Quiescent stem cells in the niche*

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Abstract

Quiescence of stem cells is critical to ensure lifelong tissue maintenance and to protect the stem cell pool from premature exhaustion under conditions of various stresses. The long-term maintenance of stem cells largely depends on the interaction with their specific microenvironments, niches. Detailed studies in recent years elucidated that the interaction of stem cells with their specialized microenvironment “niche” is critical to sustain stem cell pools in tissues over long periods and that the stem cell niche regulates stem cell-specific properties, including self-renewal, multi-potentiality, and relative quiescence in cell cycle. Here we discuss quiescent stem cells in the adult hematopoietic system and describe the regulatory mechanisms of hematopoietic stem cell (HSC) quiescence in bone marrow. Niches for HSCs have been identified in the endosteal region “osteoblastic niche” and a perivascular area “vascular niche”. Although the functional differences of these two niches still need to be investigated, HSCs are maintained via a complex interaction of cells, cytokines, adhesion molecules, and extracellular matrix. Quiescent stem cells in the hypoxic niche might be sensitive to reactive oxygen species (ROS) and show glycolysis-dependent metabolism.


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1. Niche for the quiescent stem cells

Stem cells are characterized by their self-renewal capacity and potential to differentiate into single or multiple types of daughter cells. Stem cells in different tissues are governed by general genetic programs that maintain their stem cell natures (Ivanova et al., 2002; Ramalho-Santos et al., 2002), although the critical genes functioning in these programs are likely to differ across stem cell types.

It is well established that the niche, the specific microenvironment surrounding stem cells, plays a vital role in the regulation of stem cell activity. The concept of the stem cell niche was first proposed for the human hematopoietic system (Schofield, 1978). Today, stem cells and their niches have been identified in mammalian tissue such as HSCs, muscle satellite cells, central nervous system stem cells, intestinal epithelium, bulge region of the hair follicle, interfollicular epidermis, and spermatogonial stem cells (Fuchs et al., 2004; Morrison and Spradling, 2008). In the bone marrow (BM), the HSCs reside in the osteoblastic niche (located near the endostium) and/or the vascular niche (located in the sinusoidal vasculature; Arai et al., 2004; Calvi et al., 2003; Kiel et al., 2005; Sugiyama et al., 2006; Zhang et al., 2003). Although the functional differences between these spatially distinct niches are still unclear, these two types of niches may play a complementary role in the regulation of HSCs in the BM. It has been proposed that the osteoblastic niche, which is a hypoxic niche, maintains hematopoietic stem cells in a quiescent (slow cycling or G0) state, while the vascular niche, an oxygenic niche, supports stem/progenitor cells which are actively proliferating (Yin and Li, 2006).

The epidermal stem cell niche is an ideal system to study the regulation of stem cell quiescence because stem cell identity and location are well organized. In the hair follicle, quiescent stem cells reside in the bulge region and proliferative stem cells migrate into the bulb region (Oshima et al., 2001). Similarly, HSCs shift from the quiescent to cycling states 6 days after 5-FU induced myelosuppressive treatment and that hematopoietic cell clusters form adjacent to the endosteum and move towards the central marrow area (Heissig et al., 2002). These findings suggest that cycling HSCs exit their niche and are mobilized to peripheral circulation.

2. Quiescent stem cells

A common property of stem cells is quiescence in terms of the cell cycle. The rarity of stem cells in vivo and relative quiescence has made it impossible to confirm this directly. Postnatal HSC self-renewal is closely related to the slow cell cycling or quiescence. Adult HSCs are predominantly quiescent, and it is likely that maintenance of HSC quiescence and slow cell-cycle progression could be critically involved in sustaining a self-renewing HSC compartment for life. Indeed, sub-populations of long-term HSC are in the quiescent state (see Figure 1) and have robust reconstitution activity of hematopoiesis (Arai et al., 2004; Cheshier et al., 1999; Kiel et al., 2007a; Yamazaki et al., 2006; Yoshihara et al., 2007). Therefore, it is thought that quiescence of HSCs is directly linked to the ability for the most efficient reconstitution. Quiescence is also critical for sustaining the stem cell compartment long-term; when it is disrupted, as occurs with p21Cip1 deficiency, HSCs cannot remain in G0 and long-term repopulating ability is lost (Cheng et al., 2000). In addition, quiescent HSC populations are resistant to 5-fluorouracil (5-FU)-induced myelosuppression (Arai et al., 2004), suggesting that the quiescence of HSCs is closely associated with the protection of the HSC pool from the various stresses induced by myelotoxic insults.

