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Targeting cancer stem cells in solid tumors by vitamin D

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Abstract

Cancer stem cells (CSCs) are a small subset of cells that may be responsible for initiation, progression and recurrence of tumors. Recent studies have demonstrated that CSCs are highly tumorigenic and resistant to conventional chemotherapies, making them a promising target for the development of preventive/therapeutic agents. A single or combination of various markers, such as CD44, EpCAM, CD49f, CD133, CXCR4, ALDH-1 and CD24, were utilized to isolate CSCs fromvarious types of human cancers. Notch, Hedgehog, Wnt, and TGF-β signalingregulate self-renewal and differentiation of normal stem cells andare aberrantly activated in CSCs. In addition, many studies have demonstrated that these stem cell-associated signaling pathways are required for the maintenance of CSCs in differentmalignancies, including breast, colorectal, prostate and pancreatic cancers. Accumulating evidence hasshowninhibitory effects of vitamin D and its analogs on the cancer stem cell signaling pathways, suggesting vitamin D as a potential preventive/therapeutic agent against CSCs.In this review, we summarize recent findings about the roles of Notch, Hedgehog, Wnt, and TGF-β signaling in CSCs as well as the effects of vitamin D on these stem cell signaling pathways.

Keywords

Vitamin D; Cancer stem cell; Hedgehog; Notch; TGF-β; Wnt

1 Introduction

The observation of intratumoral heterogeneity has led to a hypothesis that a small subset of cells might be responsible for the initiation, progression and recurrence of tumors [1]. These cells have been called cancer stem cells (CSCs, also known as tumor-initiating cells) since they exhibit stem cell-like characteristics [1]. The first evidence of CSCs was demonstrated

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Conflicts of interest

The authors declare that they have no conflicts of interest.

in acute myeloid leukemia [2]. Only a small fraction of primary leukemia cells was capable of initiating and sustaining leukemia when transplanted into mice [2,3]. Since then, CSCs have been isolated from many solid cancers, such as those of the breast, brain, prostate, colon and rectum, pancreas, and liver (reviewed in [4]). These cells also show strong capability to initiate tumors *in vivo* [5]. More importantly, CSCs exhibit resistance to conventional chemo- and radiotherapy, and are enriched in residual tumors after chemotherapy [5]. Many studies have demonstrated that CSCs are present in recurring tumors and distant metastases of various cancers, including those of the breast, pancreas, and colon [6,7]. Therefore, CSCs may be used as a potential target for therapeutic drug development to reduce cancer recurrence or metastasis and achieve prolonged survival of cancer patients [7]. Many new experimental agents, such as Notch and Hedgehog inhibitors, are being developed to inhibit CSCs [6,8]. Several lines of evidence have demonstrated that vitamin D plays an important role in the regulation of stem cells of the prostate and the skin [9-11]. Moreover, vitamin D is a well known inducer of the terminal differentiation of human myeloid leukemia cells into monocytes and macrophages [12], possibly via mechanisms of regulating leukemic cancer stem cells/progenitors. Recently, vitamin D and its analogs were shown to reduce the number of CSCs in breast cancer [13], further supporting their potential as therapeutic agents. In this review, we summarize recent findings on the CSC markers, CSC signaling pathways and the effects of vitamin D on the CSC signaling.

