

# Hedgehog Signaling Pathway is Linked with Age-Related Diseases

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**Abstract**

Disorders related to chronic inflammation and ageing such as metabolic syndrome, atherosclerosis, osteoporosis and cancers appear to have different pathogenesis. However, by studying the pathways related to the stem cell (SC) signaling network, like Hedgehog signaling and in particular its influence on the adipogenesis - osteogenesis interaction, we could find a close link between the pathogenesis of these disorders. Hedgehog signaling is an active pathway during embryogenesis that seems to be silent in adults. However, it strongly affects the maintenance of adult tissue homeostasis and the highly proliferative and differentiated cells (e.g., SCs, adipocytes and osteocytes). Malfunction of these cells is considered as the basic etiology of a group of age-related diseases such as atherosclerosis, osteoporosis and cancer.

**Keywords:** Hedgehog signaling pathway; Age-related diseases; Stem cell signaling network; Adipogenesis-osteogenesis interaction

**Introduction**

Proliferation, differentiation and development of zygote cell for creation of a living entity are one of the astonishing events in medical science, which still remain to be uncovered. From the early stages of development, each cell of embryo mass gains specific characteristics and gene expression properties that are different from others [1,2]. This diversity in the property of cells leads to compartmentation of a group of cells with similar properties in different segments known as organs till the end of development [3]. Hedgehog signaling is one of the highly conserved and key pathways in modulation of differentiation and determination of cell fate. Therefore, it is the regulator of developmental cell fate [4] and it remains to be active till the late stages of embryogenesis (morphogenesis) [5]. Concentration of Hedgehog proteins among embryo segments are different [6]. Hedgehog protein functions together with other oncogenic and embryogenesis pathways such as transforming growth factor beta (TGF- $\beta$ ), Wnt/Wingless, Notch and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways and receptor tyrosine kinases such as epidermal growth factor (EGF) and fibroblast growth factor (FGF) for modulation of embryonic development [3,7]. After birth, the highly proliferative, differentiative and plasticity capacities of embryonic cells remain and are represented in multipotent cells such as mesenchymal SCs (MSCs) and preadipocytes [8,9]. These cells are able to differentiate into a variety of different cells including adipocyte and osteoblast lineages [10]. The possibility for SCs to follow either the adipogenesis or osteogenesis processes [8] might be the main etiology in the pathogenesis of age-related disorders such as atherosclerosis and osteoporosis. Hedgehog signaling regulates maintenance of integrity and function of tissues/organs and proper regeneration of SCs [11,12] for proper proliferation and differentiation of tissue cells and tissue repair. Therefore, it can be considered as an anti-geriatric factor [13]. Malfunction of SC signaling networks [14] increase susceptibility of the body to cancers [7,15]. Moreover, Hedgehog signaling pathway regulates the immune system. Hyperactivity of Hedgehog signaling during embryonic development and immune impairment states such as cancer shows an intense correlation between immune system activity and Hedgehog signaling activity [7,11,15].

**Antithetical Effect of Ageing and Diabetes on Hedgehog Signaling**

There are different conditions, which function as a bilateral switching of the multipotent cells, like MSCs, to either the adipocyte or osteocyte lineages. Sonic Hedgehog (Shh) has an anti-adipogenic-osteoblastic effect on MSCs. Osteogenesis capacity of Shh is accelerated due to upregulation of osteogenic transcription factors [16]. In diabetic patients, hyperglycemia interferes with Shh signaling and Shh-induced bone regeneration; therefore, it stimulates osteoporosis. Hyperglycemia also inhibits osteogenesis through osteogenesis-related genes such as BMP4, Runx2 and osteopontin (OPN), which results in increase in the activity of alkaline phosphatase (ALP) and matrix mineralization in BMSCs [17].

Hedgehog signaling also regulates  $\beta$ -cells-insulin production [18]. During ageing, impairment of Hedgehog signaling function could be the etiology of atrophy, fatty infiltration and fibrosis in pancreas [19] and insulin production. Furthermore, in muscle satellite cells and bone marrow (BM) [20] there is an increased tendency toward adipogenesis at the cost of osteogenesis [21], which leads to unresponsiveness in peripheral tissues and hyperglycemia. In this regulation, the fate of adipocytes depends on PPAR $\gamma$  activation, which has an adipogenic and anti-osteoblastic capacity [22]. Moreover, low level of Shh also correlates to impaired osteogenesis and consequently osteoporosis during ageing [23]. In ageing and diabetic conditions the adipogenesis property of the bone marrow is increased, however the brown adipose tissue (BAT) characteristic of bone marrow is attenuated [24].

