




# Caveolin1: its roles in normal and cancer stem cells

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## Abstract

**Purpose** Stem cells are characterized by the capability of self-renewal and multi-differentiation. Normal stem cells, which are important for tissue repair and tissue regeneration, can be divided into embryonic stem cells (ESCs) and somatic stem cells (SSCs) depending on their origin. As a subpopulation of cells within cancer, cancer stem cells (CSCs) are at the root of therapeutic resistance. Tumor-initiating cells (TICs) are necessary for tumor initiation. Caveolin1 (Cav1), a membrane protein located at the caveolae, participates in cell lipid transport, cell migration, cell proliferation, and cell signal transduction. The purpose of this review was to explore the relationship between Cav1 and stem cells.

**Results** In ESCs, Cav1 is beneficial for self-renewal, proliferation, and migration. In SSCs, Cav1 exhibits positive or/and negative effects on stem cell self-renewal, differentiation, proliferation, migration, and angiogenic capacity. Cav1 deficiency impairs normal stem cell-based tissue repair. In CSCs, Cav1 inhibits or/and promotes CSC self-renewal, differentiation, invasion, migration, tumorigenicity ability, and CSC formation. And suppressing Cav1 promotes chemo-sensitivity in CSCs and TICs.

**Conclusion** Cav1 shows dual roles in stem cell biology. Targeting the Cav1-stem cell axis would be a new way for tissue repair and cancer drug resistance.

**Keywords** Caveolin 1 · Stem cells · Cancer · Self-renewal · Differentiation

## Introduction

Stem cells are characterized by the capacities to self-renew and produce multiple differentiated progenies (Rigaud et al. 2020). There are two main types of normal stem cells based on their origin, embryonic stem cells (ESCs), which can be isolated from the inner cell mass of early mammalian

blastocysts (Harvey et al. 2019), and somatic stem cells (SSCs), which can be isolated from developed tissues and organs (Ly et al. 2020). Recognized as pluripotent stem cells, ESCs cannot create extra-embryonic tissues. Nevertheless, ESCs can produce somatic cell types, like hepatocytes, endothelial cells, hematopoietic cells, etc. (Semba et al. 2020). SSCs include hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), neural stem cells (NSCs), adipose-derived stem cells (ADSCs), epidermal stem cells (EpiSCs), mammary stem cells (MaSCs), and intestinal stem cells (ISCs) (Wang et al. 2020a; Tweedell 2017). Besides, progenitor cells are also considered to be SSCs (Rebuzzini et al. 2015). SSCs are known as multipotent stem cells and possess more limited differentiation potential than ESCs. SSCs can create several terminally differentiated cells that maintain tissue homeostasis (Semba et al. 2020). Recently, scientists can reprogram somatic cells to create pluripotent stem cells in a state similar to ESCs. These cells are called induced pluripotent stem cells (iPSCs) and can be used for regenerative medicine, disease modeling, and drug testing (Takahashi and Yamanaka 2006; Soman and Vijayavenkataraman 2020).

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Nowadays, despite advances in cancer diagnosis and treatment, cancer is still considered to be the second leading cause of death in the world (Ahmed et al. 2020). Cancer stem cells (CSCs), a rare subset of cancer cells within the tumor bulk, were first launched in the researches about primary human acute myeloid leukemia (Lapidot et al. 1994). Accumulative studies demonstrate that CSCs can come from normal stem cells, progenitor cells, differentiated tissue cells, or tumor cells (Chiodi and Mondello 2020). It is determined that, based on the surface markers CD44, CD24, CD133, etc., CSCs can be collected from several malignant cancers (e.g., breast, lung, liver, prostate, pancreatic, colorectal, gastric, etc.) through the techniques of flow cytometry and Fluorescence-Activated Cell Sorting (FACS) (Thankamony et al. 2020). CSCs can form three-dimensional spheres that are also called tumorspheres. The tumorsphere formation assay can be used for CSC isolation and identification in vitro (Zhu et al. 2017). In addition to the stemness properties (i.e., self-renewal and differentiation), CSCs also have stemness-related signal pathways similar to normal stem cells. In normal stem cells, the signal pathways maintaining stemness are strictly controlled without the mutation. While in CSCs, due to genetic and epigenetic mutations, the signals are usually dysfunctional (Nimmakayala et al. 2019). CSCs are involved in tumor initiation, metastasis, relapse, and therapeutic resistance (Clara et al. 2020). At present, the significance of CSC-based anti-cancer treatment cannot be underestimated.

Caveolae, which are defined as flask-shaped membrane invaginations located at the plasma membrane, are rich in cholesterol and sphingolipids (Skotland et al. 2020). Caveolin 1 (Cav1), a 21 kDa membrane protein composed of 178 amino acids, is one of the basic components in caveolae and is pivotal for the formation of caveolae. The encoding gene *CAV1* is located on human chromosome 7q31.1 (Yan et al. 2020). Cav1 highly exists in adipocytes, fibroblasts, endothelial cells, muscle cells, and epithelial cells (Williams and Lisanti 2004). Cav1 has the N-terminal domain, the caveolin scaffolding domain (CSD), the intramembrane domain (IMD), and the C-terminal spanning domain (Root et al. 2015). Many studies emphasize that the CSD region can modulate the interaction between Cav1 and other signaling proteins, such as adenylyl cyclase, phosphatidylinositol-3-kinase (PI3K), endothelial nitric oxide synthase (eNOS), mitogen-activated protein kinase (MAPK), protein kinase A and C (Patel et al. 2008). It is proved that Cav1 can regulate stem cell biology, tissue repair, and tissue regeneration (Baker and Tuan 2013). Besides, Cav1 also displays both suppressive and oncogenic effects on cancer aggressive behaviors according to tumor type and environment (Singh and Lamaze 2020). And it is suggested that Cav1 correlates with tumor cell proliferation, migration, invasion, metastasis, stemness, and drug resistance (Qian et al. 2019).

In this review, we collected the evidence to discuss the interaction between Cav1 and stem cells, altogether describing the roles of Cav1 in stem cell self-renewal, differentiation, proliferation, and migration. We also found that Cav1 has a role in modulating CSC formation and chemoresistance.

## Caveolae and Cav1

Described as small (50–80 nm) invaginations, caveolae play vital roles in endocytosis, cell signal transduction, membrane trafficking, and dynamics (Filippini and D'Alessio 2020). The Caves and cavins are the main components of the caveolae. Caves are composed of three isoforms: Cav1, Cav2, and Cav3. Cav1 and Cav2 are expressed in non-muscle cells. Cav3 mainly exists in muscle cells (Chidlow and Sessa 2010). And the cavin family includes cavin-1 (polymerase I and transcript release factor, PTRF), cavin-2 (serum deprivation response protein, SDPR), cavin-3 (serum deprivation response factor-related gene product that binds to C-kinase, SRBC), cavin-4 (muscle-restricted coiled-coil protein, MURC). Cavin-1 is expressed in all tissues and is essential for caveolae formation (Kovtun et al. 2015). It is proved that cavin-1 can interact with Cav1 to prevent Cav1 degradation, thus, to shape caveolae structure (Hansen and Nichols 2010; Yamaguchi et al. 2016).