1.1 Identification of cancer stem cells

Isolation of CSCs from total cancer cell population is the first and most critical step to characterize CSCs [4,5]. Multiple markers that have been utilized to identify CSCs in various types of solid tumors [4] are summarized in Table 1. CD44 is a receptor for extracellular matrix components, including hyaluronan and osteopontin [14]. High CD44 protein levels have been used as a key characteristic of CSCs in solid tumors with epithelial origin, such as breast, colon, prostate and pancreas [14]. Expression of an epithelial cell adhesion molecule (EpCAM, also known as an epithelial specific antigen) was utilized as a cell surface marker in a combination with CD44 to further identify specific CSCs [4,15]. CD49f, also known as integrin α6, is a receptor for laminin, and its high expression has been a good indicator for CSCs in breast, colon and brain cancers [16]. A glycoprotein CD133, also known as Prominin 1 (PROM1), is expressed in stem cells from neural, epithelial, endothelial and hematopoietic tissues. A high expression of CD133 is a surface marker for CSCs of breast, brain, lung, colon, pancreas and liver cancers [4]. C-X-C chemokine receptor type 4 (CXCR4), a specific receptor for chemokine stromal cell-derived factor 1 (SDF-1), has been used as an additional marker in isolation of CD133-positive cancer cells to further enrich highly metastatic CSCs from breast, prostate and pancreatic cancers [4]. Aldehyde dehydrogenease-1 (ALDH-1) is an enzyme oxidizing cellular aldehydes, and its high activity has been a useful CSC marker for breast and pancreatic cancers [4,17]. CD24 is a heavily glycosylated adhesion molecule and the only known ligand for P-selectin. A low or no expression of CD24 in combination with a high expression of CD44 has been utilized as a CSC marker in breast and prostate cancers [4]. However, in pancreatic cancer, CD44-positive cells also expressing CD24 have been isolated as CSCs [4] indicating that CSCs differ depending on the types of cancer. Many studies looking for additional stem cell

markers are in progress with the goal to isolate defined CSCs from different types of cancers [6].

1.2 Stem cell-associated pathways in cancer stem cells

The two critical features of normal stem cells–self-renewal and differentiation into phenotypically diverse cells–are also required for the maintenance of CSCs in human tumors [18]. The stem cell-associated signaling pathways, such as Notch, Hedgehog, Wnt and TGF-β, regulate self-renewal and differentiation of normal stem cells as well as CSCs [8,19]. The process of epithelial-mesenchymal transition (EMT), characterized by a loss of cellular polarity and cell-cell interaction and a gain of mesenchymal properties, has been closely associated with CSCs in solid tumors [20]. Aberrant activation of the stem cell-associated signaling pathways in cancer cells induces EMT and causes cancer cells to acquire phenotypes of CSCs [21]. Therefore, the stem cell-associated signaling pathways–Notch, Hedgehog, Wnt and TGF-β–have been considered as novel targets against CSCs in human tumors [8,21].

1.3 Notch signaling pathway

The evolutionally conserved Notch signaling pathway plays a key role in deciding cellular fate during embryogenesis and in maintenance of stem cells in adult tissues [22]. Four Notch receptors (Notch1, Notch2, Notch3 and Notch4) and five ligands (JAG1, JAG2, DLL1, DLL3 and DLL4) have been discovered in mammals [22]. Upon the interaction with ligands from adjacent cells, Notch receptors undergo a series of enzymatic cleavages by a disintegrin and metalloproteinase (ADAM) and γ-secretase to produce an active intracellular domain of Notch (NICD, also known as cleaved Notch) [22]. NICD translocates to the nucleus and regulates specific target genes such as c-Myc HES and HEY [22]. Aberrant activation of Notch signaling by elevated expression of Notch receptors and ligands has been shown in various human cancers [22]. Moreover, recent studies demonstrated that Notch signaling plays an important role in self-renewal and maintenance of CSCs in breast, lung, brain, pancreatic, and ovarian cancers [23-27]. Inhibition of Notch signaling by antibodies against the Notch receptors or by γ-secretase inhibitors decreased the number of CSCs and their tumorigenic potential in preclinical models of breast and brain cancers [28-31].

1.4 Hedgehog signaling pathway

The Hedgehog signaling pathway controls stem cell maintenance during embryonic development [32]. Upon the activation by ligands–Sonic (SHH), Desert (DHH) and Indian Hedgehog (IHH)–Hedgehog receptor (Patched 1, PTCH1) releases repression on Smoothened (SMO). Then, the activated SMO initiates a signaling cascade leading to the target gene regulation by the GLI family of transcription factors [32]. The high activity of Hedgehog signaling has been found in various human cancers [33]. Hedgehog inhibitors showed anti-tumor activity in clinical studies of advanced solid tumors, such as breast cancer, medulloblastoma and basal cell carcinoma [34-36]. Activated Hedgehog signaling has been reported in CSCs of many human tumors, including brain, breast and pancreatic cancers [37-39]. Hedgehog inhibitors, such as cyclopamine, suppressed CSCs in glioblastoma and pancreatic cancer [40,41].

