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REVIEW

Stem cell quiescence and its clinical relevance

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Abstract

Quiescent state has been observed in stem cells (SCs), including in adult SCs and in cancer SCs (CSCs). Quiescent status of SCs contributes to SC self-renewal and conduces to averting SC death from harsh external stimuli. In this review, we provide an overview of intrinsic mechanisms and extrinsic factors that regulate adult SC quiescence. The intrinsic mechanisms discussed here include the cell cycle, mitogenic signaling, Notch signaling, epigenetic modification, and metabolism and transcriptional regulation, while the extrinsic factors summarized here include microenvironment cells, extracellular factors, and immune response and inflammation in microenvironment. Quiescent state of CSCs has been known to contribute immensely to therapeutic resistance in multiple cancers. The characteristics and the regulation mechanisms of quiescent CSCs are discussed in detail. Importantly, we also outline the recent advances and controversies in therapeutic strategies targeting CSC quiescence.

Key Words: Stem cell; Cancer stem cell; Quiescence; Targeting quiescence

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Core Tip: Quiescent state is very important for both adult stem cells and cancer stem cells. Quiescence of adult stem cells is regulated by multiple intrinsic mechanisms and extrinsic factors. Quiescence of cancer stem cells contributes immensely to therapeutic resistance in multiple cancers. Targeting the quiescence of cancer stem cells may be a novel strategy in clinical practice.

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INTRODUCTION

Stem cells (SCs) are present in the embryo and persist throughout the lifetime of a multicellular organism[1]. Embryonic SCs (ESCs) and adult SCs have distinct properties. The former has unlimited potential for cell division but maintains totipotency or pluripotency[1] and can differentiate into various cell types, which is regulated by specific transcription factors at each developmental stage[2]. Adult SCs are smaller cell populations with more limited capacity for self-renewal and differentiation (*i.e.*, are multipotent or oligopotent), and participate in the maintenance of tissue homeostasis and repair[3]. Besides, the growth of tumors is promoted by a few cells, termed cancer SCs (CSCs), which also possess self-renewal ability like the adult normal tissue SCs[4].

SCs mainly exist in a state of proliferation or quiescence[5]. A subset of adult SCs remains in quiescence in the absence of physiologic stimuli, which preserves genomic integrity. The quiescent state (G_0) is defined as reversible cell cycle arrest characterized by reduced metabolic activity[5]. And SCs can exit quiescence and re-enter the cell cycle in response to various types of stress or changes in the microenvironment[5]. The phenomenon of quiescence has been found in multiple adult SCs, including hematopoietic SCs (HSCs)[6], muscle SCs (MuSCs)[7], neural SCs (NSCs)[8], and hair follicle SCs (HFSCs)[9].

Like adult SCs, CSCs can switch between the state of proliferation and quiescence, and the quiescence state can explain therapeutic resistance and relapse in cancer[4]. CSCs can remain quiescent in the body for many years[10]; factors such as those present in the circulation can induce their reactivation, leading to tumor relapse[2]. CSC quiescence has been investigated in many malignancies, such as breast cancer, myeloid leukemia, and glioblastoma[11-13].

In this review, we summarize the recent advances in studies of quiescence in adult SCs and CSCs, especially about the intrinsic and extrinsic mechanisms that regulate the quiescence of adult SCs and CSCs. The clinical implications and therapeutic targeting of quiescent CSCs are also discussed.

INTRINSIC MECHANISMS REGULATING ADULT SC QUIESCENCE

Quiescence in adult SCs is mainly regulated by intrinsic mechanisms such as the cell cycle, intracellular signaling cascades, epigenetic alterations, cellular metabolism, and transcription factors controlling gene expression (Figure 1).

Cell cycle and mitogenic signaling

By definition, quiescence is the reversible G_0 phase of the cell cycle. Cyclin-dependent kinase inhibitors (CDKIs) play an essential role in regulating adult SC quiescence. CDKI1C ($P57^{Kip2}$, also known as CDKN1C) is highly expressed in human adipose-derived SCs and induces the quiescence of adipose-derived SCs *via* the downregulation of CDK2-cyclin E1 complex, which can promote the cell to re-enter into G_0 regardless of proliferative cues[14]. The CDKI2A gene (*CDKN2A*) encodes two proteins, p14arf and p16, that inhibit CDK4 and CDK6 and thereby activate retinoblastoma (Rb) protein that can block cell cycle progression[15]. Deletion of *CDKN2A* results in the loss of function of the C2H2 zinc finger transcription factor

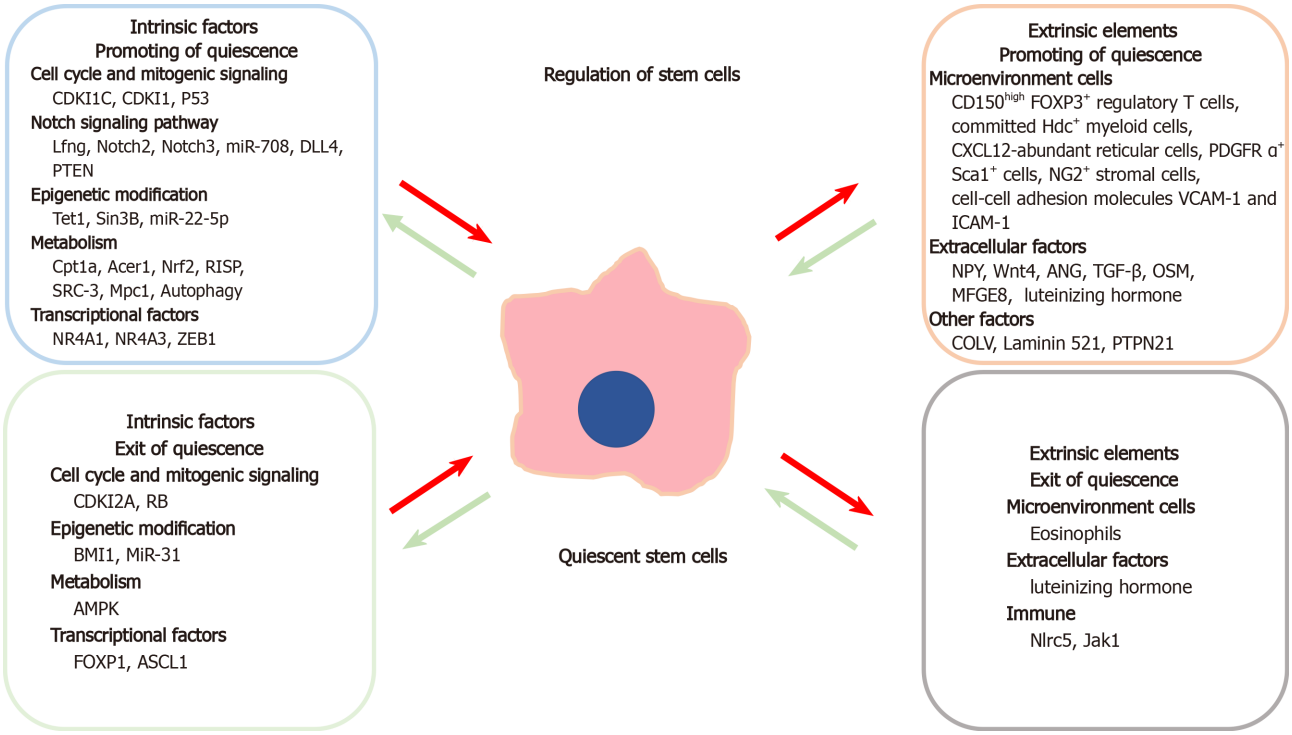

Figure 1 Schematic representation of various factors that lead to promoting or exit of quiescence in stem cells. The intrinsic elements are in the left boxes whereas the extrinsic elements are in the right boxes.

