada R, Kimura A, Abe T, Matsumoto T, Iwasaki M, Inose H, Ida T, Mieda M, Takeuchi Y (2007) Central control of bone remodeling by neuromedin U. *Nat Med* 13:1234–1240
- Sauter A, Goldstein M, Engel J, Ueta K (1983) Effect of insulin on central catecholamines. *Brain Res* 260:330–333
- Semerad CL, Christopher MJ, Liu F, Short B, Simmons PJ, Winkler I, Levesque JP, Chappel J, Ross FP, Link DC (2005) G-CSF potently inhibits osteoblast activity and CXCL12 mRNA expression in the bone marrow. *Blood* 106:3020–3027
- Shiota M, Heike T, Haruyama M, Baba S, Tsuchiya A, Fujino H, Kobayashi H, Kato T, Umeda K, Yoshimoto M (2007) Isolation and characterization of bone marrow-derived mesenchymal progenitor cells with myogenic and neuronal properties. *Exp Cell Res* 313:1008–1023
- Shizukuda Y, Buttrick PM (2002) Subtype specific roles of β -adrenergic receptors in apoptosis of adult rat ventricular myocytes. *J Mol Cell Cardiol* 34:823–831
- Shome S, Dasgupta PS, Basu S (2012) Dopamine regulates mobilization of mesenchymal stem cells during wound angiogenesis. *PLoS ONE* 7:e31682
- Silva WA, Covas DT, Panepucci RA, Proto-Siqueira R, Siufi JL, Zanette DL, Santos AR, Zago MA (2003) The profile of gene expression of human marrow mesenchymal stem cells. *Stem Cells* 21:661–669
- Sneddon A, Delday M, Steven J, Maltin C (2001) Elevated IGF-II mRNA and phosphorylation of 4E-BP1 and p70S6k in muscle showing clenbuterol-induced anabolism. *Am J Physiol-Endocrinol Metab* 281:E676–E682
- Soleimani M, Nadri S, Shabani I (2010) Neurogenic differentiation of human conjunctiva mesenchymal stem cells on a nanofibrous scaffold. *Int J Dev Biol* 54:1295–1300
- Soleimani M, Abbasnia E, Fathi M, Sahraei H, Fathi Y, Kaka G (2012) The effects of low-level laser irradiation on differentiation and proliferation of human bone marrow mesenchymal stem cells into neurons and osteoblasts—an in vitro study. *Lasers Med Sci* 27:423–430
- Song C, Li G (2011) CXCR4 and matrix metalloproteinase-2 are involved in mesenchymal stromal cell homing and engraftment to tumors. *Cytotherapy* 13:549–561
- Srivastava S, Bedi U, Roy P (2012) Synergistic actions of insulin-sensitive and Sirt1-mediated pathways in the differentiation of mouse embryonic stem cells to osteoblast. *Mol Cell Endocrinol* 361:153–164
- Stanojević S, Dimitrijević M, Kuštrimović N, Mitić K, Vujić V, Leposavić G (2013) Adrenal hormone deprivation affects macrophage catecholamine metabolism and β 2-adrenoceptor density, but not propranolol stimulation of tumour necrosis factor- α production. *Exp Physiol* 98:665–678
- Sun X, Ng YC (1998) Effects of norepinephrine on expression of IGF-1/IGF-1R and SERCA2 in rat heart. *Cardiovasc Res* 37:202–209
- Sun X, Gao X, Zhou L, Sun L, Lu C (2013) PDGF-BB-induced MT1-MMP expression regulates proliferation and invasion of mesenchymal stem cells in 3-dimensional collagen via MEK/ERK1/2 and PI3K/AKT signaling. *Cell Signal* 25:1279–1287
- Suzuki A, Palmer G, Bonjour J-P, Caverzasio J (1998) Catecholamines stimulate the proliferation and alkaline phosphatase activity of MC3T3-E1 osteoblast-like cells. *Bone* 23:197–203
- Swierczynski J (2006) Leptin and age-related down-regulation of lipogenic enzymes genes expression in rat white adipose tissue. *J Physiol Pharmacol* 57:85
- Takarada T, Hojo H, Iemata M, Sahara K, Kodama A, Nakamura N, Hinoi E, Yoneda Y (2009) Interference by adrenaline with chondrogenic differentiation through suppression of gene transactivation mediated by Sox9 family members. *Bone* 45:568–578
- Takeda S (2005) Central control of bone remodeling. *Biochem Biophys Res Commun* 328:697–699
- Takeda S, Elefteriou F, Levasseur R, Liu X, Zhao L, Parker KL, Armstrong D, Ducy P, Karsenty G (2002) Leptin regulates bone formation via the sympathetic nervous system. *Cell* 111:305–317
- Toma C, Pittenger MF, Cahill KS, Byrne BJ, Kessler PD (2002) Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation* 105:93–98
- Tormos Kathryn V, Anso E, Hamanaka Robert B, Eisenbart J, Joseph J, Kalyanaraman B, Chandel Navdeep S (2011) Mitochondrial complex III ROS regulate adipocyte differentiation. *Cell Metab* 14:537–544
- Tsang DP, Cheng AS (2011) Epigenetic regulation of signaling pathways in cancer: role of the histone methyltransferase EZH2. *J Gastroenterol Hepatol* 26:19–27
- Udelman R, Goldstein DS, Loriaux DL, Chrousos GP (1987) Catecholamine-glucocorticoid interactions during surgical stress. *J Surg Res* 43:539–545