1.5 Wnt signaling pathway

The Wnt signaling pathway determines the cell fate during embryogenesis and regulates tissue self-renewal in adults [42]. The binding of Wnt proteins to a receptor complex containing Frizzled (FZD)/low-density lipoprotein receptor related protein (LRP) initiates the canonical and non-canonical signaling cascades [42]. The activation of canonical Wnt signaling pathway leads to accumulation of β-catenin in the nucleus and subsequent transcriptional regulation of target genes [42,43]. The non-canonical Wnt signaling pathway is β-catenin independent and regulates movement and polarity of embryonic cells; however, little is known about its role in human cancer [43]. The critical role of canonical Wnt signaling in human tumorigenesis has been well-recognized in colorectal cancer with a majority of tumors harboring activating mutations in the Wnt signaling pathway [42]. In addition, canonical Wnt signaling seems to maintain CSCs by regulating their proliferation and self-renewal during intestinal and prostate tumor development [44-46]. A recent study demonstrated that an antibody targeting FZD receptors reduced tumor growth and the number of CSCs in breast and pancreatic cancer cells [47]. A phase 1 clinical study using this antibody in patients with solid tumors is ongoing [48].

1.6 TGF-β signaling pathway

The TGF-β signaling pathway is a complex pathway with 42 known TGF-β superfamily ligands, such as TGF-βs, activins, Nodal and bone morphogenetic proteins (BMPs) [49]. Depending on the ligand and its downstream signaling mediators, TGF-β signaling can be divided into two signaling cascades, TGF-β/Activin/Nodal and BMP, which activate downstream mediators SMAD2/3 and SMAD1/5/8, respectively [50]. TGF-β signaling regulates a variety of cellular processes including differentiation, proliferation, migration and cell death both in adult organisms and developing embryos [50]. In human tumors, TGF-β signaling has been shown to have either a tumor-suppressing or tumor-promoting function depending upon the cellular context and the type of ligand [50]. Recent studies have also demonstrated diverse effects of TGF-β signaling on CSCs [50]. TGF-β signaling via activated TGF-β/Activin strongly induces EMT in many cancer cells, promoting maintenance of CSCs and tumor metastasis [51]. TGF-β signaling via activated Activin/Nodal is required for self-renewal and tumorigenicity of CSCs in pancreatic cancer [52]. In contrast, BMP signaling antagonizes TGF-β-induced EMT in prostate cancer cells and represses their bone metastasis [53]. A BMP treatment strongly reduced the number of CSCs in breast cancer and inhibited bone metastasis in an animal model [54].

2 Regulation of stem cell signaling by vitamin D in solid tumors

Crosstalk between vitamin D and Notch signaling was first demonstrated in osteoblastic cells, where 1α,25-dihydroxyvitamin D_3 ($1\alpha,25(OH)_2D_3$) cooperated with HES1, a downstream effector of Notch signaling, to induce osteopontin expression [55]. In contrast, $1\alpha,25(OH)_2D_3$ treatment significantly reduced *NOTCH1*, *JAG1*, *JAG2* and *DLL1* mRNA levels in prostate epithelial cells, indicating an inhibitory effect of vitamin D on Notch signaling [56]. We have also found that treatment of breast cancer cells with $1\alpha,25(OH)_2D_3$ or its analogs markedly decreased mRNA levels of the Notch ligands and resulted in the inhibition of Notch1 signaling. Moreover, the inhibition of Notch signaling by vitamin D

analogs also resulted in the reduction of CSCs (unpublished data). However, 1α,25(OH)$_2$D$_3$ did not inhibit the Notch signaling in brain cancer cell lines and did not exhibit anti-proliferative effects in these cells [57]. These data suggest that effects of vitamin D on Notch signaling may differ based on tissue and cellular context.