BCL11b, which is associated with defects in mammary epithelial cell development and regeneration[16]. Furthermore, BCL11b is highly expressed in the mammary epithelial SC population that is located at the luminal-basal interface, and promotes the SC population to transit from S to G0 state and exit from the cell cycle[16]. CDKI1 ($p21^{Cip1/Waf1}$) is a universal inhibitor of cyclin/CDK complexes[17]. The expression of $p21^{Cip/waf}$ is increased by depleting the CDK-binding protein CDK5 and ABL1 enzyme substrate 1 (CABLES1), which promotes HSC quiescence in *Cables1* $^{-/-}$ mice[6].

The tumor suppressor protein P53 plays a critical role in maintaining genomic integrity. P53 suppresses cell proliferation by blocking cell cycle progression and accelerating cell apoptosis[18]. P53 also has the capacity of regulating SC quiescence. Knockdown of *p53* in *Rpt3*-null muscle satellite cells rescued the cell proliferation deficiency; *Rpt3* encodes the 26S protease regulatory subunit 6B, which inhibits P53 to induce cell cycle exit. Furthermore, reduced Rpt3 levels in adult resting muscle cells resulted in defective muscle regeneration and the loss of quiescent satellite cells[7]. P53 promoted the quiescence, and suppressed the self-renewal and proliferation of airway club progenitor cells, by inhibiting the expression of genes encoding cell cycle inhibitors including P21, cyclin G1 (*Ccng1*), inhibitor of growth protein 3 (*Ing3*), and erythroid differentiation regulator 1 (*Erdr1*), and by increasing that of cell cycle-promoting genes such as CDK2, Rad21, Ran, and stathmin (*Stmn1*)[19]. The posttranslational ubiquitylation and degradation of P53 in hematopoietic stem/progenitor cells are regulated by COP9 signalosome subunit 5 (CSN5). Asrij, a member of the ovarian carcinoma immunoreactive antigen domain protein family, interacts with CSN5 to maintain P53 protein levels; loss of Asrij abolished quiescence and stimulated HSC proliferation in bone marrow (BM)[20].

The tumor suppressor Rb, which serves as a gatekeeper for the G1/S transition and blocks cell division, is dysregulated in multiple cancers. The phosphorylation of Rb accelerates cell cycle re-entry mainly through binding and repression of E2F transcription factors[21]. In HSCs, inactivation of Rb induces E2F-mediated transactivation of suppressor of cytokine signaling 3, which impaired thrombopoietin-mediated Janus kinase 2 (JAK2) signaling and finally abolished HSC quiescence[22].

Notch signaling pathway

Notch signaling plays an essential role in adult SC differentiation, proliferation, and survival and tissue maintenance and regeneration[23]. The Notch signaling pathway was found to be involved in NSC quiescence. Lunatic fringe (Lfng), a selectively expressed modulator of Notch receptor in NSCs, mediates the contact between NSCs

and their daughter cells, and allows the NSC daughter cells to promote their parent NSCs to enter into quiescent state and to prevent their hyperactivation[23]. Deletion of Notch2 represses cell cycle-related genes, and thus activates quiescent NSCs and stimulates neurogenesis in the ventricular zone/subventricular zone (SVZ)[8]. The DNA-binding protein, inhibitor of differentiation 4 (ID4), is the main effector of Notch2 signaling in NSCs. In the adult dentate gyrus, ID4 was found to function in inhibiting cell cycle, and preserving NSC pool and their quiescence[24]. In the lateral and ventral walls of subependymal zone (SEZ), which is the largest neurogenic niche, Notch3 was found to be highly expressed in quiescent NSCs as compared to active NSCs. Downregulation of Notch3 in the lateral wall of the SEZ can increase NSC division and deplete the quiescent NSC population[25]. Ablation of Notch1 reduced the number of active but not quiescent NSCs, indicating that Notch1 especially promotes active NSC proliferation[26].

Notch signaling negatively regulates the differentiation of skeletal muscle satellite (stem) cells and stimulates the expression of extracellular factors in the SC niche to maintain skeletal muscle satellite (stem) cell quiescence. For example, Notch signaling induced the expression of miR-708 in quiescent skeletal muscle satellite cells, and thereby repressed the transcription of focal adhesion-related protein Tensin3 to inhibit cell migration, proliferation, and differentiation and maintain satellite cells in the quiescent state[27]. Additionally, MuSCs attract capillary endothelial cells (ECs) *via* vascular endothelial growth factor A, while ECs help to maintain MuSC quiescence through the EC-derived Notch ligand Delta-like 4 (DLL4), which interacts with Notch3 expressed by MuSCs[28,29]. Moreover, inactivation of phosphatase and tensin homolog increased Akt phosphorylation in quiescent muscle satellite cells and induced cytoplasmic translocation of Forkhead box protein O1 (FOXO1)—a major substrate of phosphorylated Akt—while repressing Notch signaling, causing muscle satellite cells to exit quiescence and leading to depletion of the SC pool[30,31].

Epigenetic modification

The transition of SCs from a quiescent to a proliferative state is a dynamic and reversible process. Epigenetic mechanisms including DNA methylation, histone modification, microRNAs (miRNAs), as well as long non-coding RNAs (lncRNAs) play an important role in regulation of quiescence[32,33].

Ten-eleven translocation (Tet) family proteins including Tet1, Tet2, and Tet3 induce DNA demethylation[34]. Tet1 is also known to promote histone methylation[35]; Tet1 deficiency leads to loss of quiescence, which depletes the HSC population and causes HSC exhaustion in *Tet1*$^{-/-}$ mice, through decreasing histone H3 Lysine 27 trimethylation (H3K27me3) and thereby increasing the levels of the cell cycle regulators p19 and p21 in HSCs[35]. Additionally, the polycomb complex protein BMI1 suppressed multiple developmental programs in BM stromal cells (BMSCs). BMI1 depletion enhanced the ability of BMSCs to maintain HSC quiescence through downregulation of repressive epigenetic modifications, including the ubiquitylation of histone H2A and the H3K27me3 of genes such as Ink4a/ADP ribosylation factor and Homeobox genes[36].

The chromatin-associated factor SIN3 transcription regulator family member B (Sin3B) is a noncatalytic scaffold protein that is a core element of histone deacetylase (HDAC) transcriptional repressor complexes and regulates cell cycle exit. Loss of *Sin3B* undermines HSC quiescence and enhances their sensitivity to myelosuppressive therapy[37].