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## Morphogens, Regulatory Proteins of Embryonic Development, Osteogenesis and Adipogenesis

In addition to Hedgehog signaling pathway other morphogens also function in the differentiation of osteoblasts and adipocytes [25]. Morphogens are regulatory proteins like Hedgehog molecules, Wnts [26], fibroblast growth factors (FGF) [27] and bone morphogenetic proteins (BMPs) that integrate together to regulate embryonic development. Morphogens are morphogen proteins that initiate, promote and maintain metabolism and homeostasis [28] and function in the development of brown adipose tissue (BAT adipogenesis), energy metabolism and iron metabolism [29] and regulate embryonic patterning [30].

BMPs morphogens belong to the TGF superfamily members [31]. TGF regulatory ligands, which operate via SMADs, mainly regulate proliferation, differentiation, development, tissue homeostasis and immune system. They inhibit adipogenesis [32] and osteoblast differentiation via inhibition of Core-binding factor alpha-1 (Cbfa1)/Runx2 [33] and stimulate chondrogenesis [34]. FGF and Wnt signaling also influences osteogenesis, chondrogenesis and adipogenesis [1,35]. Wnt proteins, as in Hedgehog signaling, have anti-adipogenesis and osteoblast differentiation properties [36]. FGF functions directly or via regulation of BMP and Wnt [37]. Activation of Wnt and BMP pathways are involved in tissue repair and triggered by skeletal injury [20]. Dysfunction of these morphogenetic pathways accounts for the susceptibility to a group of cancers [7,35].

## Role of Hedgehog Signaling in Maintenance of Cell Functions and Tissue Repair

Hedgehog signaling seems to be a silent pathway during adult life; however, during ischemia and tissue repair, it (particularly Shh) becomes re-activated. Shh regulates maintenance of vasculature and stimulates angiogenesis including vascular development and capillary morphogenesis through phosphoinositide 3-kinase (PI3K) [38]. Impairment of Shh signaling by PI3-K inhibitor (e.g. LY294002), cyclophosphamide (Shh receptor inhibitor) and diabetic hyperglycemia delays wound healing through suppression of cutaneous constitutive nitric oxide synthase (NOS) function [39] and explains the etiology of diabetic foot syndrome.

In diabetic state, via activation of Shh and consequently induction of NO release, endothelial cells are protected against injury and it improves delayed wound healing. Shh-induced neovascularization occurs via controlling of anti-apoptotic cytokines, production of proangiogenic agents and recruitment of BM-derived SCs. Control of endothelium-bone interaction by Hedgehog signaling plays a crucial role in this repair [40,41]. This interaction has a significant role in the pathogenesis of hypertension and atherosclerosis [42]. Furthermore, Shh proteins have a protective effect on cardiac injuries [43] via recruitment of endothelial progenitor cells and fibroblast proliferation. Intramyocardial gene therapy with Shh is used for treatment of myocardial infarction, which carried out through different ways including (i) expression of Shh on fibroblasts and cardiomyocytes (ii) direct activation of myocardial neovascularization (iii) stimulation of endothelial progenitor cells of BM in neovascularization and (iv) morphogenic role of Shh in embryogenesis and tissue repair [44]. However, using Hedgehog signaling as one of the therapeutic ways for treatment of myocardial infarctions or ischemia induced-cerebral

injuries is controversial because abnormal Hedgehog signaling activity and its angiogenesis induction could account for the development of cancers [7,43].

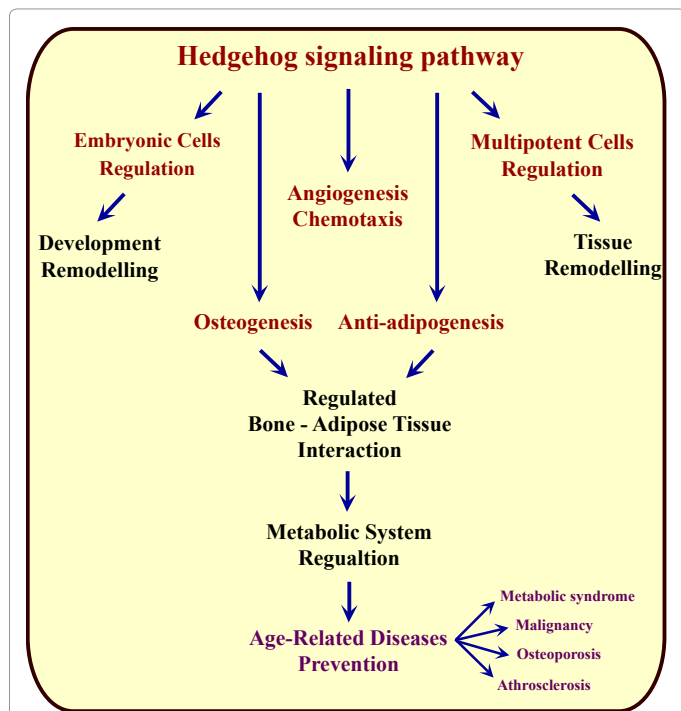
## Role of Hedgehog Signaling in Energy Metabolism