Label retention cells (LRC)

Adult stem cells in steady-state tissue may consistently retain DNA labels. This could be because chromosomes segregate randomly but stem cells divide more infrequently than other cells. A technique termed long-term retention cell (LRC), has been used to determine the putative stem cell location in mammalian tissue (Potten et al., 2002; Zhang et al., 2003). Bromodeoxyuridine (BrdU) is commonly used to label a cell’s DNA, and BrdU-labeled DNA can be tracked by an antibody against BrdU. Normally, cycling cells, including cycling stem cells, can be labeled using BrdU; but this labeling is diluted and lost during cell division.

Quiescent or slow-cycling stem cells in adult tissue, however, can retain BrdU over a long period by either segregating chromosomes asymmetrically or dividing slowly. In the hematopoietic system, Bradford et al. (1997) first reported that the primitive HSC compartment retained BrdU-labeling. Although, Li and our group previously reported that BrdU-LRCs are localized in the endosteal region and these cells express HSC markers (Zhang et al., 2003; Arai et al., 2004), it is still controversial whether label retention can consistently identify stem cells with specificity. Morrison and colleague reported that the sensitivity of BrdU-LRCs is inadequate to detect HSCs since less than 6% of long-term HSCs, which were identified by SLAM markers (CD41−CD48−CD150+), were BrdU-LRCs (Kiel et al., 2007a).
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Figure 1. LT-HSCs are in the quiescent state. Pyronin Y (PY) analysis of LT-HSCs (A: LSK-SP and LSK-CD34− cells) and ST-HSCs (B: LSK-non-SP and LSK-CD34+ cells). PY staining, which stains single RNA and DNA, is an assay for discrimination of G0 phase of cell cycle. PYlow− and PY+ cells are in G0 and G1 of the cell cycle, respectively. Most of LSK-SP and LSK-CD34− cells are PYlow−, suggesting that LT-HSCs are in G0.

LRC might depend on the purity of stem cells and detection of BrdU-positive cells, and thus it is controversial whether LRCs represent quiescent HSCs or not.

Another technique for identifying slow-cycling or quiescent cells is by using genetic manipulation approaches such as transgenic mice expressing histone H2B–green fluorescent protein (GFP) controlled by a tetracycline-responsive regulatory element. When they are crossed with mice harboring a keratin 5 promoter–driven tet repressor–VP16 transgene, offspring are then selected for doxycycline-controlled regulation restricted to skin epithelium. Without doxycycline, skin epithelial cells which have undergone cell division exhibited GFP. These transgenic mice could be utilized to assess transplantable capacity in LRCs (Tumbar et al., 2004).

Side-population

In adult mouse hematopoietic tissue, the side-population (SP) can be used to detect differences in cell cycle status of HSCs. The SP is a cell fraction that labels at low levels with Hoechst 33342-dye (Goodell et al., 1996). The SP fraction expresses an ABC transporter, Bcrp-1(ABCG2), on the cell surface, and this transporter contributes to efflux of the Hoechst dye from the cells, leading to low levels of staining (Zhou et al., 2001).
Analysis of the cell cycle status of SP cell in lineage−Sca-1+c-Kit+(LSK) cells by pyronin Y staining indicated that most (>90 %) of LSK-SP cells are in G0 phase (Arai et al., 2004). It was previously reported that PYlow portion and PY+ cells are in G0 and G1 of the cell cycle, respectively (Huttmann et al., 2001). Hence, LSK-SP cells showed resistance against 5-FU treatment, whereas non-SP cells in LSK showed susceptibility to 5-FU (Arai et al., 2004). Since 5-FU induces apoptosis of actively cycling cells, non-SP cells are mitotically active cells in HSCs. During postnatal mouse development, the frequency of SP cells in HSCs correlates closely with the proportional increase in the number of cells in G0 HSCs (Arai et al., 2004). In fact, in the fetal liver or neonatal BM, HSCs proliferate, expanding the stem cell pool; therefore are not in G0. According to the cell cycle status, neither fetal liver nor neonatal BM HSCs are in the SP fraction (Pearce et al., 2007). For the reasons stated above, we propose that SP phenotype in adult BM HSCs distinguishes the cell cycle of HSCs between quiescent and active state, and that is a suitable marker to detect quiescent stem cells in hematopoietic systems. In addition, mobilized HSCs in peripheral organs following G-CSF administration are not SP. Thus, it suggests that the cell cycle status of HSCs is dynamically controlled in vivo.