MiRNAs are small noncoding RNAs that function in RNA silencing and posttranscriptional regulation of gene expression[38]. MiRNAs are also involved in the regulation of quiescent SCs. Loss of the miRNA miR-31, which is involved in the posttranscriptional regulation of interleukin (IL)-34, stimulates asymmetric cell division of active skeletal muscle satellite cells, promotes their re-entry into a quiescence state, and enhances myogenesis[39]. HFSCs cultured with dermal papilla cells (DPCs) tend to differentiate, and the miRNA expression profiling of DPC-derived exosomes showed that miR-22-5p negatively regulates proliferation and promotes quiescence of HFSCs by targeting lymphoid enhancer-binding factor 1 (LEF1)[9].

Metabolism

The metabolic state of adult SCs influences their quiescence through complex mechanisms. Lipid anabolism in neural stem/progenitor cells (NSPCs), *i.e.*, lipid accumulation from *de novo* lipid synthesis, was found to be critical for NSPC proliferation[40], while lipid catabolism [fatty acid oxidation (FAO)] regulated NSPC quiescence[41]. Proliferative hippocampal NSPCs show reduced carnitine palmitoyltransferase 1a (Cpt1a)-dependent FAO, which is increased in quiescent

NSPCs. Application of malonyl-CoA, a Cpt1a inhibitor and regulator of FAO, facilitated NSPCs to retreat from quiescence and enhanced NSPC proliferation[41].

Mitochondrial membrane potential (MMP) is related to the quiescent state in HSCs, and MMP-low HSCs are more quiescent in contrast to MMP-high HSCs that are activated. Single-cell RNA sequencing (RNA-seq) indicated that there are different gene expression patterns of glycolysis and lysosome in HSCs of low and high MMP. Glycolytic gene expression was enriched in the MMP-high HSCs, and MMP-high HSCs took in more glucose and exhibited higher reliance on glycolysis than MMP-low HSCs *in vitro*; GO terms showed that lysosomal-mediated pathways were distinctly enriched in MMP-low HSCs, and MMP-low HSCs had a lower capacity of lysosomal degradation and a higher mitochondrial turnover relative to MMP-high HSCs[42].

Ceramides and their metabolites, which are regulated by alkaline ceramidase (*Acer1*), function as bioactive lipids to regulate various biological processes including maintaining the homeostasis of skin epidermis[43,44]. *Acer1* deficiency increased the levels of ceramides and their metabolites in the epidermal compartments and broadened the follicular infundibulum, thereby reducing the survival, stemness, and quiescence of HFSCs and leading to progressive hair loss in mice[43].

Nuclear factor erythroid 2-related factor 2 (Nrf2) regulates the oxidative stress response and inhibits cell cycle progression; dysregulation of Nrf2 contributes to hyperproliferation in the HSCs and hematopoietic progenitor cells, inducing their exit from quiescence *via* C-X-C chemokine (CXC) receptor type 4 signaling[45]. AMP-activated protein kinase (AMPK) is a regulator of cellular metabolism that targets lactate dehydrogenase (LDH); loss of AMPK resulted in a Warburg-like switch to increased glycolysis and quiescence in MuSCs[46].

Mitochondrial metabolism is important for preserving SC quiescence. In adult HSCs, defects in the mitochondrial complex III subunit Rieske iron sulfur protein (RISP) impaired mitochondrial oxidative metabolism and respiration, by decreasing the NAD+/NADH ratio, resulting in a loss of quiescence and hypocytosis[47]. Steroid receptor coactivator (SRC)-3 is highly expressed in HSCs; SRC-3 deficiency enhanced mitochondrial metabolism in HSCs, resulting in excess production of reactive oxygen species (ROS), thereby promoting HSC to re-entry into the cell cycle[48].

HFSCs produce markedly more lactate than other cells during glycolytic metabolism, and inhibition of mitochondrial pyruvate carrier 1 (Mpc1) stimulates lactate production to promote the HFSCs to exit from quiescence and progress into the hair cycle[49].

Autophagy is a normal and controlled process that segregates unnecessary or dysfunctional cellular components into autophagosomes, which are transported to the lysosome for degradation and ultimately used to generate energy and molecules for cellular reconstruction and homeostasis[50]. Compared to younger HSCs, about one-third of aged HSCs in mice show increased autophagy and elimination of metabolic byproducts along with a self-renewal capacity. Defects of autophagy in HSCs result in mitochondria accumulation and enhanced metabolism, which accelerate myeloid differentiation through epigenetic alterations and impair HSC quiescence and regenerative potential. On the other hand, autophagy was also shown to inhibit HSC metabolism by eliminating active, robust mitochondria to maintain the stemness and quiescence of HSCs[51].

Transcriptional regulation of gene expression

Transcriptional regulation is important for SC quiescence. Nuclear receptor subfamily 4 group A member 1 (NR4A1) and NR4A3, which are part of the Nur nuclear receptor family of transcription factors[52], regulate quiescence by directly binding to the enhancer of the gene encoding the hematopoiesis-specific anti-proliferative transcription factor CCAAT-enhancer-binding protein α (*Cebpa*) and inducing *Cebpa* transcription activity, and by blocking nuclear factor (NF)-κB-mediated proliferative inflammation responses in the HSCs[53].

Quiescent mammary SCs regulate the development of the ductal epithelium. Deletion of the transcription factor FOXP1 was shown to impair ductal morphogenesis and induce a rudimentary tree in mouse mammary gland, leading to enrichment of quiescent Tetraspanin (Tspan)8^{hi} mammary SCs. FOXP1 is a direct repressor of Tspan8 in basal cells, and defects of Tspan8 can rescue ductal morphogenesis failure that arising from the loss of *Foxp1*[54].

The transcription factor zinc finger E-box-binding homeobox 1 (ZEB1) is upregulated in regenerating myofibers of injured muscles[55]. ZEB1 maintains MuSC quiescence and prevents their premature activation following injury and facilitates regeneration, by inhibiting myogenic differentiation 1, the transcriptional activator of FOXO3, and upregulating Notch target genes, Hairy and enhancer-of-split (Hes), and

Hes-related with YRPW motif families[31,55,56].

Achaete-scute family basic helix-loop-helix transcription factor 1 (ASCL1) expression is upregulated in NSCs of the adult hippocampus, in response to the activation signals from surrounding niche. ASCL1 directly regulates the expression of cell cycle-associated genes to enhance the proliferation of hippocampal SCs in subventricular zone. Deactivation of ASCL1 hindered the quiescence exit in NSCs by rendering them insensitive to external stimuli[57]. Moreover, loss of the gene encoding E3-ubiquitin ligase HECT, UBA, and WWE domain-containing 1 (*Huwe1*) increased the expression of ASCL1, preventing the accumulation of cyclin D and promoting the hippocampal SCs to return to the quiescence state[58].

All the above findings highlight the contribution of cell-intrinsic mechanisms in the regulation of adult SC quiescence, including the cell cycle, intracellular signaling cascades, epigenetic mechanisms, cellular metabolism, and transcription factors controlling gene expression.

EXTRINSIC FACTORS REGULATING ADULT SC QUIESCENCE

SC quiescence is regulated not only by intrinsic molecular mechanisms but also by extrinsic factors in their surrounding microenvironment which is called 'niche'[59]; particularly by the interactions between SCs and the growth factors, cytokines, adhesion molecules, extracellular matrix components, and metabolites released from niche cells (Figure 1)[59-62]. The adult SC niche can preserve the quiescence of adult SCs, while in response to tissue damage or other stimuli, extracellular signals can also induce SC self-renewal or differentiation for tissue repair.

