The less-often-traveled surface of stem cells: caveolin-1 and caveolae in stem cells, tissue repair and regeneration

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Abstract

Stem cells are an important resource for tissue repair and regeneration. While a great deal of attention has focused on derivation and molecular regulation of stem cells, relatively little research has focused on how the subcellular structure and composition of the cell membrane influences stem cell activities such as proliferation, differentiation and homing. Caveolae are specialized membrane lipid rafts coated with caveolin scaffolding proteins, which can regulate cholesterol transport and the activity of cell signaling receptors and their downstream effectors. Caveolin-1 is involved in the regulation of many cellular processes, including growth, control of mitochondrial antioxidant levels, migration and senescence. These activities are of relevance to stem cell biology, and in this review evidence for caveolin-1 involvement in stem cell biology is summarized. Altered stem and progenitor cell populations in caveolin-1 null mice suggest that caveolin-1 can regulate stem cell proliferation, and in vitro studies with isolated stem cells suggest that caveolin-1 regulates stem cell differentiation. The available evidence leads us to hypothesize that caveolin-1 expression may stabilize the differentiated and undifferentiated stem cell phenotype, and transient downregulation of caveolin-1 expression may be required for transition between the two. Such regulation would probably be critical in regenerative applications of adult stem cells and during tissue regeneration. We also review here the temporal changes in caveolin-1 expression reported during tissue repair. Delayed muscle regeneration in transgenic mice overexpressing caveolin-1 as well as compromised cardiac, brain and liver tissue repair and delayed wound healing in caveolin-1 null mice suggest that caveolin-1 plays an important role in tissue repair, but that this role may be negative or positive depending on the tissue type and the nature of the repair process. Finally, we also discuss how caveolin-1 quiescence-inducing activities and effects on mitochondrial antioxidant levels may influence stem cell aging.

Keywords: Caveolae, Caveolin-1, Stem cells, Signal transduction, Cholesterol, Tissue repair, Regenerative medicine

Introduction

Stem cells are an important resource for tissue regeneration. Much stem cell research has focused on stem cell sourcing and stem cell regulation by external stimuli (reviewed in [1]). However, relatively little is known about the composition of the stem cell membrane, the organization of which can affect cell responses to external stimuli. Specifically, membrane lipid rafts are recognized as important platforms regulating activity at the cell surface. These cholesterol-rich and sphingolipid-rich liquid-ordered phases in the cell membrane allow compartmentalization and clustering of signaling molecules [2,3]. Concentration of signaling molecules in membrane rafts may enable amplification, cross-talk, specificity or inhibitory regulation of cell signaling. One flask-shaped subtype of membrane raft, the caveola [4,5], is the regulation center for a plethora of cell signaling events owing to the activity of its distinguishing caveolin scaffolding proteins [6]. There are three caveolin proteins, which are essential for caveolae formation, cholesterol binding [7-10] and cholesterol trafficking [10-12]. As shown in Figure 1, the caveolin proteins form a hairpin loop in the cell membrane with their N-termini and C-termini remaining in the cell cytoplasm [13,14]. The cytoplasmic portion of the caveolin protein contains a caveolin scaffolding domain sequence that can bind to
many different cell signaling molecules and effect cell signal transduction (reviewed in [6,15]). Caveolae are particularly abundant in adipocytes, endothelial cells, pulmonary type I cells and muscle cells [10]. Assays of various mouse and rat tissues have determined that caveolin-1 is most highly expressed in fat and lung tissue [16-20], but it is also expressed in many other tissues and differentiated cell types [18,19,21-28]. Caveolin-2 is usually co-expressed with caveolin-1 and appears unable to form caveolae in the absence of caveolin-1 [17,18,29]. Caveolin-3, meanwhile, is highly expressed in muscle cells [19,22,30].

Given its expression in many cell types, the role of caveolin-1 in cell activities has been well researched. The growth factor receptors and signaling molecules that localize to caveolae and/or interact with caveolin-1 include the platelet-derived growth factor receptor and the epidermal growth factor (EGF) receptor, G-protein coupled receptors, G-protein alpha and beta subunits, Src, endothelial nitric oxide synthase, and proteins in the Ras-p42/44 mitogen-activated protein kinase and phosphatidylinositol 3-kinase–Akt pathways [6,15]. While association of signaling molecules with caveolin-1 is usually inhibitory [6,15], signaling can be enhanced, probably by bringing molecules...
in close proximity to one another [31]. Furthermore, binding to the caveolin-1 scaffolding domain may enhance the activity of some enzymes. This has been demonstrated in vitro with the insulin receptor kinase [32], Figure 1 summarizes functions attributed to caveolae and caveolin-1 in various cell types. If present in stem cells, many of these activities could impact stem cell behavior. This review discusses current research findings that implicate caveolin-1 in the regulation of stem and progenitor cell activity, tissue repair and aging.