- Uemura T, Ohta Y, Nakao Y, Manaka T, Nakamura H, Takaoka K (2010) Epinephrine accelerates osteoblastic differentiation by enhancing bone morphogenetic protein signaling through a cAMP/protein kinase a signaling pathway. *Bone* 47:756–765
- Vargovic P, Ukropec J, Laukova M (2011) Adipocytes as a new source of catecholamine production. *FEBS Lett* 585:2279–2284
- Varley JE, Maxwell GD (1996) BMP-2 and BMP-4, but Not BMP-6, increase the number of adrenergic cells which develop in quail trunk neural crest cultures. *Exp Neurol* 140:84–94
- Vashisht R, Sian M, Franks PJ, O'Malley MK (1992) Long-term reduction of intimal hyperplasia by the selective α -1 adrenergic antagonist doxazosin. *Br J Surg* 79:1285–1288
- Vogel S, Peters C, Etminan N, Börger V, Schimanski A, Sabel MC, Sorg RV (2013) Migration of mesenchymal stem cells towards glioblastoma cells depends on hepatocyte-growth factor and is enhanced by aminolaevulinic acid-mediated photodynamic treatment. *Biochem Biophys Res Commun* 431:428–432
- Weiss DR, Ahn S, Sassano MF, Kleist A, Zhu X, Strachan R, Roth BL, Lefkowitz RJ, Shoichet BK (2013) Conformation guides molecular efficacy in docking screens of activated β -2 adrenergic G protein coupled receptor. *ACS Chem Biol* 8:1018–1026
- Xiao G, Jiang D, Ge C, Zhao Z, Lai Y, Boules H, Phimpilai M, Yang X, Karsenty G, Franceschi RT (2005) Cooperative interactions between activating transcription factor 4 and Runx2/Cbfa1 stimulate osteoblast-specific osteocalcin gene expression. *J Biol Chem* 280:30689–30696
- Xiao R-P, Zhu W, Zheng M, Cao C, Zhang Y, Lakatta EG, Han Q (2006) Subtype-specific α 1 and β -adrenoceptor signaling in the heart. *Trends Pharmacol Sci* 27:330–337
- Xinaris C, Morigi M, Benedetti V, Imberti B, Fabricio A, Squarcina E, Benigni A, Gagliardini E, Remuzzi G (2013) A novel strategy to enhance mesenchymal stem cell migration capacity and promote tissue repair in an injury specific fashion. *Cell Transplant* 22:423–436
- Xue P, Wu X, Zhou L, Ma H, Wang Y, Liu Y, Ma J, Li Y (2013) IGF1 promotes osteogenic differentiation of mesenchymal stem cells derived from rat bone marrow by increasing TAZ expression. *Biochem Biophys Res Commun* 433:226–231
- Yang EV, Sood AK, Chen M, Li Y, Eubank TD, Marsh CB, Jewell S, Flavahan NA, Morrison C, Yeh PE, Lemeshow S, Glaser R (2006) Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. *Cancer Res* 66:10357–10364
- Yazdani SO, Hafizi M, Zali AR, Atashi A, Ashrafi F, Seddighi AS, Soleimani M (2013) Safety and possible outcome assessment of autologous Schwann cell and bone marrow mesenchymal stromal cell co-transplantation for treatment of patients with chronic spinal cord injury. *Cytotherapy* 15:782–791
- Yousefi F, Ebtekar M, Soleimani M, Soudi S, Hashemi SM (2013) Comparison of in vivo immunomodulatory effects of intravenous

- and intraperitoneal administration of adipose-tissue mesenchymal stem cells in experimental autoimmune encephalomyelitis (EAE). *Int Immunopharmacol* 17:608–616
- Yu K, Xu J, Liu Z, Sosic D, Shao J, Olson EN, Towler DA, Ornitz DM (2003) Conditional inactivation of FGF receptor 2 reveals an essential role for FGF signaling in the regulation of osteoblast function and bone growth. *Development* 130:3063–3074
- Yu X, Chen D, Zhang Y, Wu X, Huang Z, Zhou H, Zhang Y, Zhang Z (2012) Overexpression of CXCR4 in mesenchymal stem cells promotes migration, neuroprotection and angiogenesis in a rat model of stroke. *J Neurol Sci* 316:141–149
- Zaugg M, Xu W, Lucchinetti E, Shafiq SA, Jamali NZ, Siddiqui M (2000) β -Adrenergic receptor subtypes differentially affect apoptosis in adult rat ventricular myocytes. *Circulation* 102:344–350
- Zhao L, Hantash BM (2011) TGF- β 1 regulates differentiation of bone marrow mesenchymal stem cells. In: Gerald L (ed) *Vitamins and Hormones*, vol 87. Academic, New York, p 127–141
- Zhu XH, He QL, Lin ZH (2003) Effect of catecholamines on human preadipocyte proliferation and differentiation. *Zhonghua Xing Wai Ke Za Zhi* 19:282–284
- Zisa D, Shabbir A, Suzuki G, Lee T (2009) Vascular endothelial growth factor (VEGF) as a key therapeutic trophic factor in bone marrow mesenchymal stem cell-mediated cardiac repair. *Biochem Biophys Res Commun* 390:834–838
- Zuk PA, Zhu M, Ashjian P et al (2002) Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell* 13:4279–4295
- Zweig M, Axelrod J (1969) Relationship between catecholamines and serotonin in sympathetic nerves of the rat pineal gland. *J Neurobiol* 1:87–97