Vitamin D$_3$ or 3β-hydroxysteroid (pro-) vitamin D$_3$ inhibits activation of the Hedgehog signaling by directly binding to SMO in zebrafish, yeast, and mouse fibroblast cells [58]. The mRNA levels of Hedgehog signaling molecules, *Shh*, *Gli1* and *Gli2*, were increased in chemically induced epidermal tumors of mice with knocked-out vitamin D receptor (VDR) when compared to those in tumors of wild-type mice [59]. The expression of the Hedgehog molecules was inhibited by 1α,25(OH)$_2$D$_3$ in mouse skin cells in a VDR-dependent manner [60]. In basal cell carcinoma, vitamin D$_3$ or 1α,25(OH)$_2$D$_3$ inhibited Hedgehog signaling by repressing GLI1 mRNA and exerted anti-proliferative effects *in vitro* and *in vivo* [61,62]. Vitamin D$_3$ (cholecalciferol) also inhibited Hedgehog signaling by repressing GLI2 expression and tumor growth of renal carcinoma xenografts [63].

Vitamin D and its analogs inhibit Wnt signaling by several mechanisms in cancer cells [64]. In the presence of 1α,25(OH)$_2$D$_3$, VDR can directly bind to β-catenin, competing with a T cell transcription factor (TCF)-4 and repressing the β-catenin/TCF-4 transcriptional activity [65-67]. 1α,25(OH)$_2$D$_3$ suppresses Wnt signaling by inducing the expression of DKK-1, which antagonizes Wnt signaling by binding to LRP5/6 [68]. In colon cancer cells, 1α, 25(OH)$_2$D$_3$ inhibited Wnt signaling by the induction of E-cadherin [65]. Treatment with 1α, 25(OH)$_2$D$_3$ or its analogs reduced tumor load in Apc$^{min/+}$ mice, an animal model of intestinal cancer with dysregulated Wnt signaling, by inducing E-cadherin expression and reducing nuclear β-catenin level [69,70]. In contrast to its effects in cancer cells, VDR was required for the activation of Wnt signaling in normal keratinocytes to form the hair follicle [9]. However, treatment with a vitamin D analog inhibited β-catenin induced-hair follicle tumors in mice [71], suggesting that the effects of vitamin D on Wnt signaling may differ in cancer cells where aberrant activation of β-catenin is sustained.

Vitamin D and the TGF-β superfamily signaling interact in a cellular context-dependent manner both in normal and malignant cells [72]. A recent genome-wide study demonstrated that a large number of genomic sites can be co-occupied by VDR and SMAD3. 1α, 25(OH)$_2$D$_3$ or its analog reduced the occupancy of SMAD3 on the target genes, blocking TGF-β1-mediated activation of hepatic stellate cells and the development of liver fibrosis [73]. 1α,25(OH)$_2$D$_3$ also inhibited TGF-β1-stimulated EMT and a pro-fibrotic phenotype of lung fibroblasts and epithelial cells [74]. In contrast, 1α,25(OH)$_2$D$_3$ or its analogs increased mRNA levels of BMP2 and BMP6, and activated the BMP signaling in normal and premalignant breast epithelial cells [75,76]. The expression of BMP6 mRNA was also significantly induced by 1α,25(OH)$_2$D$_3$ in prostatic epithelial and breast cancer cells [77].

Vitamin D seems to have opposite effects on stem cell signaling between normal and malignant cells. In many cases, vitamin D and its analogs exert inhibitory effects on the cancer stem cell signaling pathways, which may be due to aberrant and highly activated status of these signaling pathways in cancer cells. The diverse effects of vitamin D on the stem cell-associated signaling pathways suggest that vitamin D may regulate and target

CSCs. Some of the key vitamin D actions on stem cell signaling in cancer cells are summarized in Fig. 1.

3 Conclusion

Because of the importance of Notch, Hedgehog, Wnt and TGF-β in the maintenance of CSCs in human tumors, these signaling pathways are attractive as potential targets for the development of new anti-cancer agents. Vitamin D and its analogs have inhibitory effects on cancer stem cell signaling in various types of human cancer cells and may be promising therapeutic/preventive agents against CSCs. However, the effects of vitamin D on the stem cell signaling pathways vary depending on cell types and cellular contexts. Considering that vitamin D can differentially regulate a wide range of genes in normal and malignant cells, further investigations are required to better understand its cellular context-dependent effects on stem cell signaling.