Microenvironment cells

The balance among the adult SC state of quiescence, proliferation, differentiation, and self-renewal can also be regulated through their interactions with nearby cells in the microenvironment, such as eosinophils, mesenchymal stromal cells (MSCs), ECs, macrophages, leukocytes, and immune cells[63-66]. In addition, cell-cell adhesion molecules such as vascular cell adhesion molecule (VCAM)-1, cadherin, and intercellular CAM-1 (ICAM-1) also play important roles in promoting activation of or maintaining quiescence in adult SCs[67-69].

Eosinophils are multifunctional leukocytes responsible for initiation, enhancement, and control of the inflammatory and immune responses, especially in allergic diseases[70]. Eosinophils were shown to disrupt hematopoietic SC homeostasis and quiescence *via* ROS accumulation, which is induced by secretion of chemokine (C-C motif) ligand 6[66].

Regulatory immune cells influence HSC self-renewal and homeostasis. $CD150^{high}$ $FOXP3^{+}$ regulatory T cells located in the HSC niche of BM generate adenosine through the cell surface ectoenzyme CD39, which protects HSCs from oxidative stress and maintains HSC quiescence[63]. The increase in the number of HSCs in CD73 knockout mice can be blocked by treatment with an antioxidant or adenosine receptor agonist, indicating that CD73, a surface enzyme that converts AMP to adenosine, contributes to the maintenance of HSC quiescence by preventing oxidative stress *via* adenosine receptor 2A in $CD150^{high}$ $FOXP3^{+}$ regulatory T cells[71]. In addition, lineage-committed Hdc^{+} myeloid cells that adjoin myeloid-biased hematopoietic SCs (MB-HSCs) produce histamine, activating the H2 receptor on the MB-HSCs to regulate their quiescence and self-renewal. Accordingly, dysregulation of histamine feedback results in a failure of MB-HSCs to re-enter quiescence, leading to the depletion of these cells[72].

MSCs including C-X-C chemokine ligand 12 (CXCL12)-abundant reticular cells and platelet-derived growth factor (PDGF) receptor α^{+} $Sca1^{+}$ cells interact with HSCs and regulate hematopoietic homeostasis. These cells express the transcription factor early B-cell factor 1 (EBF1). Conditional knockdown of *Ebf1* in MSCs altered gene expression, *e.g.*, downregulation of adhesion-related genes, resulting in impaired HSC quiescence and reduction of myeloid output[64]. Stromal cells expressing nerve/glial antigen 2 (NG2) constitute special niches for arterioles and sinusoids in BM. *Cxcl12* knockdown in arteriolar $NG2^{+}$ cells was shown to induce HSCs to exit from quiescence, result in HSC exhaustion, and alter HSC localization in BM[73].

VCAM-1 is enriched in type B NSCs in adult mouse[67]. VCAM-1 signals stimulate ROS production to maintain NSC quiescence *via* NADPH oxidase 2 (NOX2). High ROS levels were shown to sustain NSC self-renewal and prevent the depletion of the NSC pool[67]. In addition, conditional deletion of N- and M-cadherin, which mediate adhesion between MuSCs and their myofiber niche, impaired MuSC quiescence and

preserved the pool of regeneration-proficient MuSCs[68]. ICAM-1, which is highly expressed in niche stroma cells such as endothelial cells, maintains quiescence and self-renew capacity of HSCs. ICAM-1 deficiency in the BM niche alters the expression profile of stroma cell factors, resulting in HSC expansion and impairing quiescence in ICAM-1-deficient mice[69].

Extracellular factors

Soluble factors secreted by neighboring cells or distant tissues can influence adult SC function and fate. Some well-known factors that regulate adult SCs include the neurotransmitter neuropeptide Y (NPY), Wnt4, transforming growth factor (TGF)-β, and oncostatin M (OSM)[74-78].

NPY receptor isoforms (except Y3) are enriched in most HSCs[79]. Sympathetic nerves secrete NPY in BM, directly inhibiting HSC proliferation by facilitating HSC to enter into G_0 phase and increasing the expression of genes such as *Foxo3* that regulate quiescence[74].

Muscle fiber-derived Wnt4 maintains MuSC quiescence by activating RhoA in a mechanistic target of rapamycin complex 1 (mTORC1)-independent manner. In contrast, deletion of Wnt4 promoted MuSC activation and muscle generation[75].

The ribonuclease angiogenin (ANG) secreted in the niche alters the functional state of HSCs by reducing their proliferative capacity and promoting their quiescence, thus protecting the cells from radiation-induced BM damage[77].

TGF-β plays a key role in the regulation of HSC quiescence[80,81]. TGF-β was found to suppress cytokine-mediated lipid raft clustering, which is essential for HSCs to increase cytokine signaling to a level that is sufficient for cell cycle re-entry, and induce HSC quiescence *ex vivo*[80]. Src homology 2 domain-containing protein tyrosine phosphatase 1 (SHP-1) interacts with the immunoreceptor tyrosine-based inhibitor motif of TGF-β receptor 1 to modulate TGF-β signaling. Dysregulation of SHP-1 in HSCs resulted in insensitivity to TGF-β-mediated regulation of HSC quiescence, induced HSCs to leave the quiescent state, and suppressed their self-renewal capacity. Megakaryocytes engulf SHP-1–activated HSCs and regulate their quiescence by producing TGF-β1 in the BM niche[78]. Additionally, TGF-β1 slows cell cycle progression in HSCs, promotes their return to quiescence, and limits their potential for self-renewal *in vitro*[82].

OSM is a member of IL-6 family that is secreted by muscle fibers and induces MuSCs' entry into G_0. Deletion of the OSM receptor caused MuSC exhaustion and decreased their regenerative potential[76]. OSM secreted by a subset of TREM2+ macrophages in the hair follicle niche negatively regulated hair growth by maintaining HFSC quiescence *via* JAK–signal transducer and activator of transcription 5 (STAT5) signaling[83].

Radial glia-like neural SCs (RGLs) in the dentate gyrus generate adult nerves throughout the lifetime of mammals[84]. Milk fat globule epidermal growth factor 8 (MFGE8), which is involved in phagocytosis, is highly expressed in quiescent RGLs[85]. Knockout of *Mfge8* in mice decreased neurogenesis in the adult dentate gyrus, and *Mfge8*-deficient RGLs showed hyperactivation and exhaustion of NSCs *via* mTOR1 signaling[86].

Sex hormones regulate HSC proliferation and self-renewal[87,88]. Luteinizing hormone-releasing hormone antagonist, a sex steroid inhibitor, suppressed luteinizing hormone levels to promote HSC's entry into G_0 and prevent their exhaustion after total-body irradiation at a lethal radiation dose[89].