Energy metabolism is a chemical process for the regulation of energy return in the body via its components; lipoproteins and metabolic tissues mainly adipose tissue. Hedgehog signaling affects all components of lipid return including carriers and adipose tissue cells. In humans, Indian Hedgehog (Ihh) is presented on VLDL particle. Transport of VLDL-Ihh to endothelium is essential for maintaining of primary endothelial cells (ECs). The similarity between lipid compositions of insect lipoproteins and LDL [4] and existence of Indian Hedgehog on VLDL [45] represents the conserved property of carrying Hedgehog proteins by lipoproteins. Furthermore, adipose tissue consists of macrophages, ECs, fibroblasts, SCs and adipocytes that have metabolic and immunological roles [46]. Adipocytes are one of the sites of Ihh synthesis [8,45]. In rodent adipocytes, Hedgehog signaling (mainly Shh) interferes with adipocytes differentiation. One speculation in this regard is that in adipogenic conditions, Shh functions upstream of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ); induce GATA2 and 3 anti-adipogenic transcription factors. Another argument would be due to the inhibitory effect of Hedgehog signaling on pro-adipogenic genes via influence on transcription and/or activity of key adipogenic factors like CCAAT/enhancer binding protein alpha (CEBPA), Sterol Regulatory Element Binding Protein (SREBP)-1c and PPAR $\gamma$ . The third possibility could be through its influence on TAZ (transcriptional cofactors with PDZ-binding motif) or retinoblastoma protein because these cofactors activate osteogenic genes and inhibit adipogenic genes. Hedgehog signaling also plays a role downstream of the anti-adipogenic proteins like Wnt proteins, preadipocyte factor (pref)-1 and plasminogen activator inhibitor 1 (PAI-1). Therefore, reduction in the function of Hedgehog signaling is essential for induction of adipocyte differentiation [8]. It is shown that there is a crosstalk between Hedgehog and Wnt pathways, whereby inhibition of  $\beta$ -catenin occurs by direct interaction with Gli3 repressor. Therefore, Hedgehog signaling activation via prevention of Gli3R protein and Wnt signaling activation, inhibits adipocyte differentiation [47].

During adipocyte differentiation, activity of Hedgehog signaling is decreased. However, inhibition of Hedgehog signaling alone does not stimulate adipocyte differentiation and it merely alters adipocyte morphology and insulin sensitivity [10]. Wnt signaling has an important influence on muscle insulin sensitivity, and this is mediated by effect on myogenic and adipogenic systems [21]. Hedgehog signaling controls fat storage via blocking the level of white adipose tissue (WAT), but has no effect on BAT. Cyclic adenosine monophosphate (cAMP) and glucocorticoid induce obesity through blocking of Hedgehog signaling [48]. In metabolism, there is a close interaction between the bone and adipose tissue [49,50] (Figure 1).

## Hedgehog Signaling Pathway and Cancer

Fibroblasts are the main cells of the connective tissue that are involved in the synthesis of the extracellular matrix and collagen in the wound healing process. They also have a close similarity with SCs [51]. These two properties influence the function of the fibroblasts on cancer induction. Fibroblasts are produced by epithelial-to-mesenchymal transition (EMT) mechanism, which has a role in many developmental processes [52]. Tissue damage enhances fibroblast proliferation. Hedgehog signaling has an anti-adipogenic, pro-EMT capacity. In liver fibrosis, stellate cells, which have epithelial



**Figure 1:** Hedgehog signaling pathway and age-related diseases. Hedgehog signaling pathway is a morphogen, which regulates the embryonic cells during development and the multipotent cells in adults for tissue remodelling and maintenance of the function of tissues. The anti-adipogenesis and osteogenesis properties of Hedgehog signaling pathway regulate bone – adipose tissue interaction and consequently metabolic system function. Therefore, it has a direct effect in prevention of the age-related diseases.

and adipocyte phenotypes, differentiate to myofibroblastic-hepatic stellate cells (MF-HSC) through activation of Hedgehog signaling. Leptin, through activation of Hedgehog signaling and inhibition of adiposity, stimulates differentiation toward EMT; therefore, leptin is modulator of fibrogenesis. Leptin also induces JAK/STAT pathway for gene expression of MSCs. Thus, leptin-related Hedgehog signaling activation is important for expression of genes that mediate cells fate and have an influence on different EMT-related processes including liver fibrosis and cancer metastasis during obesity [53].