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Glossary

CSC	Cancer stem cell
1α,25(OH)2D3	1α 25-dihydroxyvitamin D3
EpCAM	Epithelial cell adhesion molecule
PROM1	Prominin 1
CXCR4	C-X-C chemokine receptor type 4
SDF1	Stromal cell-derived factor 1
ALDH-1	Aldehyde dehydrogenase-1
EMT	Epithelial-mesenchymal transition
ADAM	A disintegrin and metalloproteinase
NICD	Intracellular domain of Notch
SHH	Sonic Hedgehog
DHH	Desert Hedgehog
IHH	Indian Hedgehog
PTCH1	Patched 1
SMO	Smoothened
FZD	Frizzled receptor
LRP	Low-density lipoprotein receptor-related protein

BMP	Bone morphogenetic protein
TCF4	T cell factor 4
VDR	Vitamin D receptor

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Highlights

- Provides a list of various markers of cancer stem cells (CSCs) from solid tumors.
- Reviews roles of stem cell signaling, Notch, Hedgehog, Wnt and TGF-β, in CSCs.
- Summarizes recent findings for the effects of Vitamin D on stem cell signaling.
- Suggests vitamin D and its analogs as potential agents against CSCs.

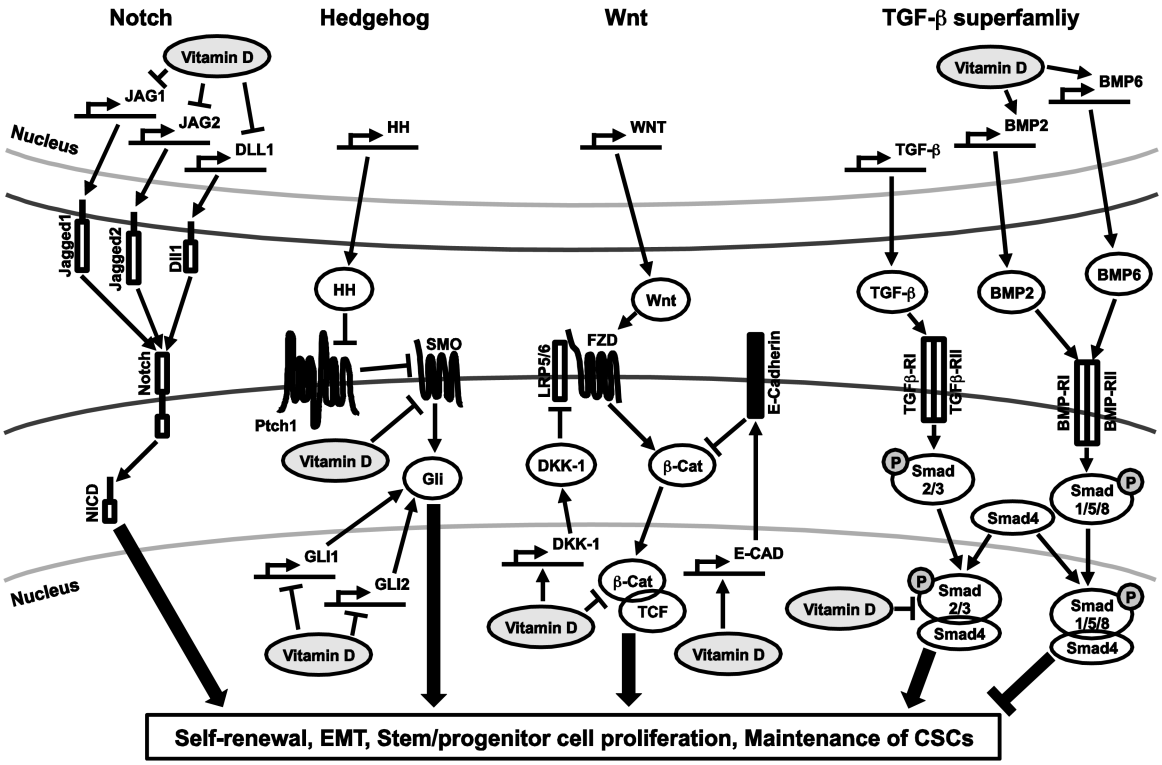

Fig. 1.