Immune response and inflammation in the microenvironment

Adult SCs are long-lived and their continuous self-renewal leads to the acquisition of mutations and generation of neoantigens[90]. The neoantigens make these adult SCs to be the potential targets of immune surveillance. Immune evasion is an inherent characteristic of quiescent SCs and is achieved through downregulation of the antigen presentation mechanism mediated by the trans-activator NOD-like receptor family CARD domain-containing (Nlrc)5. Circulating adult SCs such as intestinal, ovarian, and mammary SCs are eliminated by activated T cells, while quiescent MuSCs and HFSCs that express low levels of Nlrc5 are resistant to T cell-mediated killing[91]. Proinflammatory cytokines and immune factors play critical roles in SC quiescence, while an abnormal immune response links to immunologic and neoplastic diseases[92,93]. Conditional *Jak1* knockdown in HSCs diminished their potential for lymphoid/myeloid differentiation, induced quiescence, and reduced sensitivity to hematopoietic stress and immune factors such as type I interferons and IL-3[94].

Other factors in the microenvironment

Adult muscle satellite cell-derived collagen V (COLV) is a key component of the SC niche; knockdown of the *Col5a1* caused aberrant cell cycle re-entry, exit from quiescence, and depletion of the SC pool[95].

Laminin 521 coating improved cell adhesion, increased the expression of quiescence-associated genes such as glial fibrillary acidic protein, and preserved quiescence in cultured rat hepatic stellate cells[96]. Thus, laminin 521 is a critical element in the space of Dissé where hepatic stellate cells (mesenchymal SCs) exist in a quiescent state.

Protein tyrosine phosphatase non-receptor type 21 (PTPN21) is highly expressed in HSCs. Inhibiting PTPN21 reduced quiescence, enhanced mobility, impaired self-renewal capacity of HSCs, and induced their egress from the niche[97].

Adult SCs are influenced by adjacent cells and extracellular factors in the microenvironment. Signals and nearby cells in the niche stimulate the expression or activity of quiescence-associated molecules and regulate the switch between quiescence and proliferation.

QUIESCENCE OF CSCS AND THEIR CLINICAL RELEVANCE

Definition of quiescent CSCs

CSCs have been detected in most malignancies and are implicated in tumorigenesis, metastasis, and posttreatment relapse[98,99]. Like normal adult SCs, CSCs are characterized by stemness, self-renewal capacity, and differentiation potential. CSCs also can switch between proliferative and quiescent states in response to external signals and stress[3,99].

CSCs tend to remain in a quiescent state (*i.e.*, reversible G_0 phase) to survive under conditions of environmental stress over a long period time[100]. The fraction of quiescent CSCs in a neoplasm is difficult to estimate and depends on the type of cancer. CSCs were reported to account for < 1% to > 80% (glioblastomas) of all tumor cells in solid tumors[101-103]. Quiescent CSCs constitute an even smaller proportion, which was estimated as 5% of total breast CSCs[11].

Quiescent CSCs are difficult to be distinguished from other CSCs owing to the lack of specific surface markers and universal genotypic and phenotypic features[104]; however, quiescent CSCs still have some specific characteristics, including label retention, low RNA content, and absence of proliferative marker expression[11,105,106].

CSCs can remain quiescent for decades before metastasizing and causing relapse in cancer patients[107]. Quiescent CSCs are thought to be the main cause of cancer treatment failure because of their resistance to harsh environmental conditions, insensitivity to therapeutics, and ability to evade immune surveillance[108-110]. For instance, quiescent breast CSCs can exist in the blood as circulating tumor cells or remain in premetastatic organs as disseminated tumor cells, contributing to late relapse after radical mastectomy[111,112]. Thus, clarifying the biological properties of quiescent CSCs is essential for developing novel anticancer treatments and preventing metastasis and relapse.

Regulations of quiescent CSCs

Common molecular mechanisms and signaling pathways similarly regulate quiescence in both adult SCs and CSCs. Signaling molecules and microenvironmental factors that regulate CSC quiescence include tumor suppressors, CDKs, Notch signaling pathway components, regulators of metabolism, epigenetic modifications, niche-secreted factors, and immune cells (Table 1, Figure 2).

Autophagy accelerates cancer progression by allowing tumor cells to respond to intracellular and environmental insults and protects them from programmed cell death[113,114]. Ovarian cancer spheroid cells, which acquire SC characteristics, exhibit high levels of autophagy. Knockdown of autophagy-related 5 (ATG5) suppressed autophagy and arrested ovarian cancer spheroid cells in G_0/G_1. Conversely, exposure to the autophagy inducer rapamycin impaired self-renewal and quiescence in these cells[115].

Tumors have a highly varied epigenetic landscape that includes DNA methylation and histone modification[116]. Epigenetic modifications play an important role in regulating CSC quiescence. SET domain–containing protein 4 (SETD4) was shown to regulate breast CSC quiescence by facilitating the formation of heterochromatin *via* trimethylation of histone H4 lysine 20. Quiescent breast CSCs with the expression of SETD4 are chemoradiotherapy-resistant, have high tumorigenic potential, and remain

Table 1 Regulation of quiescent stem cells

Stem cells	Regulatory factors
Adipose-derived stem cells	CDKI1C[14]
Airway club progenitor cells	P53[19]
Hepatic stellate cells	Laminin 521[96]
Hair follicle stem cells	MiR-22-5p[9], Acer1[43,44], Mpc1[49], OSM[83], Nlrc5[91]
Hematopoietic stem/progenitor cells	CDKI1[6], Asri[20], RB[22], Tet1[35], BMI1[36], SIN3[37], MMP[42], NRF2[45], RISP[47], SRC-3[48], Autophagy[51], NR4A1 and NR4A3[53], $CD150^{high}$ $FOXP3^{+}$ regulatory T cells[63,71], Ebf1[64], Eosinophils[66], ICAM-1[69], lineage-committed Hdc+ myeloid cells[72], $NG2^{+}$ cells[73], NPY[74], ANG[77], SHP-1[78], TGF-β[80], luteinizing hormone[89], Jak1[84], PTPN21[97]
Mammary stem cells	BCL11b[16], FOXP1
Muscle satellite (stem) cells	Rpt3[7], miR-708[27], Notch3[28,29], PTEN[30,31], ZEB1[31,55,56], miR-31[39], AMPK[46], N-cadherin and M-cadherin[68], Wnt4[75], OSM[76], Nlrc5[91], Col5a1[95]
Neural stem/progenitor cells	Notch2[8], Lfng[23], ID4[24], Notch3[25], Cpt1a[41], ASCL1[57], Huwe1[58], VCAM-1[67], MFGE8[86]