This epithelial stromal reaction also has a crucial role in pathogenesis of a group of diseases including breast cancer. Normal breast tissue is composed of stromal and epithelial cells that communicate with each other through extracellular matrix (ECM). Normal crosstalk between these two parts is important for prevention of breast cancer. Epithelial cells also react with human adipose fibroblasts (HAFs) [54]. In carcinomatous breast cancer, a layer of these undifferentiated fibroblasts (HAFs) surround malignant epithelial cells. Epithelial cells secrete tumor necrosis factor (TNF), which via binding to its receptor, TNF receptor (TNFR)-1, inhibits adipogenesis. Fibroblasts, via over-expression of aromatase, which produce estrogen, influence the growth and progression of malignant epithelial cells. Estrogen selectively modulates TNFRs synthesis in HAF, whereby it stimulates TNFR1 expression and inhibits TNFR2 expression. TNFR1 inhibits adipogenesis and TNFR2 stimulates adipogenesis. Therefore, estrogen enhances anti-adipogenic property of TNF through TNFR1 stimulation. In breast cancer, cholesterol derivatives such as specific oxysterol (LXR-independently) and estrogen [55] have anti-

adipogenic-osteoblastic effect via influence on Hedgehog signaling. Estrogen, via stimulation of estrogen receptor alpha (ERα), can induce Shh expression [56,57] and promote motility and invasion of breast cancer cells. This characteristic of estrogen is applied through upregulation of Shh signaling in ERα cells. Reduction of estrogen leads to down-regulation of Shh gene expression [57]. Treatment of cells with estradiol (E2) enhances osteogenesis and inhibits adipogenesis via ER. Another factor that enhances the invasive properties of breast cancer is EGF receptor (EGFR), which enhances tissue factor (TF) expression. TF is a coagulation factor which is secreted by cancer cells and ECs after injury. Alteration of EMT-like features (controlled by Hedgehog signaling) in breast cancer cells modulate EGFR-mediated expression of TF-FVIIa, which consequently stimulate coagulopathy, angiogenesis and metastasis properties of cancer cells [58].

The influence of Hedgehog signaling on fibroblasts and cancer progression is also proved on pancreatic cancer [59,60], ovarian cancer [61], basal cell carcinoma [62], lung malignancy [63] and hepatocarcinogenesis [64]. Hence, Hedgehog pathway blockers [62], together with tyrosine kinase inhibitors [65], proteasome inhibitors, mTOR inhibitors, PI3K inhibitors [66], histone deacetylase inhibitors [67], growth factor inhibitors [68], 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMG-CoAR) inhibitors [69], angiogenesis inhibitors and agents targeting matrix metalloproteinases, cyclooxygenase-2 (COX-2) [70] are considered as the cancer growth blockers.

### Hedgehog Signaling Pathway and Atherosclerosis

Atherosclerosis is a complex process, which is caused through disturbance of SMC proliferation, EC dysfunction, coagulation and immune system [71]. In the process of atherosclerosis, plaque calcification has a close relation to the anti-adipogenesis osteogenesis properties of Hedgehog signaling pathway. Calcification of plaque is an active process and is composed of hydroxyapatite and regulatory proteins including osteopontin, TGFβ, BMPs and RANKL. These proteins, together with oxidized cholesterol, stimulate muscle segment homeobox 2 (Msx2) transcription factor (activator of Wnt signaling) and osteogenic pathway. They also stimulate vascular smooth muscle cells (vSMCs) for OPN expression and upregulation of chondro-osteogenic pathway in fibroblasts. Hyperphosphatemia of end-stage renal diseases, via stimulation of Cbfa1/Runx2 transcription factor, can stimulate vascular calcification. Other stimulators of vascular calcification are hyperglycemia, estrogen, Vitamin D toxicity, PTH/PTHrP receptors [72] and Wnt/LDL receptor-related protein 5 (Lrp5)/β-catenin pathway [73].