It is indicated that Cav1 has two isoforms: Cav1 $\alpha$  and Cav1 $\beta$ . Cav1 $\alpha$  contains 178 amino acids and Cav1 $\beta$  contains residues 32–178. Both Cav1 $\beta$  and Cav1 $\alpha$  can be phosphorylated on serine 80 (Lajoie and Nabi 2010). One study suggested that Cav1 $\alpha$  has additional two phosphorylation sites, tyrosine 14 and serine 37. And Cav1 $\beta$  can also undergo phosphorylation on serine 5 (Vainonen et al. 2004). The tyrosine 14 in Cav1 is the target of non-receptor tyrosine kinases Src, Fyn, and c-Abl in response to certain stimuli. The Cav1 phosphorylation on tyrosine 14 can promote cell migration, invasion, and metastasis (Wong et al. 2020). And the Cav1 phosphorylation on serine 80 is implicated in cholesterol transport, protein retention in the endoplasmic reticulum, and protein secretion (Campos et al. 2019). It is shown that mechanical stress can come from the cell's cytoskeleton or external loads applied to the cell surface. And mechanical stress is implicated in gene expression, cell division, cell migration, cell differentiation, cell adhesion, etc. (Belaadi et al. 2016; Nogueira et al. 2015). Accumulative evidence reveals that under mechanical stress, caveolae open and flatten, thereby, to prevent cell membrane rupture (Cheng and Nichols 2016). The Cav1–cavin-1 interaction is impaired by mechanical stress. When the mechanical stress is disappeared, Cav1 and cavin-1 are reassembled in the plasma membrane and promote caveolae formation (Sinha et al. 2011; Nassoy and Lamaze 2012). Teo et al. reported

that Cav1 depletion recruits the formin FMNL2 to stabilize filamentous actin (F-actin), which can elevate epithelial contractile tension to reduce oncogenic cell extrusion. Finally, Cav1 absence represses the elimination of tumor cells from the epithelium monolayer (2020). Cav1 phosphorylation can be stimulated via periodic mechanical stress, leading to the activation of insulin-like growth factor-1 receptor (IGF-1R) and extracellular signal-regulated kinase 1/2 (ERK1/2). Cav1 phosphorylation eventually potentiates chondrocyte proliferation through the IGF-1R/ERK1/2 pathway in response to periodic mechanical stress (Ren et al. 2018).

## Cav1 and embryonic stem cells

Found in the early blastocysts, ESCs are capable of multi-directional differentiation, self-renewal, and proliferation properties (Wang et al. 2019a). ESCs can create all of the ectodermal, mesodermal, and endodermal cell layers (Soleimani et al. 2020). ESC self-renewal and pluripotency are involved in both proliferation and maintaining an undifferentiated state. And the ESC self-renewal potential is unlimited (Romeo et al. 2012).

### Self-renewal

Down-regulated Cav1 can attenuate ESC proliferation and diminish messenger RNAs (mRNAs) of pluripotent effectors like octamer-binding transcription factor 4 (Oct4), Sox2, FoxD3, and Rex1. These suggest a positive relationship between Cav1 and ESC self-renewal (Lee et al. 2010). LacdiNAc (GalNAc $\beta$ 1-4GlcNAc) is a cell surface glycan involved in ESC self-renewal. Cav1 can interact with the LacdiNAc-expressed leukemia inhibitory factor (LIF) receptor (LIFR) and glycoprotein 130 (gp130), leading to strong transduction of LIF/signal transducer and activator of transcription 3 (STAT3) signaling pathway. Eventually, the improved LIF/STAT3 signal transduction can promote mouse ESC self-renewal (Sasaki et al. 2011).

### Proliferation

Estradiol-17 $\beta$  (E<sub>2</sub>), one of the female sex steroid hormones, has been found to stimulate mouse ESC migration (Yun et al. 2012). One study shows that Cav1 is a downstream mediator of E<sub>2</sub> in mouse ESC cells. E<sub>2</sub> can increase Cav1 expression via activating PI3K/protein kinase B (AKT) and ERK1/2 pathways. Inhibiting Cav1 can repress proto-oncogene (*c-fos*, *c-Myc*, and *c-jun*) transcription and decrease cell cycle regulator (cyclin D1, cyclin E, cyclin-dependent kinase 4 (CDK4), and CDK2) expressions. As a result, Cav1 can contribute to E<sub>2</sub>-modulated ESC proliferation (Park et al. 2009). Galectin-1 is an animal lectin that can enhance stem

cell proliferation (Yanagisawa and Yu 2007). Src kinase can phosphorylate Cav1 on tyrosine 14 (Cao et al. 2002). It is shown that Galectin-1 can activate Src to induce Cav1 activation. Activated Cav1 can promote mouse ESC proliferation through activating AKT and mammalian target of rapamycin (mTOR) (Lee et al. 2009). Cav1 expression can also be up-regulated by high glucose through p38 MAPK phosphorylation. Cav1 can stimulate F-actin reorganization through  $\beta$ 1 integrin/focal adhesion kinase (FAK)/PIP complex (PINCH1/2, integrin-linked kinase (ILK), and  $\alpha$ -parvin) signaling pathway, ultimately, leading to potentiating ESC proliferation under high glucose (Lee et al. 2011). Fibronectin, one of the extracellular matrix (ECM) components, can promote cell proliferation and migration. One report observed that Cav1 phosphorylation can be induced by fibronectin through Src/FAK signal pathway in mouse ESCs. Subsequently, Cav1 can activate Rho-associated protein kinase (ROCK) and RhoA, which can contribute to ESC proliferation through PI3K/AKT and ERK1/2 signals (Park et al. 2011).

### Migration

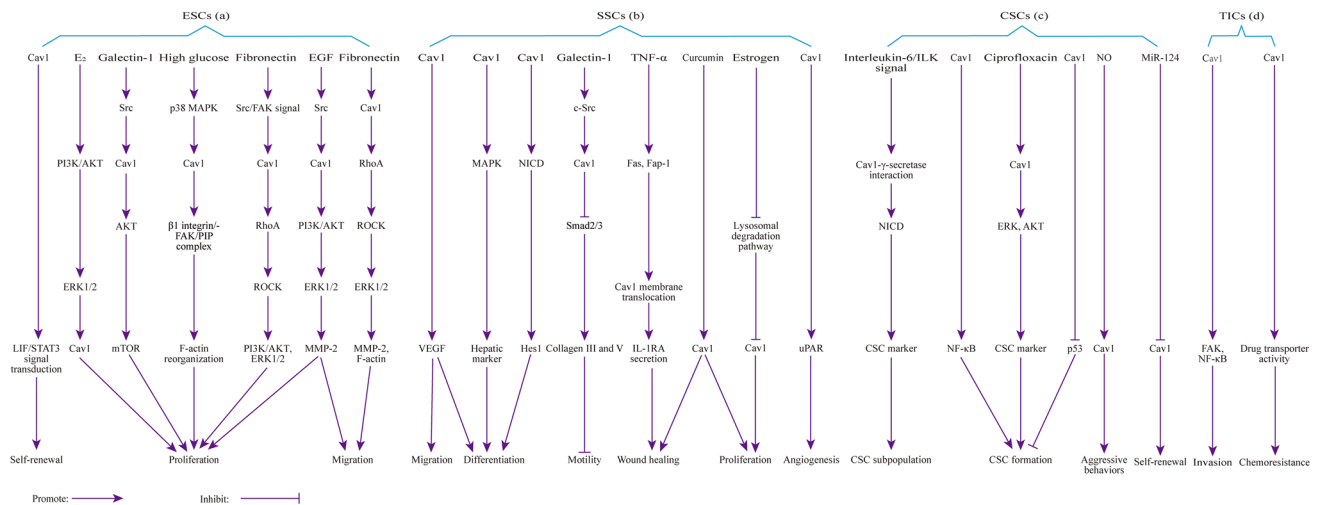
Park et al. proved that fibronectin-induced Cav1 can augment MMP-2 and F-actin expressions via RhoA/ROCK/ERK1/2 signal, resulting in increased migration in mouse ESCs (Park et al. 2012). Epidermal growth factor (EGF), a well-known mitogen, can bind to the EGF receptor (EGFR) to activate the MAPK pathway, which plays a critical role in intercellular communication in mouse ESC colonies (Fong et al. 2014). Cav1 in mouse ESCs is phosphorylated by the EGF/Src signal. And Cav1 can improve mouse ESC proliferation and migration via the PI3K/AKT/ERK1/2/matrix metalloproteinase-2 (MMP-2) pathway (Park and Han 2009).