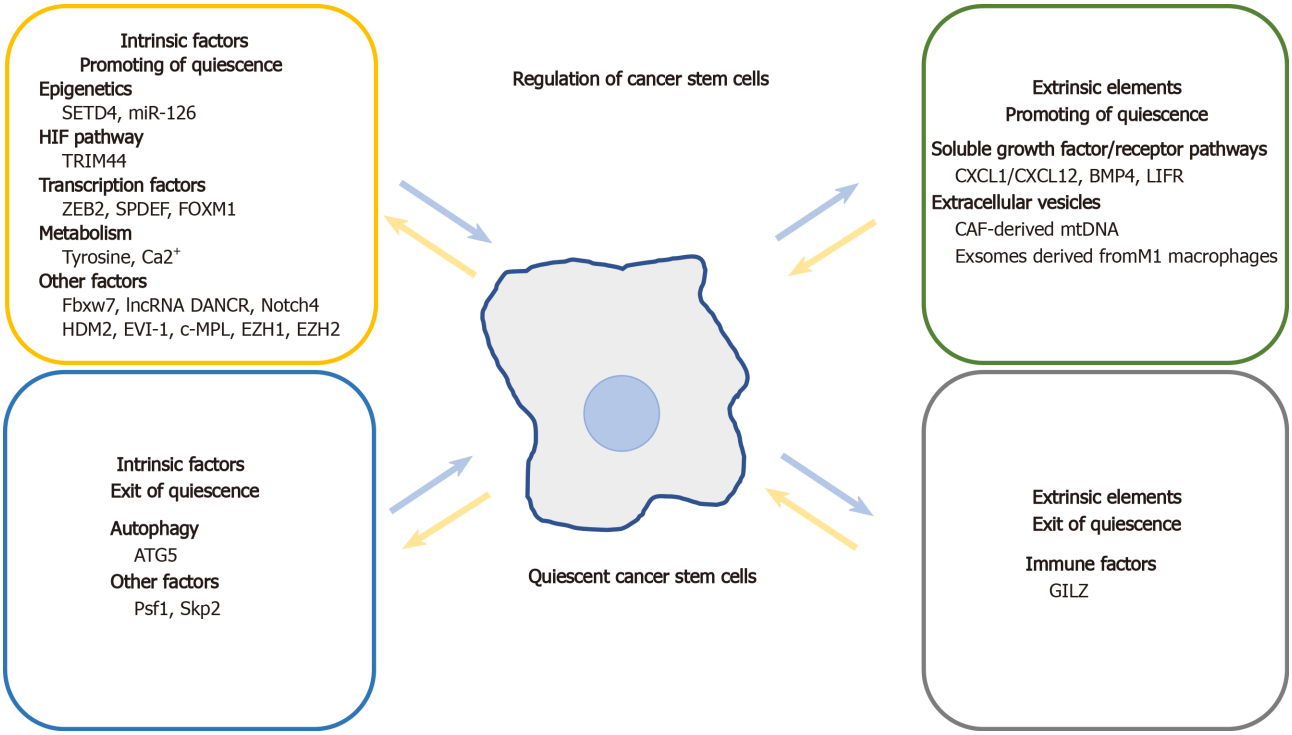

Figure 2 Schematic presentation of main factors that regulate quiescent cancer stem cells in intrinsic and extrinsic aspects.

in a state of quiescence through asymmetric division. Cancer cells expressing SETD4, which are derived from clinical samples (cervical, liver, ovarian, gastric, and lung cancers), show elevated levels of CSC markers and resistance to chemotherapy and radiotherapy[11]. ECs express miR-126, which promotes quiescence and chemotherapy resistance in BM leukemia SCs in chronic myeloid leukemia (CML)[12]. In mouse CML models, miR-126 blocked cell cycle by targeting the phosphatidylinositol 3-kinase/AKT/mTOR signaling pathway[12,117].

The hypoxia-inducible factor (HIF) pathway is a major regulator of quiescence and a promising therapeutic target in leukemia and solid tumors[118,119]. Using the fluorescent tracer PKH26, quiescent stem-like cancer cells were identified in multiple myeloma (MM). Those quiescent stem-like cancer cells were present in the osteoblast niche of BM and expressed high levels of tripartite motif containing 44 (TRIM44)[119], an E3 ubiquitin ligase that deubiquitinates and stabilizes the expression of HIF-1α under normoxia and hypoxia. TRIM44 overexpression was in turn shown to stabilize the expression of HIF-1α, which contributed to SC survival and cell quiescence in MM[120].

Transcription factors, including zinc finger E-box-binding homeobox 2 (ZEB2), SAM pointed domain-containing ETS transcription factor (SPDEF), and FOXM1, are involved in CSC quiescence. ZEB2, which is related to stemness and epithelial-mesenchymal transition (EMT), was reported to be highly expressed in quiescent/slow-cycling SCs isolated from colorectal cancer (CRC) by PKH26 labeling. The CSCs showed chemotherapy resistance and slow growth *in vivo* and *in vitro*. Accordingly, exogenous expression of ZEB2 in colorectal CSCs increased the G_0/G_1 cell fraction. High ZEB2 levels were also correlated with worse relapse-free survival in CRC patients[121]. Conditional expression of SPDEF inhibited intestinal tumorigenesis in leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5)-positive intestinal SCs in transgenic mice expressing an oncogenic form of β-catenin[122]. SPDEF inhibits proliferation of tumor cells and induces them to stay in a quiescent state, by obstructing the binding of β-catenin to DNA-binding T cell factor 1 (TCF1) and TCF3, thereby modulating the expression of cell cycle-associated genes such as *Ccnd1*, *Hdac4*, *Cdk6*, *Myc*, and *Axin2*[122]. Additionally, in mixed lineage leukemia-rearranged acute myeloid leukemia (AML), upregulation of FOXM1, a regulator of the cell cycle, preserved LSC quiescence by preventing the polyubiquitination degradation of β-catenin, thereby activating Wnt/β-catenin signaling[123].

Metabolic reprogramming including tyrosine metabolism and Ca^{2+} homeostasis plays a key role in CSC biology[124,125]. Dysregulation of metabolic pathways in CSCs can lead to tumor recurrence and treatment resistance. Quiescent $CD13^+$ hepatic CSCs mainly rely on aerobic metabolism of tyrosine rather than glucose for energy. Targeting tyrosine metabolism with nitisinone depleted the population of $CD13^+$ hepatic CSCs, impaired quiescence, and delayed tumor recurrence by accelerating the degradation of FOXD3[125]. Moreover, inhibition of store-operated channels alters Ca^{2+} homeostasis; this increases Ca^{2+} sequestration by mitochondria in glioblastoma stem-like cells (GSLCs) and induces their return to quiescence[13]. Reducing extracellular pH can also promote the maintenance of a quiescent state in GSLCs[13].

Several immune factors have been shown to act on quiescent CSCs. Melanoma stem-like cells express low levels of glucocorticoid-induced leucine zipper (GILZ), which mediates the anti-inflammatory and immunosuppressive effects of glucocorticoids[126]. In an *in vivo* model, GILZ deficiency arrested melanoma cells in G_0 even after vaccination with irradiated murine melanoma cells[127].

Soluble growth factor/receptor pathways such as CXCL1/CXCL12, bone morphogenetic protein 4 (BMP4), and leukemia inhibitory factor (LIF) modulate quiescence in activated CSCs. CXCL1 in mice—a homolog of human IL-8—induced quiescence and chemotherapy resistance in hepatocellular carcinoma (HCC) SCs *via* activation of mTORC1 kinase[128]. *Cxcl12* knockout in MSCs can decrease HSC numbers, and promote LSC to exit from quiescent state through downregulation of quiescence related genes such as TGF-β and STAT3[129]. Tyrosine kinase inhibitor treatment induced a subpopulation of BMP receptor $1B^+$ ($BMPR1B^+$) cells adhering to stromal cells to enter quiescence[130]. Quiescent LSCs do not produce BMP4 but rely on BMP4 that is produced by stromal cells within their niche. BMP4 was shown to directly regulate the quiescence of CML LSCs *via* the JAK/STAT3 pathway, which is dependent on BMPR1B kinase activity. Targeting both BMPR1B and JAK2/STAT3 depleted quiescent LSCs in the BM niche[130]. Breast cancer cells may enter a quiescent state before establishing bone metastasis through LIF. Breast cancer patients with bone metastases express lower levels of LIF receptor (LIFR), which is associated with poor prognosis[131]. Furthermore, loss of LIFR in quiescent breast cancer cells decreased the expression of quiescent CSC-associated genes such as *Tgfβ2* and *Notch1*, while knocking down *Lifr in vivo* enhanced bone destruction and tumor cell proliferation[131].