Caveolin-1 regulation of cell proliferation
Inhibitory association of signaling molecules with caveolin-1, as well as caveolin-1 regulation of intracellular cholesterol levels [33], may be responsible for the mostly inhibitory effects of caveolin-1 on differentiated cell proliferation [29,34-38]. In the caveolin-1 null mouse, enlarged populations of cells expressing stem cell markers in the gut, mammary gland and brain have been observed [39-41], suggesting that caveolin-1 may also negatively regulate stem cell proliferation. Furthermore, others have noted that the bone marrow-derived mesenchymal stem cells (MSCs) from the caveolin-1 null mouse have a higher proliferative rate in culture [42], and in mouse neural progenitor cells caveolin-1 facilitates glucocorticoid receptor signaling that leads to inhibition of proliferation [43]. Meanwhile, in human MSCs, Park and colleagues showed that caveolin-1 expression increases when cells are cultured to senescence [44], suggesting that caveolin-1 expression is inversely associated with the proliferative rate of human MSCs. In agreement, we have shown that siRNA-mediated knockdown of caveolin-1 expression in human MSCs increases their proliferation [45]. Conversely, in mouse embryonic stem cells (ESCs), caveolin-1 and caveolae structure appear to be required for cell renewal. Treatment of ESCs with caveolin-1 siRNA or with methyl-β-cyclodextrin, which depletes membrane cholesterol thus disrupting the caveola structure, reduces the cell proliferation index [46]. Furthermore, when mouse ESCs are seeded on fibronectin, caveolin-1 phosphorylation and caveolae integrity are required in downstream events that activate DNA synthesis [47]. Caveolin-1 also mediates estradiol-17β-induced cell proliferation [48] and its expression is required for EGF-induced cell proliferation and glucose induction of DNA synthesis in ESCs [49]. Caveolin-1 may therefore negatively regulate the proliferation of adult murine and human progenitor cells, but in murine ESCs caveolin-1 may be positively involved in proliferative signaling.

Caveolin-1 effects on cell differentiation
Caveolin-1 is known to regulate Wnt/β-catenin signaling [50-54], transforming growth factor beta signaling [55-62] and bone morphogenetic protein (BMP) signaling [63-67], all pathways that can guide stem cell fate. Meanwhile, caveolin expression typically increases upon cell differentiation in vitro [16-20,23,30,68-72], including upon osteogenic differentiation of human MSCs [45] and neurogenesis of rat MSCs [73]. This may reflect negative feedback, where caveolin-1 expression increases as cells differentiate to stabilize the phenotype and prevent continued growth and differentiation. For example, bone marrow MSCs from the caveolin-1 null mouse have greater osteogenic potential [74], suggesting that caveolin-1 inhibits osteogenesis. This may explain the increased postnatal bone formation rate in these animals [74]. We have also shown that caveolin-1 knockdown enhances human MSC osteogenesis [45]. Caveolin-1 also inhibits murine and rat neuronal and oligodendral differentiation [73,75,76] and human MSC adipogenesis [44]. Caveolin-1 regulation of differentiation probably occurs within caveolae through interactions with receptors and downstream signaling molecules for differentiation stimuli. In accordance with this idea, MSC osteogenic differentiation can be promoted by the cholesterol biosynthesis inhibitor simvastatin [77-79], and by oxysterols, which suppress caveolin-1 expression and cause caveolin-1 translocation out of caveolae [80,81]. Also, bone marrow MSCs isolated from mouse models of osteoporosis or high bone mineral density have decreased and increased responsiveness to BMP2, respectively, due to dysregulated localization of the BMP receptor 1a with caveolin-1 isoforms, and dysregulated caveolae trafficking in response to BMP2 [82,83]. Caveolae endocytosis of BMP receptors can also affect rat MSC differentiation [84] (as described further below) and active β-catenin levels are elevated in cells expressing stem cell markers in the intestinal crypts and mammary gland of the caveolin-1 null mouse [39,40], while caveolin-1 regulation of neurogenesis may occur via effects on Notch signaling [73].