A group of conditions such as T2D, ageing, abnormal valve functions, hypercholesterolemia and chronic renal failure [72] are involved in pathogenesis of atherosclerosis. The pathogenesis related to these metabolic disorders including chronic inflammation induction via recruitment of immune cells (macrophages, lymphocytes) and their cytokines (TNFα, IL-6, IL-1β), retention of lipoproteins, oxidative modifications and renin-angiotensin system (RAS) activation in particular angiotensin converting enzyme (ACE), AngII and Angiotensin II type-1 receptor (AT1-R). Accumulation of extracellular matrix proteoglycans and its interaction with apolipoprotein B (ApoB) of LDL mediates deposition of atherogenic lipoproteins such as LDL, which contains ACE and Hedgehog molecules [13,73] (Figure 2). LDL-ACE, together with chymase of mast cells, converts Ang I to Ang II, which via activation of AT1-R, promotes fibrosis [74], proteoglycans synthesis and expression of enzyme generating oxidants (e.g., reactive

oxygen species (ROS)), which further oxidizes lipoproteins. AT1-R is expressed pathologically in fibroblasts. Oxidation of LDL-cholesterol stimulates fibroblasts toward osteoprogenitor activity and calcification. Oxidized LDL (ox-LDL) recruits monocytes from circulation to initiate inflammation via induction of adhesion and chemotactic molecules on ECs. Monocytes are converted to macrophages to infiltrate toward and phagocytize ox-LDLs to form foam cells [75]. Activated macrophages secrete RANKLs, IL-1 $\beta$  and TNFs and express ROS. Foam cells increase oxidant stress in cells, resulting in impairment of fibrinolysis and increased expression of proteoglycan in myofibroblast and lipoprotein retention. In summary, atherosclerotic calcification appear to be induced via Ang II and lipids oxidation by foam cells cytokines through influence on nuclear factor-kappa B (NF $\kappa$ B) and mitogen-activated protein kinase (MAPK) pathways. In addition, expression of matrix metalloproteinases (MMPs) is increased with a role in regulation of vascular calcification, degradation of extracellular matrix and plaque instability.

Besides, Hedgehog signaling, together with FGF, plays an important role in vascular remodeling. This property is also important in tissue engineering for bone regeneration and plaque calcification. During wound healing, Shh signaling stimulates angiogenesis using FGF. Among cells of blood vessels, fibroblasts, periosteal cells and SCs derived from perivascular adipose tissue express Shh gene. During atherosclerosis, Shh and FGF enhance induction of angiopoietins (Ang I or Ang II) and probably vascular endothelial growth factor (VEGF) in fibroblasts [40,76]. In vascular calcification state, pericyte-myofibroblasts are differentiated to osteogenic lineage [77]. Pericytes also regulate angiogenesis and thereby link neovascularization with calcification. One assumption in this regard is that EC cytokines induce differentiation and calcification of osteoprogenitor cells. Moreover, some angiogenic factors such as FGF-2 and VEGF-C have also osteogenic and chondrogenic effects. Progenitor cells of both ECs and perivascular cells including pericytes or SMCs are similar. Pericytes are derived from different origins e.g., SMCs, fibroblasts, ECs, BM cells and can differentiate into many different cell types including osteoblasts, chondrocytes, SMCs, adipocytes, fibroblasts and Leydig cells. Therefore, they act as sources of progenitor cells in inflammatory states to repair the disease state [78] (Figure 3).

Fibroblasts can also modulate atherosclerosis progression [79] via regulation of EMT, stimulation of fibrosis and synthesis of proteoglycan (regulated by coagulation factors) [80]. Coagulation system in close association with inflammation is also important in atherothrombosis. Rupture of endothelium releases coagulation factors and exposes the subendothelial layer to circulation to attract circulatory platelets and monocytes to the place of injury. Shh is one of these chemoattractants [2], which is expressed on monocytes and plaque cells including fibroblasts and SMCs [81]. Release of TF from ECs [82] enhances angiogenesis, which has a negative effect on plaques [58]. Another coagulation factor which could have an interaction with Hedgehog signaling and have a role in atherosclerosis is factor V (FV), as it may be involved in early mammalian development [83].