Extracellular vesicles (EVs) derived from tumor and niche cells regulate tumor progression and therapeutic resistance by transferring their contents (proteins, lipids, mRNAs, and miRNAs) to recipient cells[132]. There is accumulating evidence that EVs are involved in the regulation of CSC quiescence. EVs extracted from xenograft models or cancer-associated fibroblasts (CAF) from hormone therapy-resistant breast cancer patients contains mitochondrial DNA (mtDNA), which promotes estrogen receptor-independent oxidative phosphorylation and hormone therapy resistance. These EVs facilitate exit from quiescence in hormone therapy-naive breast cancer stem-like cells or hormone therapy-treated quiescent populations[133]. Additionally, BM macrophages with an M1 phenotype reversed breast CSC quiescence by secreting exosomes that activated NF-κB signaling. In contrast, macrophages with an M2 phenotype promoted quiescence as well as reduced proliferation and carboplatin resistance in breast CSCs through gap junction-mediated intercellular communication[134].

The perinecrotic niche harbors quiescent CSCs with high tumorigenic potential in glioblastoma. These CSCs express low levels of GINS components including SLD5,

PSF1, PSF2, and PSF3. *Psf1* deficiency was shown to suppress reactivation of quiescent CSCs after serum supplementation or reoxygenation[135].

Chemotherapeutic drugs including 5-fluorouracil target CSCs in lung cells by increasing F-box and WD repeat domain-containing (Fbxw) 7 and by decreasing S phase kinase associated protein (Skp) 2 expression, thereby downregulating c-Myc and upregulating CDKI 1B (p27), which pushes cells into quiescence[136].

The lncRNA DANCR is upregulated in AML LSCs. Knockdown of *DANCR* transcript reduced self-renewal capacity and quiescence of LSCs in a AML murine model[137]. The lncRNA growth arrest-specific 5 was highly expressed in the $CD133^+$ pancreatic CSC population and was found to suppress proliferation by inhibiting glucocorticoid receptor-mediated cell cycle regulation[138].

NOTCH4 receptor is highly expressed in triple-negative breast cancer progression and is associated with breast CSC regulation. NOTCH4 upregulates SLUG to promote EMT and activates transcription of GAS1, a regulator of cell cycle arrest, to sustain quiescence of breast CSCs. It was also demonstrated that, compared to the well-known cell surface marker $CD44^+CD24^-$, NOTCH4 expression level can better identify mesenchymal-like breast CSCs[139].

Therapeutic strategies targeting CSC quiescence

A potential treatment for relapse is using agents that target quiescence-related markers and signaling pathways such as human double minute 2 (HDM2), ecotropic viral integration site-1 (EVI-1), chronic myeloproliferative leukemia (c-MPL), enhancer of zeste 1 (EZH1) and EZH2, and autophagy (Table 2).

The E3 ligase HDM2 can regulate p53 activity and is expressed on the membrane of AML blasts including LSCs but not by normal HSCs. Higher membrane (m) HDM2 level in AML blasts is directly proportional to leukemia-initiating potential, cellular quiescence, and chemoresistance. A recent study showed that the synthetic peptide PNC-27 had the capacity to bind to and promote the interaction of mHDM2 with E-cadherin on the membrane of AML blasts, leading to E-cadherin ubiquitination and degradation, thereby inducing the membrane injury and necrobiosis. In both human and murine AML models, PNC-27 treatment eliminated both AML "bulk" blasts and LSCs, but had little impact on HSCs[140].

A subtype of AML, which is characterized by high expression of EVI-1, has very poor outcome, and shows sensitivity to all-trans retinoic acid (ATRA)[141]. EVI-1 suppresses the maturation of leukemic cells and promotes LSC quiescence *in vivo*. ATRA enhances these effects in an EVI-1–dependent process. Pan-retinoic acid receptor antagonists play an opposite role to that of ATRA, delaying leukemogenesis and reducing LSC quiescence in EVI-1^{high} AML LSCs[142].

A $c\text{-}MPL^+$ population of LSCs exists in a quiescent state but is highly tumorigenic and chemotherapy-resistant. The ratio of $c\text{-}MPL^+$ cells to CD34+ leukemia cells relates to poor prognosis in AML patients[143]. AMM2, a synthetic inhibitor of c-MPL, stimulated quiescent LSCs to re-enter the cell cycle and enhanced the survival of AE9a leukemia mice when used in combination with chemotherapy drugs[143].

Polycomb repressive complex 2 (PRC2) trimethylates histone H3 lysine 27 to maintain LSC stemness[144]. PRC2 suppression of cyclin D preserves LSCs in a quiescent state, which was associated with LSCs' sensitivity to chemotherapy in AML patients[145]. Additionally, quiescent LSCs in AML have elevated levels of the PRC2 catalytic subunits EZH1 and EZH2. In a mouse AML model, *Ezh1/2* knockout was shown to promote cell cycle progression and differentiation of quiescent LSCs, resulting in LSC depletion. In AML mouse models and patient-derived xenograft models, a novel EZH1/2 inhibitor has been developed to eliminate LSCs and impair leukemia progression, demonstrating its therapeutic potential for improving AML patient survival[145].

Autophagy can induce tyrosine kinase inhibitor (TKI) resistance in LSCs and decrease survival in CML patients[146]. However, hydroxychloroquine—the only clinically permissible autophagy inhibitor—did not consistently improve the overall survival of glioma patients because of its high toxicity[147]. PIK-III-a selective inhibitor of vacuolar protein sorting 34 and the lysosomotropic agent Lys05 are two new autophagy inhibitors that drive LSCs out of quiescence and promote myeloid cell amplification. Moreover, combined TKI and Lys05 or PIK-III treatment reduced the size of primary CML and xenografted LSC populations, suggesting that it is an effective treatment for CML patients with persistent LSCs[146].