From these studies, we found that Cav1 can improve proto-oncogene transcription, pluripotent effector expressions, cell cycle regulator expressions, and F-actin reorganization in ESCs. Taking as a whole, Cav1 can promote ESC self-renewal, proliferation, and migration (Fig. 1).

## Somatic stem cells

### Hematopoietic stem cells

HSCs, a very rare cell population with self-renewal and multi-potency, are critical for hematopoiesis. HSCs can be detected in bone marrow (BM), peripheral blood, umbilical cord blood (UCB), and placenta (Yadav et al. 2020). Young HSCs can remain balanced in myeloid and lymphoid differentiation. While elderly HSCs are capable of enhanced myeloid-biased differentiation and declined lymphoid-biased differentiation (Akunuru and Geiger 2016). The HSC



**Fig. 1** The positive role of Cav1 in stem cells and tumor-initiating cells (TICs). Cav1 can regulate related signaling pathways to promote: **a** self-renewal, proliferation, and migration in ESCs; **b** migration, differentiation, motility, and proliferation in SSCs, and stem

cell-based wound healing and angiogenesis; **c** CSC subpopulation, CSC formation, self-renewal, and aggressive behaviors in CSCs; **d** invasion and chemo-resistance in TICs

transplantation can reconstitute the whole-blood system and maintain long-term hematopoiesis in a recipient, which can be a therapy for hematological diseases (Khaddour et al. 2020). Cav1 deletion can not only impair HSC self-renewal, but also abolish the differentiation of HSCs into mature blood cells. Cav1 deficiency can also accelerate cellular senescence in HSCs. Besides, Cav1 silence in mice can decrease the percentage of HSCs in BM. And the transplantation of HSCs from Cav1-deficient mice can't reconstitute hematopoiesis in irradiated mice (Bai et al. 2014). PTRF, one putative caveolar coat protein, plays a vital role in caveolae formation at the plasma membrane (Hill et al. 2008). In addition to destroying self-renewal, over-expressed PTRF can also induce cellular senescence and skewed myeloid differentiation in HSCs. Cav1 levels in HSCs are increased by PTRF. Knocking out Cav1 in HSCs can restore self-renewal and inhibit cell senescence in response to up-regulated PTRF (Bai et al. 2020). In sum, these studies indicate that Cav1 is necessary to maintain HSC physiological functions. And the interaction of Cav1 with caveolar protein PTRF impairs self-renewal and stimulates cell senescence in HSCs.

## Mesenchymal stem cells

MSCs can exist in BM, adipose tissue, UCB, placenta, peripheral blood, and gingiva (Fan et al. 2020; Jayaramayya et al. 2020). Notably, MSCs can differentiate into several tissue-specific cell lineages, including osteocytes, chondrocytes, cardiomyocytes, adipocytes, neurocytes, and endothelial cells (Ramazzotti et al. 2019; Ma et al. 2020).

## Motility

In human UCB-derived MSCs, Cav1 can be activated via galectin-1 through c-Src. The Smad2/3 phosphorylation can be reduced by galectin-1 through Cav1, resulting in down-regulating collagen III and V. Eventually, decreased collagen III and V can increase MSC motility (Yun et al. 2014).

## Differentiation

In human BM-derived MSCs (BMSCs), Cav1 is up-regulated during osteogenesis progression. Cav1 can dampen the PI3K/AKT signaling pathway in lipid rafts to inhibit BMSC osteogenesis (Baker et al. 2015). Decreased Cav1 expression can facilitate BMSC proliferation. And Cav1 depletion can also improve BMSC matrix mineralization and the expressions of osteogenic regulators (e.g., osteocalcin, bone sialoprotein 2, Col1a2, and Runx2). Cav1 can function as an antagonist of BMSC proliferation and osteogenic differentiation (Baker et al. 2012). Further, one study demonstrated that Cav1 absence is failed to express bone sialoprotein or form mineralized nodules of murine BMSCs, which suggests that Cav1 knockout can lead to dysfunctional osteogenic differentiation (Case et al. 2010). Cav1 is highly expressed in rat BMSCs undergoing cardiomyocyte differentiation. Cav1 silence can potentiate BMSC differentiation into cardiomyocytes by reducing the STAT3 pathway (Chen et al. 2017). Cav1 up-regulation can attenuate insulin signaling and decline peroxisome proliferator-activated receptor gamma 2 (PPAR $\gamma$ 2, one positive effector for adipocyte development) expression. Up-regulated Cav1 eventually represses the adipogenic differentiation of human BMSCs (Park et al. 2005).

Cav1 is decreased during neuronal differentiation in human adipose-derived MSCs. Cav1 down-regulation can potentiate MSC differentiation into dopaminergic-like neurons through increasing dopamine levels and dopaminergic neuronal marker (e.g., tyrosine hydroxylase, *Lmx1a*, and *Nurr1*) expressions (Han et al. 2021). Additionally, the combination of reduced Cav1 with increased ATP6AP2 (a key component of the renin-angiotensin system) in lipid raft microdomains can facilitate MSC neurogenesis (Makdissy et al. 2018). Once cleaved after interacting with Notch ligands (Delta and Jagged), Notch can release Notch intracellular domain (NICD) into the cell nucleus, thereby, to induce the transcription of its target genes, for example, the hairy enhancer of split (*Hes*) family (Zanotti and Canalis 2016). In rat BMSCs, silencing Cav1 can abrogate the Notch-1, NICD, and *Hes5* expressions. The impaired Notch signaling pathway ultimately stimulates BMSC neuronal differentiation (Wang et al. 2013).

### Therapy

Wound healing is a complex process in humans and abnormal wound healing leads to high healthcare costs (Rodrigues et al. 2019). Extracellular vesicles (EVs) are cargo-carrying vesicles that can affect cell communication (Teng and Fussenegger 2020). The gingiva-derived MSCs (GMSCs) can produce and secrete small EVs (sEVs) expressing interleukin-1 receptor antagonist (IL-1RA). Cav1 membrane translocation in GMSCs can be increased via tumor necrosis factor-alpha (TNF- $\alpha$ ) through up-regulating Fas and Fas-associated phosphatase-1 (Fap-1). Increased membrane translocation of Cav1 can promote IL-1RA-sEVs release in GMSCs, which can ultimately accelerate cutaneous wound healing in mouse gingiva (Kou et al. 2018).

Taken together, activated Cav1 promotes MSC motility, while increased Cav1 inhibits osteogenic differentiation, cardiomyocyte differentiation, adipogenic differentiation, and neuronal differentiation in MSCs. And enhanced Cav1 membrane translocation in MSCs enhances skin wound healing.