Caveolin-1/caveolae regulation of matrix-directed stem cell differentiation
Engler and colleagues showed that MSCs can differentiate according to their substratum elasticity [85]. MSCs seeded on a soft substrate with an elastic modulus similar to brain tissue differentiate into nerve cells, while MSCs seeded on a substrate with an elastic modulus similar to bone differentiate into osteoblasts, and those seeded on a substrate with an elastic modulus similar to muscle differentiate into myoblasts [85]. This phenomenon depends on nonmuscle myosin II activity [85]. As summarized in Figure 2, Du and colleagues have shown that, at least on soft substrates, the mechanism involves caveolin-1 and caveolar endocytosis [84]. In MSCs seeded on a soft substrate, there is increased activation and internalization of β1-integrin via caveolae endocytosis. BMP receptor 1a co-localized with β1-integrin is consequently also internalized, thus inhibiting pro-
Du and colleagues calculated that integrin adhesions to the substratum should be more easily ruptured on soft than on stiff substrates [84]. Therefore, when an adherent cell pulls on (or deforms) its matrix, more integrin contacts should be ruptured if that matrix is soft. Ruptured integrin contacts may then be endocytosed in caveolae [84]. In sum, this means tensile forces generated by nonmuscle myosin II when a cell deforms its matrix could be coupled to caveolar endocytosis to modulate availability of cell signaling platforms necessary for directing cell differentiation.

Intriguingly, culture of muscle stem cells on substrates with a similar rigidity to muscle improves their viability and proliferation in culture and maintains their stemness and regenerative potential [86]. Thus, stem cells possibly respond to changes in matrix elasticity only when it is different to their tissue of origin [85]. The mechanism behind this and the potentially important role of caveolae is a very interesting topic that deserves further exploration.

Meanwhile, it is interesting to note that caveolin-1 may promote astroglial differentiation [87] and is required for human microvascular endothelial cell tubule formation in a Matrigel differentiation assay [70]. Perhaps this observation indicates that caveolin-1 inhibition of some signaling pathways protects or promotes activation of other pathways. We have found that knockdown of caveolin-1 expression in MSCs decreases mRNA expression of the pluripotency marker Pou5F1/Oct4 (unpublished observations), and others have found that caveolin-1 expression and caveolae structure are important for maintaining mouse ESC expression of pluripotency markers (Oct4, Sox2, FoxD3, Rex1) [46]. One could hypothesize that caveolin-1 may act to maintain the stemness of MSCs by holding growth factor receptors and signaling molecules in an inhibited state in caveolae, and/or committing them to caveolar endocytosis. Meanwhile, alterations to caveolin-1 expression or activity may release inhibition of signaling molecules to allow MSCs to be more responsive to other growth and differentiation stimuli. Then, as MSCs differentiate, caveolin-1 expression or activity may release inhibition of signaling molecules to allow MSCs to be more responsive to other growth and differentiation stimuli. This idea is schematically summarized in Figure 3A. Coupling the activity of caveolin-1 and caveolae to cell–matrix interactions would be one way to couple caveolin-1/caveolae regulatory activity on differentiation signals to a cell’s environment. Another way caveolin-1/caveolae activity may be controlled is via cholesterol, which is discussed later.
In cells where caveolin-1 activity inhibits growth and differentiation, a transient decrease in caveolin-1 expression should be required for cell proliferation and differentiation to be activated. Studies investigating mammary gland development support this idea (Figure 3B). The hormone prolactin, which activates the growth and differentiation of the mammary epithelium during pregnancy and lactation, suppresses caveolin-1 expression during lactation in mice [88]. In HC11 cells (used as a model of mammary epithelial cell differentiation), caveolin-1 inhibits prolactin signaling by binding and retaining the prolactin receptor-associated kinase Jak2 in caveolae [89]. Caveolin-1 inhibition of prolactin signaling may also occur in vivo, as during pregnancy the caveolin-1 null mouse mammary gland shows dramatically accelerated lobuloalveolar development, early milk production and a premature lactation phenotype [89]. Furthermore, in immortalized primary human mammary epithelial cells,
estrogen and progesterone together upregulate caveolin-1 expression, and the authors of these findings have proposed that in vivo the drop in these hormones upon birth (when prolactin levels are high) is responsible for de-repression of prolactin signaling and decreased caveolin-1 expression during lactation [89]. In summary, this hypothesis is an example where transient, carefully timed regulation of caveolin-1 expression is important for cell differentiation (summarized in Figure 3B).