Table 2 Regulation of quiescent cancer stem cells

Type of cancer	Regulatory factor	Regulatory mechanism
Ovarian cancer	Autophagy	Knockdown of ATG5 inhibits autophagy and arrests ovarian cancer cells in G0/G1 state through upregulating production of ROS[115]
Breast cancer	SETD4	SETD4 regulates breast CSC quiescence by facilitating the formation of heterochromatin *via* H4K20me3 catalysis[11]
Breast cancer	LIFR	Loss of LIFR in dormant breast cancer cells reduces the expression of quiescence and cancer stem cell-associated genes, such as TGF-β2 and Notch1[131]
Breast cancer	Mitochondrial DNA	CAF-derived EVs, containing mitochondrial DNA, promote estrogen receptor-independent oxidative phosphorylation and facilitate an exit from quiescence in HT-naive breast cancer stem-like cells[133]
Breast cancer	Macrophages	Macrophages with an M1 phenotype secrete exosomes to activate NF-κB pathways, and thus reversebreast CSCs (BCSCs) quiescence; macrophages exhibiting an M2 phenotype causes quiescence and lessened proliferation *via* gap junctional intercellular communication[134]
Breast cancer	NOTCH4	NOTCH4 transcriptionally activates GAS1 to sustain quiescence in BCSCs[139]
Colorectal cancer	ZEB2	ZEB2 upregulates cell cycle-related factors including HDAC9, Cyclin A1, Cyclin D1, HDAC5, and TGFβ2 to keep stem cells quiescent[121]
Colorectal cancer	SPDEF	SPDEF breaks binding of β-catenin to TCF1 and TCF3, and regulates cell cycle-associated genes, such as CCND1, HDAC4, CDK6, MYC, and AXIN2, to induce a quiescent state[122]
Liver cancer	Tyrosine metabolism	Targeting tyrosine metabolism impairs quiescence by accelerating degradation of Forkhead box D3[125]
Liver cancer	CXCL1	CXCL1 induces quiescence in hepatocellular carcinoma stem cells by activation of the mTORC1 kinase[128]
Multiple myeloma	TRIM44	TRIM44 deubiquitinates HIF-1α to stabilize HIF-1α expression and HIF-1α contributes to MM stem cell quiescence[120]
Glioblastoma	Ca^{2+}	Inhibition of store-operated channels increases capacity of mitochondria to capture Ca2+ in GSLCs, and thus impels proliferous GSLCs to turn to quiescence[9]
Glioblastoma	PSF1	Defect of PSF1 suppresses reactivation of quiescent CSCs after serum supplement or reoxygenation[135]
Melanoma	GILZ	Deficiency of GILZ expression *in vivo* arrests these cells in the G0 phase, and induces quiescence[127]
Pancreatic cancer	lncRNA GAS5	GAS5 restrains the cell cycle to suppress proliferation by inhibiting glucocorticoid receptors (GR) mediated cell cycle regulation[138]
Lung cancer	Fbxw7, Skp2	Knockdown of Fbxw7 upregulated c-myc and knockdown of Skp2 increased the expression of p27, and then transforms cells into quiescence[136]
AML	FOXM1	FOXM1 binds to β-catenin and decreases degradation of β-catenin protein, and thus activates the Wnt/β-catenin signaling pathways, and preserves leukemia stem cell (LSC) quiescence[123]
AML	lncRNA DANCR	Knockdown of DANCR in LSCs causes reduced stem-cell renewal and quiescence[137]
AML	EVI-1	Evi-1 depression promotes the quiescence of LSCs possibly through Notch4[141]
AML	PRC2	PRC2 regulates suppression of Cyclin D to maintain quiescence in LSCs[145]
CML	Mir-126	Endothelial cells provide miR-126 for CML LSCs to restrain cell cycle progression through targeting PI3K/AKT/mTOR signaling pathway[8,117]
CML	CXCL12	Knockout of CXCL12 in mesenchymal stromal cells promotes leukemic stem cell (LSC) expansion *via* downregulation of genes associated with quiescence such as TGF-β and STAT3[129]
CML	BMP4	BMP4 directly regulates quiescence of CML LSCs through regulating JAK/Stat3 pathway, dependent upon BMPR1B kinase activity[130]

AML: Acute myeloid leukemia; CML: Chronic myelogenous leukemia; LSC: Leukemia stem cell; CSC: Cancer stem cells.

CONCLUSION

Quiescence of SCs including adult normal SCs and CSCs has been a topic of intense research in recent years. This review highlights the following aspects of quiescent adult SCs and CSCs: (1) Under normal conditions, quiescence protects normal adult SCs from exhaustion and senescence, thus preserving their multipotency, regenerative potential, and ability to maintain tissue homeostasis. The identification of factors that regulate quiescence in normal adult SCs can also facilitate the study of CSC behavior; (2) Elucidating microenvironmental factors that induce or maintain quiescence in SCs

is critical for exploiting their clinical potential; (3) In malignant disease, quiescent CSCs exhibit resistance to conventional treatments and are responsible for relapse; and (4) Significant progress has been made in our understanding of molecular mechanisms governing quiescence in CSCs, thus expanding the scope of potential strategies for the treatment of specific types of cancer.

The therapeutic targeting of quiescent CSCs is an emerging concept. More basic and clinical research is required before widespread clinical application is possible. Several drugs that target molecules or signaling pathways in CSC quiescence have been evaluated for their efficacy *in vivo* or *in vitro*. However, more agents targeting different classes of molecules or pathways are needed, and their development is hindered by the absence of appropriate markers for CSCs and small CSC population size.

Drugs targeting quiescent CSCs should be designed based on specific markers expressed in these cells or should act on molecules controlling the switch between quiescence and proliferation. The following considerations apply to the development of any new drugs: (1) Validated markers can be used to target quiescent CSCs, especially those that are expressed on the cell surface. However, if the marker is universally expressed by adult SCs, there is a risk of accidental injury to normal cells. Thus, candidate markers are those that are highly expressed in target cells but have low or no expression in normal tissue SCs; (2) Awakening quiescent CSCs allows them to re-enter the cell cycle, increases their sensitivity to conventional therapies, and enables their extermination. However, a risk associated with CSC reactivation is that it could facilitate cancer progression by inducing a proliferative state. Therefore, drugs in this category should be used in combination with or after standard anticancer regimens, and may be more effective when tumors are better controlled; (3) Adjuvant drugs to protect normal SCs must be developed alongside the CSC-targeted therapies, to mitigate any potential damage to normal tissue SCs; and (4) A therapeutic approach that maintains CSCs in a state of quiescence for a long period of time is inherently less risky than CSC reactivation. However, quiescent CSCs may acquire mutations and become resistant to these drugs during treatment. One way to avoid this problem is to use these drugs alongside standard treatments in cases of tumor relapse. Quiescent CSCs are promising targets that need to be taken into consideration in the development of novel anticancer drugs. Nonetheless, therapeutic strategies that can harness CSCs by exploiting the unique characteristics of CSCs have the potential to reduce recurrence and improve outcomes in cancer treatment (Table 3).

Table 3 Therapeutic strategies against quiescence

Type of cancer	Therapeutic target	Potential therapy	Therapeutic mechanism
AML	HDM2	PNC-27	PNC-27 binds to mHDM2, leads to E-cadherin degradation, and causes membrane injury and cell necrobiosis[140]
AML	EVI-1	ATRA	ATRA enhances EVI-1-dependent depression of the maturation and promotes the quiescence[141,142]
AML	c-MPL	AMML2	AMML2 blocks c-MPL, stimulates entry of quiescent LSCs into the cell cycle, and increases the sensitivity of LSCs to chemotherapy[143]
AML	EZH1, EZH2	OR-S1, OR-S2	OR-S1 and OR-S2 inhibit EZH1/2, inactivate PRC2, and then eliminate quiescent LSCs, induce cell differentiation, and turn chemotherapy-resistant LSCs into a chemotherapy-sensitive population[145]
CML	Autophagy	Lys05, PIK-III	Lys05 achieves autophagy inhibition in LSCs and promotes differentiation; Lys05 and PIK-III inhibit TKI-induced autophagy and increase the sensitivity of LSCs to TKI[146]

AML: Acute myeloid leukemia; CML: Chronic myelogenous leukemia; LSC: Leukemia stem cell.

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