### Neural stem cells

NSCs can proliferate, self-renew and give rise to neurons and glial cells (e.g., astrocytes and oligodendrocytes) (Kobayashi and Kageyama 2020). In the adult brain, NSCs reside in the subventricular zone (SVZ) and subgranular zone (SGZ). When the brain gets injured, the endogenous quiescent NSCs become active and migrate to the damaged area, subsequently, repair the brain (Othman and Tan 2020). In the ischemic brain of rats, Cav1 and vascular endothelial growth factor (VEGF) protein levels are significantly increased by treadmill exercise. Down-regulated Cav1 can reduce VEGF expression, thereby, to abolish exercise-induced

NSC migration and neural differentiation in the ischemic brain. Cav1/VEGF pathway can contribute to the exercise-promoted recovery of brain function after middle cerebral artery occlusion through improving neurogenesis (Zhao et al. 2017). In short, there is a positive relationship between Cav1 and NSC neurogenesis, which are beneficial for functional recovery in the ischemic brain.

### Adipose-derived stem cells

ADSCs, which are abundant in adipose tissues, display multi-potency and have the potential to differentiate into hepatocytes, osteocytes, adipocytes, and so on (Megaloukonomos et al. 2018). Cav1 protein expression and phosphorylated MAPK are increased during human ADSC hepatocyte differentiation. Cav1 suppression can abrogate the MAPK pathway to decrease the levels of hepatic marker proteins, including albumin and hepatocyte nuclear factor-1- $\alpha$ , resulting in repressing ADSC hepatic differentiation (Guan et al. 2016). The phenylalanine at position 92 (F92) in the Cav1 scaffolding region is responsible for eNOS suppression. The mutation of F92 to alanine can result in mutant Cav1 (F92A-Cav1), which reverses the impact on eNOS and thereby increases nitric oxide (NO) synthesis (Bernatchez et al. 2011). In equine ADSCs, the interaction of F92A-Cav1 with eNOS can augment NO production, which can promote the activation of the Wnt3a/ $\beta$ -catenin signaling pathway. Finally, the activated Wnt3a/ $\beta$ -catenin signal can facilitate osteogenesis of equine ADSCs (Bandara et al. 2016). In summary, in ADSCs, Cav1 positively regulates hepatic differentiation and the mutation in Cav1 at position 92 reduces Cav1 inhibition on osteogenesis differentiation.

### Epidermal stem cells

EpiSCs preserve self-renewal and proliferative properties. And they are enriched in hair follicles, sebaceous glands, and inter-follicular epidermis. Importantly, EpiSCs can migrate to wound sites and promote wound healing (Yang et al. 2019a). It is showed that Cav1 can potentiate EpiSC proliferation. And the treatment of EpiSCs over-expressing Cav1 can accelerate angiogenesis and skin wound healing in rats. Additionally, the conditioned medium of EpiSCs with over-expressed Cav1 can increase endothelial cell tube formation in human umbilical vein endothelial cells (HUVECs) (Yang et al. 2019b). Curcumin isolated from turmeric belongs to traditional Chinese medicine and it can act as treatment methods for skin diseases, obesity, and cancer (Kocaadam and Şanlıer 2017). Cav1 can be elevated via curcumin in mouse EpiSCs. And suppressing Cav1 can attenuate EpiSC proliferation, HUVEC tube formation, and EpiSC-based wound healing under curcumin (Yang et al. 2019c). As mentioned above, Cav1 improves EpiSC

proliferation and is necessary for EpiSC-related HUVEC tube formation and wound healing.

### Mammary stem cells

MaSCs mainly reside in mammary glands and normally keep quiescent. Upon certain stimuli, for example, the steroid hormones, multipotent MaSCs become active and then give rise to both luminal and basal progenitor cells, which can promote mammary gland development (Lee et al. 2019). It is indicated that Cav1 deficiency can enhance the expressions of MaSC markers stem cell antigen-1 (Sca-1), keratin 5 (K5), and K6 in mammary glands. Cav1 deletion can also significantly increase  $\beta$ -catenin expression. Sotgia et al. suggested that Cav1 silence can increase MaSC populations through activating the  $\beta$ -catenin pathway (Sotgia et al. 2005). As mentioned above, it can be seen that Cav1 can be considered to be an inhibitor for MaSC populations.

### Intestinal stem cells

ISCs are highly proliferative cell populations mainly located at the intestinal crypts. They are beneficial for epithelial renewal and injury-related regeneration in the intestine (Bankaitis et al. 2018). Cav1 attenuation can enhance proliferation via promoting the Wnt/ $\beta$ -catenin pathway in intestinal crypt stem cells. Moreover, Cav1 abrogation can increase apoptosis of crypt stem cells in response to radiation, indicating the increased sensitivity to radiation (Li et al. 2005). In summary, Cav1 displays negative effects on ISC proliferation and radiation sensitivity.

### Neural progenitor cells

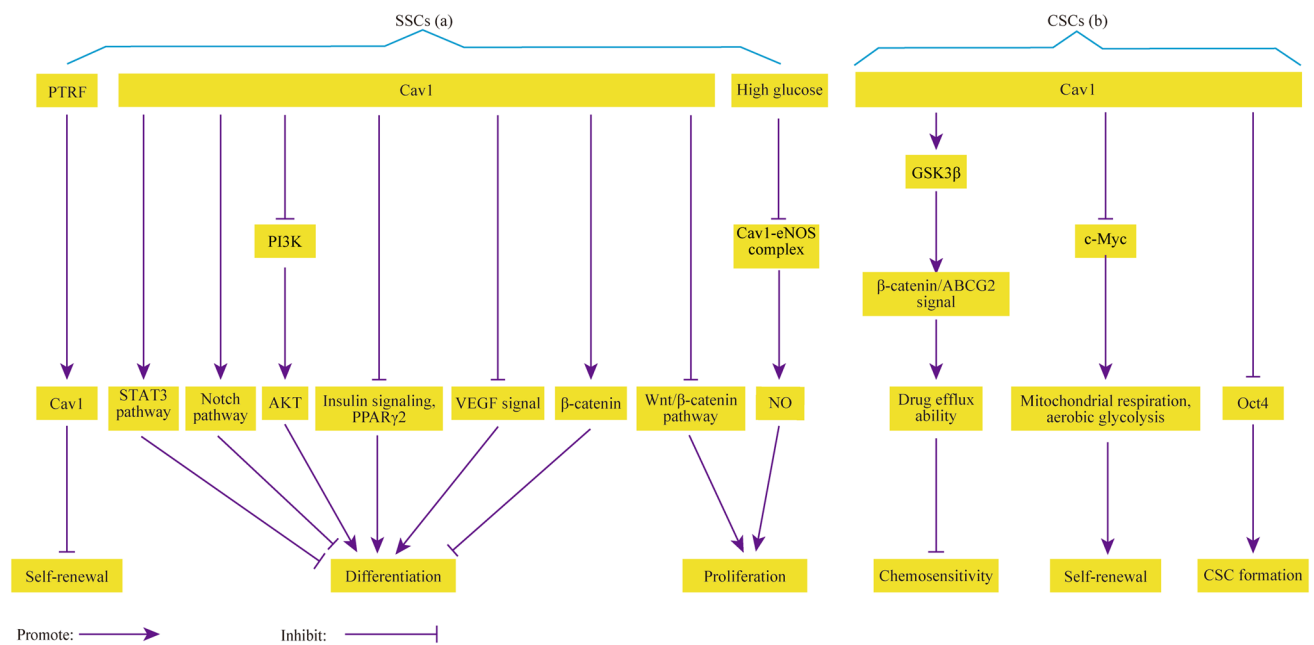
Neural progenitor cells (NPCs) can be produced by NSCs and have the potential to differentiate into neurons, astrocytes, and oligodendrocytes (Beattie and Hippenmeyer 2017). Besides, NPCs can also be generated by ESCs or iPSCs (Martínez-Cerdeño and Noctor 2018). In rat NPCs, Cav1 can accelerate astroglial differentiation via up-regulating NICD and Hes1 expressions (Li et al. 2011a). Another study proved that Cav1 can attenuate oligodendroglial differentiation of rat NPCs through increasing  $\beta$ -catenin expression (Li et al. 2011b). The Ras and Rho GTPases (i.e., cell division cycle 42 (Cdc42), Rac1, etc.) can improve axonal growth and guidance. And it is said that appropriate axonal growth and guidance are essential for functional neuronal network development (Hall and Lalli 2010). In NPCs derived from human iPSCs, both Cav1 expression and its phosphorylation levels are elevated by constitutively active Cdc42 and Rac1. Phosphorylated Cav1 can facilitate axonal growth during neuronal differentiation in NPCs (Wang et al. 2019b). In normoxic conditions, Cav1 is increased. Cav1 can