**Caveolin-1 effects on tissue repair**

If transient downregulation of caveolin-1 expression/activity is required for cell proliferation and differentiation, it may also be required for tissue repair. Volonte and colleagues have shown that such temporal changes in caveolin expression occur during tissue regeneration in skeletal muscle [90]. Caveolin-1 is expressed in muscle satellite cells in mice and in myogenic precursor cells in vitro [90]. Downregulation of caveolin-1 expression in these cells was shown to be a pre-requisite for their proliferation, migration and differentiation to repair muscle wounds in vivo and in vitro [90]. Following myogenic differentiation, caveolin-3 is expressed in mature multinucleated myotubes, and caveolin-1 is re-expressed in undifferentiated myogenic precursor cells that surround myotubes after wound healing is complete [90] (summarized in Figure 4A). This event agrees with a requirement for transient downregulation in caveolin expression for progenitor cell proliferation and differentiation to mediate tissue repair. Further supporting this idea, muscle regeneration is delayed in caveolin-1 overexpressing mice [90] and caveolin-1-overexpressing myogenic precursor cells fail to differentiate, to migrate and to proliferate to repair wounds in vitro [90].

There are other examples of drops in caveolin expression during reparative processes. For example, in the corneal epithelium, levels of caveolin-1 expression are inversely related to wound healing capacity [91]. In the rat sciatic nerve, caveolin-1 expression also increases as Schwann cells differentiate into a myelinating phenotype, but decreases upon their de-differentiation in response to injury [92]. This may occur because caveolin-1 is only present in the differentiated Schwann cell, with a functional role in cholesterol transport, and/or occur because the drop in caveolin-1 expression allows cells to proliferate in response to injury [92] (Figure 4B). Meanwhile, caveolin-1 appears to inhibit rat fetal neural progenitor cell neuronal differentiation, and downregulation in caveolin-1 occurs in these cells upon hypoxia-induced neuronal differentiation [76].

Caveolin-1 expression is also reduced in mouse hearts 3 days following cryoinjury [93]. The return of caveolin-1 expression to normal levels is important for later stages of cardiac repair, however, suggestive of a positive role for caveolin-1 in part of the process [93]. Also, in rat heart tissue, translocation of caveolin-3 and the caveolin-1α isoform out of caveolae upon aging or infarction may contribute to tissue degeneration/disease pathology [94], while the caveolin-1 scaffolding domain can protect against polymorphonuclear neutrophil reperfusion injury [95]. Caveolin proteins may thus be positively involved in the maintenance of healthy heart tissue. Caveolin-1 may be particularly important for repair in the cardiovascular system, because it is required for the formation of new blood vessels [21,96]. In contrast to its anti-proliferative role in most other cell types, caveolin-1 is needed for the induction of mouse pulmonary microvascular endothelial cell proliferation in response to a disruption in laminar flow [97]. The requirement for caveolin-1 in new blood vessel formation may be a reason why caveolin-1 is vital for collateralization following ischemia in tissues such as the hindlimb [98] and why caveolin-1 deficiency can lead to an increased infarction volume upon cerebral ischemia [99].

Liver regeneration is another example where caveolin-1 may actually be required for cell proliferation and tissue repair. Caveolin-1 null mice have reduced survival after partial hepatectomy [100], and those that survive have a greatly reduced liver regeneration index compared with controls [100]. Caveolin-1 appears to be required for lipid droplet formation, a crucial step in the proliferative response of hepatocytes during liver regeneration [100]. A lack of caveolin-1 regulation of mitochondrial cholesterol levels in these mice has also been suggested to impair metabolism (and thus affect proliferation) to contribute to the phenotype [12]. However, others have found that caveolin-1 is dispensable for liver regeneration in mice [101] and that caveolin-1 deficiency even accelerates liver regeneration [102]. This discrepancy in results could be due to the use of two different knockout animals [100,101]. Meanwhile, caveolin-1 may also have a positive role in regeneration in the kidney; it is expressed in regenerating proximal tubules after gentamicin-induced acute renal failure in rats and may have a role in the regenerative process by modulating EGF and platelet-derived growth factor signaling [103]. Indeed, perhaps in cases where caveolin-1 is required for repair and regeneration, caveolin-1 inhibition of other pathways is beneficial for signal pathways that activate repair.