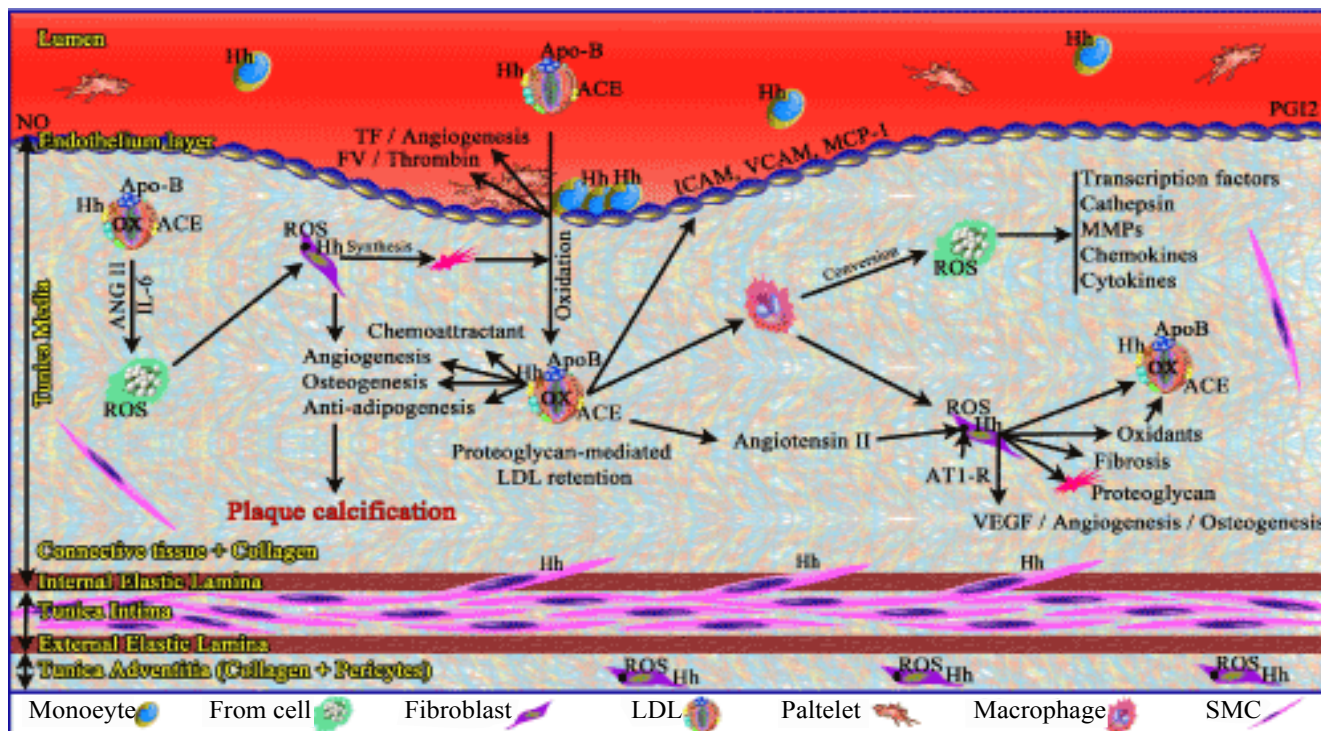
## Role of Cholesterol in Hedgehog Signaling and Atherosclerosis

There is a direct association between hypercholesterolemia with initiation and exacerbation of atherosclerotic plaque formation. Sterol metabolites are one of the mediators of Hedgehog signaling pathway. In Hedgehog producing cells, cholesterol joins to the produced Hedgehog molecules and functions for destination of Hedgehog molecules to

target cells. In Hedgehog receiving cells, sterol secretion induces the inhibitory function of Ptch receptor on Smo receptor in the absence of Hedgehog molecules [84]. Thus, sterol disorders affect Hedgehog pathway and development either by improper sterolation of Hedgehog protein or by a reduced responsiveness of cells to Hedgehog proteins. Transport of Hedgehog molecules occurs via lipophorin in *Drosophila* and via VLDL in mammals, which is loaded by Hedgehog molecules in adipocytes. VLDL has a crucial role in atherosclerosis pathogenesis; which would be due to the effect of Hedgehog signaling. Existence of Hedgehog molecules on LDL is also speculated [4,85,86]. After trapping of lipoproteins in plaques, Hedgehog molecules stimulate different events in plaques including the regenerative processes (e.g., chemotaxis, revascularization of surrounding tissue, anti-adipogenesis and osteogenesis), proliferation and migration of SMCs [87,88] and T cell activation. T cell activation secretes receptor activator of nuclear factor kappa-B ligand (RANKLs) that in addition to its role in the immune system, plays a role in bone formation and calcification within atherosclerotic plaques and breast cancer [89]. This represents the existence of a close cross-talk between bone metabolism and the immune system [90,91]. RANKLs via TRAF6 adaptor protein stimulate different inflammatory pathways [92]. Therefore, Hedgehog signaling affects bone formation via RANKL (and PTHrP) expression [93,94]. Moreover, Ihh and Shh signaling play an important role in vascular remodeling through induction of VEGF and angiopoietin in fibroblasts [76]. In atherosclerosis, this property may enhance the calcification process [95] in plaques because stimulation of angiogenesis is one of the requirements of the ectopic calcification [78]. Another parameter that affects osteogenesis during atherosclerosis is cathepsin K enzyme that is produced by BM-derived macrophages and stimulates fragmentation of the elastin layer and SMC migration to plaques (Figure 2) [13,96]. Hedgehog signaling stimulates osteoclastic activity via upregulation of Cathepsin K [56].