abrogate VEGF signals, which can reduce neuronal differentiation in NPCs. However, when exposed to hypoxia, the Cav1 expression is decreased, resulting in enhancing NPC differentiation into neurons. These results can explain the reason why hypoxia can promote neuronal differentiation (Li et al. 2011c). Exosomes, a kind of extracellular vesicles with a diameter of ~40 to 160 nm, can deliver many cell constituents (DNA, RNA, proteins, etc.) and mediate intercellular communication (Kalluri and LeBleu 2020). Cav1 is rich in exosomes originated from brain microvascular endothelial cells. Exosomal Cav1 can repress NeuroD1 expression and VEGF signal, leading to inhibiting neuronal differentiation of NPCs in post-ischemic brains (Li et al. 2020). It is can be seen that Cav1 promotes astroglial differentiation and suppresses oligodendroglial differentiation and neuronal differentiation in NPCs.

### Endothelial progenitor cells

Endothelial progenitor cells (EPCs) are undifferentiated cells with the potential to proliferate and differentiate into endothelial cells. EPCs can be discovered in peripheral blood, BM, UCB, and adipose tissues (Kaushik and Das 2019). In response to several stimuli (e.g., hypoxia, injury, etc.), EPCs can migrate to the peripheral circulation from BM, therefore, to form or repair blood vessels. EPCs are critical for vascularization and angiogenesis, and EPC-associated therapies are helpful for diabetes and diabetes-related diseases (Ambasta et al. 2017). Cav1 expression is increased by aerobic and resistance training in EPCs obtained from the mice with type 2 diabetes mellitus. Aerobic and resistance training can improve EPC proliferation, migration, and angiogenesis (Dai et al. 2020). Cav1 knockdown can impair EPC proliferation and adherent ability upon aerobic and resistance training (Zhai et al. 2020). In rat BM EPCs, Cav1 expression can be up-regulated via estrogen through suppressing the lysosomal degradation pathway. And increased Cav1 can contribute to EPC proliferation (Tan et al. 2012). Under high glucose stimuli, Cav1 mRNA and protein levels are increased, while the eNOS protein expression is declined. Impaired Cav1–eNOS complex can decrease NO synthesis, resulting in reduced EPC proliferation, migration, and angiogenesis (Cao et al. 2012). The urokinase-type plasminogen activator receptor (uPAR) is linked to the caveolae organization. In UCB-derived EPCs, Cav1 depletion can cause the absence of full-length uPAR in the caveolae, which can abrogate EPC angiogenesis (Margheri et al. 2011). Taken together, Cav1 can promote EPC proliferation, migration, and angiogenesis. However, the impaired Cav1–eNOS complex reverses Cav1 effects on EPC biology.

As mentioned above, in addition to showing positive roles in SSCs, Cav1 also displays negative effects. The realization



**Fig. 2** The negative roles of Cav1 in SSCs and CSCs. Cav1 modulates relevant pathways to repress **a** self-renewal, differentiation, and proliferation in SSCs; **b** self-renewal, chemo-sensitivity, CSC formation in CSCs

of these influences mostly depends on the Cav1-related signaling pathway (Figs. 1 and 2).

## Cav1 and cancer stem cells

### Breast cancer stem cells

Breast cancer is the most frequently diagnosed malignancy and the second leading cause of cancer-related death among female populations (Siegel et al. 2020). According to the protein expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), breast cancer can be divided into luminal A (ER+, PR+, HER2-), luminal B (ER+, PR+, HER2+), basal-like (triple-negative breast cancer) (ER-, PR-, HER2-), and HER2-enriched (ER-, PR-, HER2+) subtypes (Testa et al. 2020). Breast cancer stem cells (BCSCs), a subpopulation of cells within the breast tumor bulk, are more frequently observed in luminal and triple-negative breast cancer tissues than in HER2-enriched ones. BCSCs possess self-renewal properties and can repopulate the entire tumor through differentiation (Urueña et al. 2020). The mutations of breast tumor cells, mammary stem cells, mammary progenitor cells, or differentiated breast tissue cells can contribute to BCSC formation. Importantly, CD24, CD44, CD133, aldehyde dehydrogenase (ALDH), ATP-binding cassette subfamily G member 2 (ABCG2), and epithelial cell adhesion molecule

(EpCAM) are commonly considered to be surface markers to identify BCSCs (Bai et al. 2018). Cav1 levels are lower in BCSCs than those in normal breast stem cells. Cav1 up-regulation can reduce BCSC subpopulation. Cav1 can accelerate c-Myc ubiquitination and degradation via the proteasome pathway. When Cav1 is lost, c-Myc is up-regulated. c-Myc destroys mitochondrial respiration and elevates aerobic glycolysis activity, leading to promoted BCSC self-renewal and mammary tumor formation. As a result, Cav1 can attenuate c-Myc-induced BCSC metabolic reprogramming and self-renewal. And low Cav1 levels can predict poor overall survival in breast cancer patients (Wang et al. 2020b). In BCSCs sorted from MDA-MB-231 and MCF-7 cells, Cav1 can improve self-renewal but limit their differentiation into basal-like and luminal-like breast cancer cells. Additionally, Cav1 depletion can suppress the  $\beta$ -catenin/ABCG2 signaling pathway via activating glycogen synthase kinase 3 beta (GSK3 $\beta$ ) and repressing AKT phosphorylation. Removing Cav1 can inhibit drug efflux ability via  $\beta$ -catenin/ABCG2 signal, which can contribute to enhanced chemo-sensitivity in BCSCs (Wang et al. 2014a). Hsu et al. revealed that Cav1 knockdown can reduce  $\gamma$ -secretase activity. The interaction of Cav1 with  $\gamma$ -secretase can be potentiated by the interleukin-6/ILK signal, resulting in Notch-1 cleavage to release NICD into the cell nucleus. NICD can increase CSC-related marker (Hes1, c-Myc, Nestin, and ABCG2) expressions. Eventually, BCSC subpopulations are increased (Hsu et al. 2015). As mentioned above, Cav1 plays dual roles in BCSC

self-renewal and BCSC subpopulations. Cav1 acts as a suppressor for BCSC differentiation and chemo-sensitivity.