Caveolin-1 may also have a positive role in cutaneous wound healing. Endocytosis of β₁-integrins in fibroblasts occurs via a pathway involving syndecan-4, protein kinase C alpha, RhoG and caveolin-1, and this process is crucial for fibroblast recruitment and migration during wound healing [104]. Indeed, caveolin-1 null mice have significantly slower skin wound healing than wild-type mice [105]. Caveolin-1 may also have a positive role in regulating the formation of the lipid-rich outermost layer of the epidermis following injury by promoting keratinocyte terminal differentiation (programmed cell death) into corneocytes [106].
In summary, caveolin-1 may positively or negatively contribute to tissue repair depending on the tissue. This context dependence is possibly due to caveolin-1-negative and caveolin-1-positive regulation of different cell signaling pathways, but much further research is required to understand the role of caveolin-1 in tissue repair.

**Caveolin-1 regulation of stem cell homing and mobilization**

Migration is an important aspect of stem cell function. Caveolin-1 has an important role in promoting directional cell migration in other cell types (reviewed in [107]), and may also be involved in stem cell migration. Caveolin-1 expression is required for EGF and fibronectin-induced migration of ESCs [49,108] and may also affect stem cell mobilization and homing. Caveolin-1 expression appears to enhance murine renal MSC adhesion to post-ischemic renal tissue [109]. This adhesion occurs via interaction of stem cell CXCR4 receptors with stromal cell-derived factor-1 on the target cell, and \( \alpha_4 \beta_1 \) (VLA4)–vascular cell adhesion molecule-1 interactions [109]. Caveolin-1 may be required for CXCR4 interactions (Figure 5A), because membrane rafts are important for CXCR4–stromal cell-derived factor-1 interactions in human CD34+ hematopoietic stem/progenitor cells [110]. Meanwhile, as summarized in Figure 5B, studies...
by Sbaa and colleagues suggest caveolin-1 expression is required for mobilization of progenitor cells from bone marrow reserves in mice [111]. In vitro experiments suggest this may be because caveolar internalization of CXCR4 receptors in response to soluble stromal cell-derived factor-1 may be important for progenitor cell mobilization [111].

**Aging**

Traditionally, reactive oxygen species-mediated damage to cellular components has been thought to cause aging [112]. Caveolin-1 can protect against oxidative stress by regulating mitochondrial cholesterol levels, which affect the levels of the antioxidant glutathione in mitochondria [113] (Figure 1).

**Figure 5 Caveolin-1 regulation of progenitor cell homing and mobilization.** (A) Renal stem cell homing. Caveolin-1 may positively contribute to renal stem cell adhesion to ischemic tissue [109], possibly by promoting CXCR4 clustering in caveolae and allowing its interaction with stromal cell-derived factor-1 (SDF-1) in the ischemic tissue. (B) Bone marrow stem cell mobilization. In the bone marrow, caveolar internalization of CXCR4 may be important for progenitor cell de-adhesion to marrow stromal cells. Upon tissue ischemia, endothelial progenitor cells from the bone marrow may be recruited to the ischemic site to form new vasculature to restore blood flow. Caveolin-1 null mice (Cav−/−), unlike wild-type (WT) mice, fail to restore perfusion when ischemia is induced in their hind limbs. However, this phenotype can be rescued by direct intravenous infusion of Cav−/− or WT progenitor cells in the affected area, or by transplanting WT bone marrow into irradiated Cav−/− mice [111]. These results suggest that caveolin-1 is involved in the process of progenitor cell mobilization from the bone marrow in response to soluble SDF-1, which normally triggers progenitor cell mobilization. HSPC, hematopoietic stem/progenitor cell; MSC, mesenchymal stem cell.
Accordingly, the accumulation of mitochondrial cholesterol and reactive oxygen species in the liver and brain of caveolin-1 null mice contributes to disease progression in degenerative disease models (steatohepatitis, Huntington’s disease, Alzheimer’s disease) [113], and these animals demonstrate some signs of accelerated aging, particularly in the brain [114,115]. This aging may be due to decreased brain mitochondrial glutathione levels [113]. However, the aging may also or solely be due to increased production of amyloid-β protein from amyloid precursor protein, the processing of which is normally regulated in membrane rafts [114]. Meanwhile, it is now clear that reactive oxygen species do not initiate aging and that, although they may have damaging effects on macromolecules, they may have beneficial effects on age-related cell signaling [116].