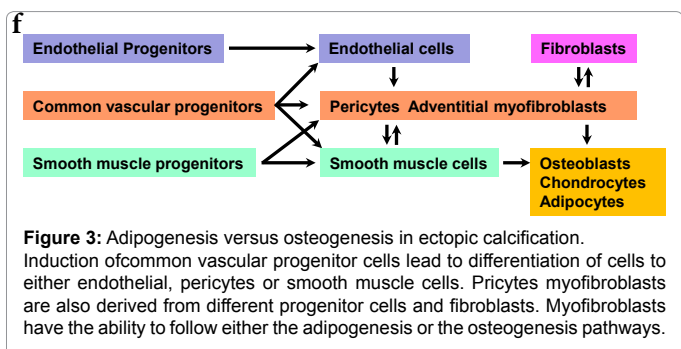
Other derivatives of cholesterol oxide in the circulation are oxysterols [23]. The levels of these molecules are modified during diseases, ageing and drug intervention states. Oxysterols have diverse roles in inflammation, differentiation, steroid production, cholesterol metabolism, lipoprotein metabolism, calcium uptake, atherosclerosis and apoptosis [97]. The natural form of oxysterols is 20s, which has both the anti-adipogenesis and pro-adipogenesis activity that is mediated by PPAR $\gamma$ . PPAR $\gamma$  is the early stage adipogenic transcription factor that stimulates adipogenesis in adipocytes together with CEBP $\alpha$ . 20s is also one of the regulators of bone metabolism, linking adipogenic to osteogenic pathways. 20s oxysterol has the ability to inhibit PPAR $\gamma$  via stimulation of Hedgehog signaling. It also stimulates both SREBP-1c/ adipogenic differentiation of factor 1 (ADD1) and PPAR $\gamma$  via enhancement of liver X receptor (LXR). The inhibitory role of 20s in adipogenesis in vascular cells induces the osteoblastic activity of oxysterols and triggers calcification within atherosclerotic plaques (Figure 4) [22].

Stressor hormones like cortisol, growth hormone and norepinephrine also regulate bone remodeling. Stress hormones simulate interleukin (IL)-6 secretions that, together with other proinflammatory cytokines such as IL-1 $\beta$  and TNF alpha, are involved in age-related diseases such as T2D, cancer, osteoporosis and atherosclerosis. Steroidal hormones regulate expression of IL-6, which together with Ang II stimulates lipid absorption by macrophages in atherosclerotic plaques. Among these hormones, estrogen has the same properties as Hedgehog signaling in anti-adipogenic and osteogenic pathways [98]. During ageing, IL-6 mediated inflammation also plays a role in osteoporosis. Indirect inhibition of IL-6-induced inflammation by endogenous cholesterol