### Lung cancer stem cells

Lung cancer is the most common malignancy around the world and is histologically classified as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Olbromski et al. 2020). Increasing evidence reported that lung CSCs can arise from differentiated lung tissue cells, normal lung stem cells, or lung progenitor cells. And lung CSCs can form tumorspheres and possess multipotent differentiation and tumorigenic potential (Rivera et al. 2011). Recently, several biomarkers can be used to label lung CSCs for further experiments, such as CD44, CD24, CD133, ABCG2, and ALDH (Wang et al. 2014b). Cav1 is strongly up-regulated under ciprofloxacin stimuli in lung CSC populations. Activated Cav1 can phosphorylate ERK and AKT to increase CSC marker (CD44, CD133, ABCG2, and ALDH) expressions. Activated Cav1 finally promotes the induction of lung CSCs (Phiboonchaiyanan et al. 2016). Carbon nanotubes are nanomaterials that are known to be attributed to inflammation, fibrosis, and cancer under certain conditions (Dong and Ma 2019). Cav1 expression is increased in lung CSCs induced by the exposure of chronic single-walled carbon nanotubes. Cav1 can promote lung CSC induction via reducing p53 (Luanpitpong et al. 2014). One study reported that Cav1 can be up-regulated by NO. Increased Cav1 can stimulate aggressive behaviors of lung CSCs, including migration, colony-forming activity, and resistance to anoikis (Yongsanguanchai et al. 2015). When NO is absent, Cav1 down-regulates Oct4 expression through ubiquitin-proteasomal degradation, resulting in diminishing CSC formation. In the existence of NO, the phosphorylation of Cav1 on the tyrosine14 is induced by the NO/AKT signal, which can facilitate Oct4 dissociation from the Cav1-Oct4 degradation complex. Oct4 accumulation in the cell nucleus increases stemness-related gene expressions. Ultimately, lung CSC formation is enhanced (Maiuthed et al. 2018). Taken together, in response to certain conditions, Cav1 enhances or reduces lung CSC formation. And the Cav1 phosphorylation on tyrosine 14 can inhibit the negative effects of Cav1 on lung CSC formation.

### Liver cancer stem cells

Liver cancer, a malignant tumor with high incidence and mortality, can be divided into primary liver cancer (i.e., hepatocellular carcinoma (HCC, major type), liver angiosarcoma, and hepatoblastoma) and secondary liver cancer (Liu et al. 2020a). Liver CSCs are a subpopulation of cancer cells within liver cancer. On the one hand, liver CSCs can

promote tumor growth in primary liver cancers. On the other hand, liver CSCs can also enhance distant metastasis, which can cause liver cancer recurrence (Fan et al. 2011). MicroRNAs (miRNAs), a class of small non-coding RNAs with 18–25 nucleotides in length, can bind to mRNA 3' untranslated regions (3'UTRs) of their targets and reduce target gene expressions (de Sousa et al. 2019). Cav1 is increased in liver CSCs derived from primary HCC patients. MiR-124 is down-regulated in liver CSCs and can suppress liver CSC expansion. As a target miR-124, Cav1 can be inhibited by miR-124. In the presence of up-regulated miR-124, over-expressed Cav1 can suppress miR-124 effects on liver CSCs and promote liver CSC self-renewal and tumorigenic ability (Feng et al. 2020). As mentioned above, it can be seen that Cav1 can be repressed by miRNAs. And Cav1 serves as a promoter of liver CSC properties.

### Prostate cancer stem cells

Prostate cancer (PCa), the second-most common cancer and the sixth in cancer mortality among men globally (Bray et al. 2018), develops from the prostate gland due to many risk factors (e.g., age, high-fat diet, family history, and obesity) (Kaler et al. 2020). Prostate CSCs can come from normal prostate stem cells, differentiated prostate tissue cells, or PCa cells. Further, prostate CSCs are responsible for prostate tumor initiation, metastasis, colonization, and therapeutic resistance (Qin et al. 2017). Cav1 mRNA and protein expression levels are elevated in prostate CSCs. Exogenous Cav1 protein can stimulate prostate sphere formation. Additionally, Cav1 can be delivered into PCa cells by tumor-derived exosomes. Exosomal Cav1 can promote prostate CSC formation via activating the nuclear factor kappa B (NF- $\kappa$ B) signaling pathway (Lin et al. 2019). Altogether, exosomal Cav1 can regulate the cell–cell communication between PCa cells and prostate CSCs. Cav1 plays a positive role in prostate CSC formation.

As mentioned above, Cav1 serves as a promoter or inhibitor in CSC self-renewal and CSC formation (Figs. 1 and 2). Cav1 can improve CSC aggressive behaviors (Fig. 1) and suppress chemo-sensitivity (Fig. 2).

### Cav1 and tumor-initiating cells

TICs can exist in various solid cancers, like breast, colon, liver, lung, pancreas, prostate, etc. Similar to ESCs and HSCs, TICs possess the capacity to survive under the stimuli of genotoxic stress and injury. TICs can also self-renew and produce differentiated tumor cells (Mathews et al. 2011). It is said that the cell of origin is the normal cell with the first cancer-promoting mutations. And the cell of origin is distinct from the CSC. While the TIC can be referred to as

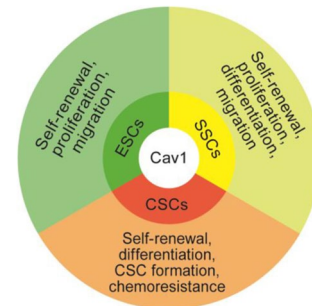


the cell of origin (Visvader 2011). The tumor transplantation assay and lineage-tracing assay are commonly used to identify CSCs and determine the cell of origin, respectively (Rycaj and Tang 2015). It is proved that CSCs can derive from TICs. TICs and CSCs have distinct markers. TICs are related to tumor initiation. CSCs are responsible for tumor maintenance and tumor growth (Chatterji et al. 2018). Pancreatic cancer is one of the most aggressive malignancies with a poor prognosis and a low five-year survival rate despite decades of unremitting efforts. Among pancreatic cancer cases, pancreatic ductal adenocarcinoma accounts for more than 90% (Paternoster and Falasca 2020). Characterized by the capacity to self-renew, differentiate and form colonies, pancreatic TICs can be separated from pancreatic cancer tissues and cell lines based on the expression of surface markers CD44, CD24, CD133, and EpCAM (Cabarcas et al. 2013; Shimizu et al. 2013). Cav1 is higher in CD133-positive pancreatic TICs compared with human pancreatic cancer cell lines. Cav1 depletion abolishes the activation of FAK and NF- $\kappa$ B to suppress the invasion of pancreatic TICs. Besides, diminishing Cav1 reduces drug transporter (ABCG2 and ATP-binding cassette subfamily C member 4 (ABCC4)) activity and therefore destroys chemo-resistance in pancreatic TICs. Additionally, high Cav1 levels can also indicate poor survival in pancreatic cancer patients (Gupta et al. 2018). Taken together, Cav1 plays a positive role in pancreatic TIC invasion and drug resistance (Fig. 1).

## Discussion and conclusion

Both normal stem cells and CSCs possess two basic stemness signatures (self-renewal and differentiation) and use common stemness-associated signaling pathways. Normal stem cells are essential for tissue repair and regeneration. CSCs are related to tumor initiation, metastasis, and therapy resistance. Cav1, a scaffolding protein in the caveolae, can regulate cell lipid transport, cell migration, cell proliferation, cell signal transduction, etc. Recently, the rational design of therapies based on the Cav1-stem cell axis for human diseases has attracted widespread attention. In this review, we have collected evidence to reveal the involvement of Cav1 in stem cells (Fig. 3). We hope that this review will provide new sights for more clinical therapies, thereby allowing us to treat human diseases more effectively.

In the current review, we discussed how Cav1 can exert positive or negative roles in stem cells (Tables 1 and 2). In normal stem cells, Cav1 can play dual roles in HSC self-renewal and senescence (Bai et al. 2014, 2020), MSC neuronal differentiation (Wang et al. 2013; Du et al. 2011), and EPC proliferation (Tan et al. 2012; Cao et al. 2012). Cav1 displays a positive role in ESCs (migration (Park and Han 2009; Park et al. 2012), proliferation (Park et al.