A positive role for caveolin-1 in aging agrees more with the mostly quiescent effects of caveolin-1 on cell biology discussed above. Also, caveolin-1 promotes insulin signaling and adipocyte lipid droplet storage [117-119]. Caveolin-1 could therefore have a general role in inhibiting continued growth and differentiation and slowing metabolism, perhaps as a response to completion of tissue formation and aging. In turn, this may mean that reducing caveolin-1 expression/activity could reverse aging effects in certain cells/tissues. Indeed, caveolin-1 expression increases with age in a number of rat tissues and in human diploid fibroblasts [120], and reducing caveolin-1 expression in the latter restores responsiveness to EGF [121]. Moreover, caveolin-1 null mice are lean, resistant to diet-induced obesity [119], insulin resistant [118] and have decreased levels of the adipokine leptin [119]. Conversely, plasma levels of leptin are increased in aged mice [122] and reducing the activity of nutrient sensing pathways (for example, insulin signaling) is known to increase longevity in several species [123]. In humans, insulin resistance is a side effect of treatment with rapamycin, the inhibitor of mammalian target of rapamycin [124], which is known to slow aging in mice [125,126]. Whether rapamycin’s anti-aging effects could be partly attributed to inhibition of caveolin-1/caveolar activity remains to be elucidated and warrants further investigation; one would not be surprised if caveolin-1 could affect stem cell aging, which rapamycin has been shown to do [126].

The activation of stem cells is dysregulated with age in mouse muscle [127-129] and, as Volonte and colleagues have shown that caveolin-1 expression delays murine skeletal muscle regeneration [90], one could hypothesize that an age-related increase in caveolin-1 expression may be responsible for an age-related decline in mouse muscle regenerative potential. Interestingly, aged satellite cells have impaired activation of Notch-Delta signaling [128], and premature activation of Wnt signaling in these cells causes fibrosis [129]. Caveolin-1 can affect the propagation of both Wnt and Notch signaling pathways in other progenitor cells [39,40,73,87]. Furthermore, parabiotic pairings of old rats with young rats increases aortal and muscle cholesterol uptake in the older animals [130]. An increase in intracellular cholesterol levels promotes caveolin-1-directed cholesterol efflux and caveolar formation, and free cholesterol promotes caveolin-1 expression [33,80]. Perhaps older tissues thus have a greater tendency to absorb cholesterol, which in turn increases caveolin-1 activity and caveolar formation. Meanwhile, systemic factors released by young mouse can reactivate resident stem cells in aged mice and replenish their reparative capacity [128]. One would therefore be interested to determine whether factors in young plasma affect cholesterol metabolism and caveolar activity in old cells.

Mechanosensing
Mechanical stimulation and focal adhesion signaling can regulate stem cell differentiation [131], including fluid shear forces at the surface of the cell [132]. Caveolae and caveolin-1 are important for mechanosensing and the propagation of mechanotransduction pathways in many cell types, particularly cells exposed to shear forces [133-144]. The actual structure of caveolae even provides a membrane reserve that can buffer stresses on the cell membrane caused by mechanical stretch and osmotic swelling [145-147] (as shown in Figure 1). The role of caveolae and caveolin-1 in stem cell mechanoresponses may therefore also be worth investigation. Perhaps it is possible that mechanical perturbations to caveolae can activate differentiation and proliferation and repair pathways in quiescent stem cells.

Conclusions
In summary, caveolin-1 affects several aspects of stem cell biology, including proliferation, differentiation, substrate-driven differentiation, homing and mobilization. We predict that alteration to caveolin-1/caveolar activity is a prerequisite for stem cell activation and differentiation, and that increased caveolin-1 expression with age may implicate the protein in age-related declines in tissue regenerative potential. However, because of the multiple (and probably context-dependent) effects of caveolin-1, this will not apply to all cells and tissues. Promotion of caveolin-1 activity may be desirable for some areas of regenerative medicine (for example, mobilization of bone marrow stores of progenitor cells), while inhibition may be desirable in others (for example, to reverse muscle aging, increase bone density, or improve in vitro expansion of adult stem cell harvests). Manipulation of caveolin-1 expression/activity may be possible in specific tissues in vivo; for example, via siRNA approaches or modulation of cholesterol biosynthesis. However, much research is required to define caveolin-1 function in different stem cells and to determine whether manipulation of membrane signaling platforms such as...
caveolae could be beneficial in stem cell therapies and regenerative medicine.

Abbreviations
BMP: Bone morphogenetic protein; EGF: Epidermal growth factor; ESC: Embryonic stem cell; MSC: Mesenchymal stem cell; siRNA: Small interfering RNA.

Competing interests
The authors declare that they have no competing interests.

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