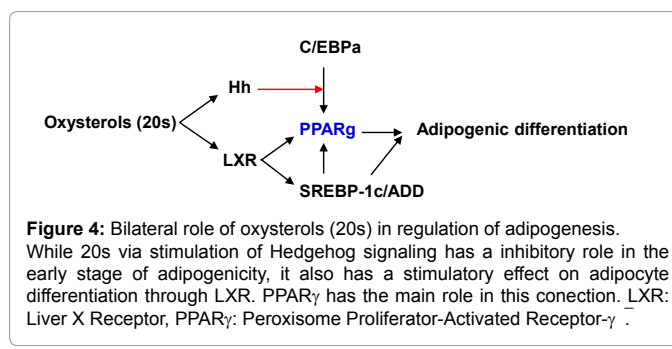


**Figure 2:** Pathogenesis of atherosclerotic plaque. Normal arteriole is composed of endothelium and the subendothelium or BM. An intact endothelium produces PGI2 and NO, which retain hemostatic components in an inactive form and inhibits monocyte and platelet aggregation. An injured endothelium releases Vwf and TF to start coagulation and exposes BM to the circulation to stimulate circulatory platelets and monocytes to the place of injury. This forms a plaque for repairing the injury and prevention of blood loss. BM composed of a collagen and elastic fibers as well as SMCs that provide support around vessels. IEL and EEL line two sides of tunica intima and separate SMCs from the media and adventitial layers. In normal state, intact IEL prevents migration of SMCs into media space, however in atherosclerotic state, the intima layer growth and macrophage-cathepsin K degrades IEL. This leads to migration of SMCs from intima to media for release of collagen and plaque stabilization. Moreover, pericyte myofibroblasts in atherosclerotic plaque is able to differentiate into osteoblasts and chondrocytes, adventitial myofibroblasts, calcifying vascular cells, valvular interstitial cells and foam cell macrophages, which release cytokines, chemokines and transcription factors. They, as well as fibroblasts, express enzymes generating oxidants (ROS). The process of plaque formation and inflammation starts by trapping of LDL containing ACE and Hedgehog (Hh) molecules and binding of them to the proteoglycan (lipid core). Hedgehog molecules function for T cell activation and cytokine production and SMC proliferation and migration into plaque. It functions in regenerative processes including chemotaxis, revascularization, anti-adipogenesis and osteogenesis that are crucial in plaque calcification. Thereafter, LDL follows the oxidative modification processes and forms ox-LDL, which is taken up by macrophages and form foam cells. IL-6 and Ang2 produced by ox-LDL activate foam cell. Ox-LDL also enhances expression of the adhesion and chemoattractant molecules (VCAM-1, ICAM-1, MCP-1) by endothelial cells, which lead to leukocyte recruitment to the plaque. ACE of LDL converts Ang I to Ang II, which activates (AT1-R) on fibroblasts and produce both proteoglycans and oxidants by fibroblast/myofibroblasts. Hh particle is assumed to be present on the monocytes, LDL, fibroblasts and SMCs. TF and factor V are assumed to have a role in plaque calcification (Dashty, et al, BioEssays, 2012).

BM: Basement Membrane; PGI2: Prostacyclin; NO: Nitric Oxide; vWF: vonwillebrand Factor; TF: Tissue Factor; SMC: Smooth Muscle Cells; IEL: Internal Elastic Lamina; EEL: External Elastic Lamina; ROS: Reactive Oxygen Species; Ox-LDL: Oxidized-Low Density Lipoprotein; IL: Interleukin; Ang: Angiotensin; VCAM: Vascular Cell Adhesion Protein; ICAM: Intercellular Adhesion Molecule; MCP: Monocyte Chemoattractant Protein; ECs: Endothelial Cells. ACE: Angiotensin-Converting Enzyme; AT1-R: Angiotensin II Type I Receptors.



**Figure 3:** Adipogenesis versus osteogenesis in ectopic calcification. Induction of common vascular progenitor cells lead to differentiation of cells to either endothelial, pericytes or smooth muscle cells. Pericytes myofibroblasts are also derived from different progenitor cells and fibroblasts. Myofibroblasts have the ability to follow either the adipogenesis or the osteogenesis pathways.



**Figure 4:** Bilateral role of oxysterols (20s) in regulation of adipogenesis. While 20s via stimulation of Hedgehog signaling has an inhibitory role in the early stage of adipogenicity, it also has a stimulatory effect on adipocyte differentiation through LXR. PPAR $\gamma$  has the main role in this connection. LXR: Liver X Receptor, PPAR $\gamma$ : Peroxisome Proliferator-Activated Receptor- $\gamma$ .

synthesis is one of the therapeutic ways for treatment of atherosclerosis [99]. Schieffer et al. show that a balance between IL-6 and IL-10 is required in protection against atherosclerosis [100].

### Conclusion

Regulation of energy metabolism is one of the most complicated events in the body and is fundamental for a healthy life. Dysregulation

of the metabolic system is considered as one of the main etiology of ageing. There is a vast interaction between the energy metabolic system of the body and other systems in order to regulate its function. Bone-adipose tissue interaction is considered as one of these fundamental events in regulation of metabolism. Dysregulation of this interaction is represented in the pathophysiology of age-related diseases. Hedgehog signaling pathway is the linker between the energy metabolism and bone metabolism. It is active in all cells of adipose tissue including fibroblasts, ECs, SCs and adipocytes and its anti-adipogenesis and osteogenesis property has a significant role in regulation of the energy metabolism” prevention of age-related diseases. Hedgehog signaling is considered as one of the regulators of multipotent cells. multipotent cells like SCs, fibroblasts, osteocytes and adipocytes are cells with the high capacity of proliferation, differentiation and plasticity as it is in embryonic cells. Hedgehog signaling is active during embryogenesis and after birth it has a strong role in the maintenance of tissues. It is activated during tissue repair; therefore, it has an anti-geriatric effect. A close association between chronic inflammation as one of the main triggers of age-related diseases with an important role of Hedgehog signaling in the pathogenesis of these diseases, would be a proof of a close correlation between an active Hedgehog signaling and tolerogenic states of the immune system.

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