A schematic diagram depicting actions of vitamin D on the Notch, Hedgehog, Wnt and TGF-β superfamily signaling pathways. Main components of the Notch, Hedgehog, Wnt and TGF-β superfamily and their regulation by vitamin D are presented. Detailed explanation and related references can be found in the text. Full names of the abbreviations shown in the diagram are listed; JAG1, Jagged1; JAG2, Jagged2; DLL1, Delta-like protein 1; NICD, Intracellular domain of Notch; HH, Hedgehog; Ptch1, Patched1; SMO, Smoothened; LRP5/6, Low-density lipoprotein receptor-related protein 5/6; FZD, Frizzled; β-Cat β-Catenin; DKK-1, Dickkopf-related protein 1;TCF, T cell factor; E-cad, E-cadherin; BMP2, Bone morphogenetic protein 2; BMP6, Bone morphogenetic protein 6; TGFβ-RI, TGF-β receptor 1; TGFβ-RII, TGF-β receptor 2; BMP-RI, BMP receptor 1; BMP-RII, BMP receptor 2.gr1

Table 1

Cancer stem cell markers in different cancers.

Cancer Types	Cancer Stem Cell Markers	Associated Functions	Reference
Breast	$CD44^{+}/CD24^{-/low}$	Tumor Initiation	[78]
	$CD44^{+}/CD24^{-/low}/EpCAM^{+}$	Tumor Initiation, Drug Resistance	[79]
	$CD44^{+}/CD49^{high}/CD133^{+}$	Tumor Initiation	[80]
	$CD133^{+}$	Tumor Initiation, Drug Resistance	[81]
	$CD133^{+}/CXCR4^{+}$	Tumor Initiation, Tumor Metastasis	[82]
	$ALDH\text{-}1^{+}$	Tumor Initiation, Poor Prognosis	[83]
Colorectal	$CD133^{+}$	Tumor Initiation	[84,85]
	$EpCAM^{+}/CD44^{+}/CD166^{+}$	Tumor Initiation	[86]
	$EpCAM^{+}/CD44^{+}/ALDH1^{+}$	Tumor Initiation, Drug Resistance	[87]
	$CD44^{+}/ALDH\text{-}1^{+}$	Tumor Initiation	[88]
	$CD44^{+}/CD133^{+}/CD49f^{+}$	Tumor Initiation	[89]
Prostate	$CD44^{+}/\alpha2\β\ 1^{high}/CD133^{+}$	Tumor Initiation	[90]
	$CD44^{+}/CD24^{-}$	Tumor Initiation, Poor Prognosis	[91]
Brain	$CD133^{+}$	Tumor Initiation	[92,93]
	[a] $Integrin\ \alpha6^{+}$	Tumor Initiation	[94]
Pancreatic	$CD44^{+}/CD24^{+}/EpCAM^{+}$	Tumor Initiation	[95]
	$CD133^{+}/CXCR4^{+}$	Tumor Initiation, Tumor Metastasis	[96]
	$ALDH\text{-}1^{+}$	Tumor Initiation, Drug Resistance	[97,98]
Lung	$CD133^{+}$	Tumor Initiation, Drug Resistance	[99,100]
	$ALDH\text{-}1^{+}$	Tumor Initiation, Poor Prognosis	[101]
Liver	$CD133^{+}$	Tumor Initiation	[102,103]
	$CD90^{+}/CD44^{+}$	Tumor Initiation, Tumor Metastasis	[104]
Head and Neck	$CD44^{+}$	Tumor Initiation	[105]
	$ALDH\text{-}1^{+}$	Tumor Initiation	[106,107]

[a] Integrin α6 is also known as CD49f.