**Fig. 3** The involvement of Cav1 in stem cells. Cav1 involves self-renewal, proliferation, and migration in ESCs. And Cav1 implicates self-renewal, proliferation, differentiation, and migration in SSCs. Moreover, Cav1 also influences self-renewal, differentiation, CSC formation, and chemo-resistance in CSCs

2009, 2011; Lee et al. 2009, 2011) and self-renewal (Lee et al. 2010; Sasaki et al. 2011)), NSC neural differentiation (Zhao et al. 2017), ADSC hepatic differentiation (Guan et al. 2016), EpiSC proliferation (Yang et al. 2019b, c), and NPC astroglial differentiation (Li et al. 2011a). Cav1 exhibits a negative role in MSC osteogenic differentiation (Baker et al. 2012, 2015), MSC cardiomyocyte differentiation (Chen et al. 2017), MSC adipogenic differentiation (Park et al. 2005), NSC proliferation (Peffer et al. 2014; Jasmin et al. 2009), MaSC populations (Sotgia et al. 2005), ISC proliferation (Li et al. 2005), NPC oligodendroglial (Li et al. 2011b) and neuronal differentiation (Li et al. 2011c, 2020). In response to high glucose, Cav1 promotes ESC proliferation (Lee et al. 2011), however, inhibits EPC proliferation, migration, and angiogenesis (Cao et al. 2012). F92A-Cav1 can increase NO production to improve MSC endothelial differentiation (Bandara et al. 2019) and ADSC osteogenesis (Bandara et al. 2016). In CSCs, Cav1 exerts dual roles in BCSC self-renewal (Wang et al. 2014a, 2020b), lung CSC formation (Phiboonchaiyanan et al. 2016; Maiuthed et al. 2018). Cav1 plays a positive role in self-renewal, CSC formation, and cell invasion in liver CSCs (Feng et al. 2020), prostate CSCs (Lin et al. 2019), and pancreatic TICs (Gupta et al. 2018), respectively. Furthermore, normal stem cells and CSCs can share stemness effectors, for example, the Oct4 (Lee et al. 2010; Maiuthed et al. 2018), and use the same stem cell-related signals, like Notch (Wang et al. 2013; Li et al. 2011a; Hsu et al. 2015), AKT (Lee et al. 2009; Park and Han 2009; Park et al. 2011; Baker et al. 2015; Phiboonchaiyanan et al. 2016) and NO (Cao et al. 2012; Yongsanguanchai et al. 2015; Maiuthed et al. 2018) signals. Interestingly, in our study, we found that the mutation of phenylalanine to alanine at position 92 in Cav1 suppresses Cav1 repression on ADSC osteogenesis differentiation (Bandara et al. 2016). In lung CSCs, the Cav1 phosphorylation on tyrosine 14 inhibits Cav1 suppression on CSC formation (Maiuthed et al. 2018). Taken together, it can be seen that the effects of Cav1 on stem

**Table 1** The roles of Cav1 in normal stem cells

Stem cells	Effects	Signaling cascades	Role	References
ESCs	Self-renewal	Cav1 → LIF/STAT3 signal transduction↑	Promoter	Sasaki et al. (2011)
	Proliferation	E <sub>2</sub> → PI3K/AKT pathway↑, ERK1/2 pathway↑ → Cav1↑	Promoter	Park et al. (2009)
	Proliferation	Galectin-1 → Src↑ → Cav1↑ → AKT↑, mTOR↑	Promoter	Lee et al. (2009)
	Proliferation	High glucose → p38 MAPK↑ → Cav1↑ → β1 integrin/FAK/PIP complex signal↑ → F-actin reorganization↑	Promoter	Lee et al. (2011)
	Proliferation, migration	EGF → Src↑ → Cav1↑ → PI3K/AKT/ERK1/2/MMP-2 pathway↑	Promoter	Park and Han (2009)
	Proliferation	Fibronectin → Src/FAK signal↑ → Cav1↑ → ROCK↑, RhoA↑ → PI3K/AKT signal↑, ERK1/2 signal↑	Promoter	Park et al. (2011)
	Migration	Fibronectin → Cav1↑ → RhoA/ROCK/ERK1/2 signal↑ → MMP-2↑, F-actin↑	Promoter	Park et al. (2012)
HSCs	Self-renewal	PTRF↑ → Cav1↑	Suppressor	Bai et al. (2020)
MSCs	Motility	Galectin-1 → c-Src↑ → Cav1↑ → Smad2/3↓ → collagen III and V↓	Promoter	Yun et al. (2014)
	Differentiation	Cav1↑ → PI3K/AKT signal↓	Suppressor	Baker et al. (2015)
	Differentiation	Cav1↓ → STAT3 pathway↓	Suppressor	Chen et al. (2017)
	Differentiation	Cav1↑ → insulin signaling↓, PPARγ2↓	Suppressor	Park et al. (2005)
	Differentiation	Cav1↓ → Notch pathway↓	Suppressor	Wang et al. (2013)
	Wound healing	TNF-α → Fas↑, Fap-1↑ → Cav1 membrane translocation↑ → IL-1RA secretion↑	Promoter	Kou et al. (2018)
	NSCs	Migration, differentiation	Cav1↓ → VEGF↓	Promoter
ADSCs	Differentiation	Cav1↓ → MAPK pathway↓ → hepatic marker↓	Promoter	Guan et al. (2016)
	Differentiation	F92A-Cav1, eNOS → NO↑ → Wnt3a/β-catenin pathway↑	Promoter	Bandara et al. (2016)
EpiSCs	Proliferation, wound healing	Curcumin → Cav1↑	Promoter	Yang et al. (2019c)
MaSCs	Cell populations	Cav1↓ → β-catenin↑	Suppressor	Sotgia et al. (2005)
ISCs	Proliferation	Cav1↓ → Wnt/β-catenin pathway↑	Suppressor	Li et al. (2005)
NPCs	Differentiation	Cav1 → NICD↑ → Hes1↑	Promoter	Li et al. (2011a)
	Differentiation	Cav1 → β-catenin↑	Suppressor	Li et al. (2011b)
	Differentiation	Cav1↑ → VEGF signal↓	Suppressor	Li et al. (2011c)
	Differentiation	Cav1 → NeuroD1↓, VEGF signal↓	Suppressor	Li et al. (2020)
EPCs	Proliferation	Estrogen → lysosomal degradation pathway↓ → Cav1↑	Promoter	Tan et al. (2012)
	Proliferation, migration	high glucose → Cav1↑, eNOS↓ → NO↓	Suppressor	Cao et al. (2012)
	Angiogenesis	Cav1↓ → uPAR absence↑	Promoter	Margheri et al. (2011)

ESCs embryonic stem cells, Cav1 Caveolin1, LIF leukemia inhibitory factor, STAT3 signal transducer and activator of transcription 3, E<sub>2</sub> estradiol-17β, PI3K phosphatidylinositol-3-kinase, AKT protein kinase B, ERK extracellular signal-regulated kinase, mTOR mammalian target of rapamycin, MAPK mitogen-activated protein kinase, FAK focal adhesion kinase, PIP complex PINCH1/2, integrin-linked kinase (ILK), and α-parvin, F-actin filamentous-actin, EGF epidermal growth factor, MMP-2 matrix metalloproteinase-2, ROCK Rho-associated protein kinase, HSCs hematopoietic stem cells, PTRF polymerase I and transcript release factor, MSCs mesenchymal stem cells, PPARγ2 peroxisome proliferator-activated receptor gamma 2, TNF-α tumor necrosis factor-alpha, Fap-1 Fas-associated phosphatase-1, IL-1RA interleukin-1 receptor antagonist, VEGF vascular endothelial growth factor, NO nitric oxide, NSCs neural stem cells, ADSCs adipose-derived stem cells, MAPK mitogen-activated protein kinase, eNOS endothelial nitric oxide synthase, EpiSCs epidermal stem cells, MaSCs mammary stem cells, ISCs intestinal stem cells, NPCs neural progenitor cells, NICD Notch intracellular domain, Hes1 hairy enhancer of split 1, EPCs endothelial progenitor cells, uPAR urokinase-type plasminogen activator receptor

cells mostly depend on cell types, related signal transduction (Figs. 1 and 2; Tables 1 and 2), Cav1 phosphorylation, and Cav1 mutation (Williams and Lisanti 2005).

Interestingly, there is evidence that Cav1 has dual roles in the development of some cancers. At early tumor stages, Cav1 acts as a tumor suppressor. While in the late stages of cancer, Cav1 serves as a tumor promoter (Simón et al. 2020). In breast cancer cells, Cav1 can activate Rab5 by recruiting p85α, subsequently, to increase Rac1 activity. The Cav1/Rab5/Rac1 signal finally potentiates cell migration

and cell invasion (Díaz et al. 2014). In BT-474 cells, Cav1 promotes cell proliferation via activating the ERK1/2 pathway and increasing the expression of cell cycle-associated proteins (Wang et al. 2014c). In MCF-7 cells, the interaction of Cav1 with CD95 can be enhanced by Antarctic krill docosahexaenoic acid, which can repress cell migration and cell invasion (Zheng et al. 2018). Moreover, increased Cav1 represses Ca<sup>2+</sup>-activated potassium channel, resulting in suppressing cell proliferation and invasion in breast cancer (Du et al. 2014). In lung cancer, Cav1 up-regulates

**Table 2** The roles of Cav1 in CSCs

CSCs	Effects	Signaling cascades	Role	References
Breast	Self-renewal	Cav1↓→c-Myc↑→mitochondrial respiration↓, aerobic glycolysis↑	Suppressor	Wang et al. (2020b)
	Chemo-sensitivity	Cav1↓→GSK3β↑, AKT↓→β-catenin/ABCG2 signal↓→drug efflux ability↓	Suppressor	Wang et al. (2014a)
	CSC subpopulation	Interleukin-6/ILK signal→Cav1-γ-secretase interaction↑→NICD↑→CSC marker↑	Promoter	Hsu et al. (2015)
Lung	CSC induction	Ciprofloxacin→Cav1↑→ERK↑, AKT↑→CSC marker↑	Promoter	Phiboonchaiyanan et al. (2016)
	CSC induction	Cav1→p53↓	Promoter	Luanpitpong et al. (2014)
	Aggressive behaviors	NO→Cav1↑	Promoter	Yongsanguanchai et al. (2015)
	CSC formation	NO→AKT↑→Cav1 phosphorylation↑→Oct4↑	Suppressor	Maiuthed et al. (2018)
Liver	Self-renewal	MiR-124→Cav1↓	Promoter	Feng et al. (2020)
Prostate	CSC formation	Cav1→NF-κB pathway↑	Promoter	Lin et al. (2019)

CSCs cancer stem cells, *Cav1* Caveolin1, *GSK3β* glycogen synthase kinase 3 beta, *AKT* protein kinase B, *ABCG2* ATP-binding cassette subfamily G member 2, *ILK* integrin-linked kinase, *NICD* Notch intracellular domain, *ERK* extracellular signal-regulated kinase, *Oct4* octamer-binding transcription factor 4, *NO* nitric oxide, *miR* microRNA, *NF-κB* nuclear factor kappa B

Snail protein and mRNA expressions, which can accelerate NSCLC brain metastasis (Kim et al. 2019). Volonte et al. indicated that Cav1 can enhance oncogenic K-Ras-induced lung cancer cell senescence. And low Cav1 can predict poor survival of lung cancer patients (Volonte et al. 2018). It is suggested that the communication between cells and their microenvironment is essential for normal tissue homeostasis and tumor growth (Quail and Joyce 2013). In recent years, the roles of the tumor microenvironment in cancer development have received a lot of attention. The tumor microenvironment encompasses immune cells, blood vessels, extracellular matrix, fibroblasts, lymphocytes, inflammatory cells, and signaling molecules (Spill et al. 2016; Prete et al. 2017). Cancer-associated fibroblasts (CAFs) are the most abundant stromal cells in the tumor microenvironment. CAFs repress cancer cell apoptosis and promote tumor cell proliferation, tumor metastasis, and tumor angiogenesis (Jang and Beningo 2019; Chen and Che 2014). It is demonstrated that Cav1 down-regulation stimulates the transformation of fibroblasts into CAFs (Martinez-Outschoorn et al. 2010). Shi et al. demonstrated that Cav1 depletion in CAFs increases the expression and secretion of stromal cell-derived factor-1, EGF, and fibroblast-specific protein-1, and all of them enhance breast cancer cell proliferation (Shi et al. 2016). And down-regulation and up-regulation of Cav1 in CAFs can predict poor (Ren et al. 2014) and good (Shan-Wei et al. 2012) outcomes in breast cancer patients, respectively. In summary, it is suggested that decreased stromal Cav1 is always beneficial for tumor progression (Chen and Che 2014; Martinez-Outschoorn et al. 2010; Shi et al. 2016; Ren et al. 2014; Shan-Wei et al. 2012).

In the current review, we found that treadmill exercise increases Cav1 and VEGF levels in NSCs, which can

improve neurological recovery of the brain after ischemic injury (Zhao et al. 2017). Curcumin, the traditional Chinese medicine used to treat skin diseases, can elevate Cav1 expression in EpiSCs. Inhibiting Cav1 in the curcumin-treated EpiSCs can significantly repress wound healing (Yang et al. 2019c). In various cancer types, Cav1 is related to chemo-drug resistance. Taking lung cancer as an example, it is reported that Cav1 attenuation reduces NSCLC sensitivity to albumin-bound paclitaxel (Chatterjee et al. 2017). Liu et al. suggested that Cav1 silence increases lung cancer sensitivity to cisplatin (Liu et al. 2020b). Furthermore, suppressing Cav1 can sensitize BCSCs and pancreatic TICs to epirubicin (Wang et al. 2014a) and paclitaxel (Gupta et al. 2018), respectively. These results indicate potential treatment strategies associated with the combination of Cav1 and stem cells for ischemic injury, wound healing, and cancer drug resistance. Increasing evidence suggests that nano-drugs are widely used for anti-tumor drug delivery, gene therapy, and imaging diagnosis. Cav1-mediated endocytosis pathway can increase the entrance of nano-drugs into tumor cells and promote antitumor response. The strategies for Cav1 targeting nano-drugs will be a new way to achieve antitumor efficacy (Yang et al. 2021). Presently, great efforts have been made in stem cell-based therapies for human tissue repair and cancer treatment resistance. As mentioned above, Cav1 is widely involved in stem cell biology. Targeting Cav1 will strongly influence stem cell properties, which might provide new insights to more effectively treat human tissue repair and cancer drug resistance. However, these studies previously mentioned are performed mainly on stem cells, and studies on tissues are still lacking. Therefore, further explorations in these

microenvironments are required to elucidate the roles of Cav1 in stem cells more completely.

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**Code availability** Not applicable.

## Declarations

**Conflict of interest** The authors declare no conflict of interest.

**Ethical approval** Not applicable.

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