3. Signaling for quiescent stem cells

There is much interest in understanding the signals in the niche that keep HSCs in a quiescent state. It is believed that the interaction of HSCs with the niche is crucial for the long-term maintenance of HSC quiescence.

Tie2/Angiopoietin-1 (Ang-1)

HSCs expressing the receptor tyrosine kinase Tie2 are quiescent and anti-apoptotic and comprise an SP of HSCs, which adheres to the osteoblastic niche in adult BM (Arai et al., 2004). Angiopoietin-1 (Ang-1), which is cloned as a ligand of Tie2 (Davis et al., 1996), is predominantly expressed by osteoblastic cells in endosteum (Arai et al., 2004). In the human BM, it was demonstrated that Ang-1 is expressed in mesenchymal stem/stromal cells (Sacchetti et al., 2007), suggesting that mesenchymal progenitor cells provide the niche for human HSCs. We previously reported that Tie2/Ang-1 signaling activates β1-integrin and N-cadherin in LSK-Tie2+ cells and promotes HSC interactions with extracellular matrix and cellular components of the niche (Arai et al., 2004; Takakura et al., 1998). We also found that Ang-1 inhibited HSC division in vitro and promoted quiescence of HSCs in vivo. Quiescence or slow cell cycling of HSCs induced by Tie2/Ang-1 signaling contributes to the maintenance of long-term repopulating ability of HSCs and for the protection of the HSC compartment from various cellular stresses (see Figure 2; Arai et al., 2004).

Genetic evidence for the importance of Tie2 signaling in HSC–niche interaction has been provided by analysis of chimeric mice composed of normal and Tie family receptor (Tie2 and related receptor Tie1)-deficient embryonic cells (Puri and Bernstein, 2003). Puri and Bernstein reported that embryonic cells lacking Tie2 and Tie1 contributed the development of HSCs and fetal hematopoiesis, whereas Tie2/Tie1-double mutant cells were not maintained in the adult hematopoietic organ, including BM. Since Tie1-deficient cells, which express normal levels of Tie2, contribute to hematopoiesis (Partanen et al., 1996; Rodewald and Sato, 1996), these findings indicate that Tie2 function in HSCs is required for the adult hematopoiesis, but not for the emergence of HSCs and the fetal hematopoiesis. Furthermore, analysis of chimeric mice that included Tie receptor deficient donor cells and Rag2-deficient hosts, which do not produce mature lymphocytes, showed that Tie-deficient cells contribute to lymphopoiesis in the absence of competing host cells (Puri and Bernstein, 2003). These findings strongly suggest that Tie2/Ang-1 signaling plays a critical role in the HSCs for exclusive possession of the niche that is required for the long-term maintenance and survival of HSCs in BM niche. Further studies may reveal other molecules or pathways, which correlate between cell adhesion and cell cycle regulation.

Mpl/Thrombopoietin (THPO)

It is well known that Mpl and its ligand THPO regulate megakaryopoiesis (Kaushansky, 1995). In addition, it has been shown that Mpl/THPO signaling synergistically induced HSC proliferation with other cytokines. Yagi et al. (1999) reported that THPO support HSCs in the long-term Dexter culture of the BM cells. Furthermore, Thpo or Mpl-deficient mice showed fewer HSCs in the BM (Alexander et al., 1996; Carver-Moore et al., 1996; Kimura et al., 1998), suggesting that Mpl/THPO signaling is crucial for the maintenance of LT-HSCs. Recently, Qian et al. (2007) and Yoshihara et al. (2007) reveal that thrombopoietin modulates HSC cell-cycle progression at the endosteal surface, linking a single cytokine with a specific postnatal niche cell. We found that Mpl expression in LT-HSCs was closely correlated with cell cycle quiescence and Mpl+ HSCs in close contact with THPO producing osteoblastic cells at the endosteal surface in trabecular bone area (Yoshihara et al., 2007). Inhibition and stimulation of Mpl/THPO signaling in LT-HSCs showed reciprocal expression of cell cycle regulators (see Figure 2). In particular, we found that THPO treatment increased and anti-Mpl antibody treatment decreased the expression of p57Kip2, which is specifically...
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Figure 2. Role of the osteoblastic niche in the regulation of HSC quiescence. A. Tie2/Ang-1 and Mpl/THPO signaling between HSCs and osteoblastic niche induced quiescence of HSC through the activation of cell adhesion molecules such as β1-integrin and N-cadherin, and CDK inhibitors such as p21Cip1 and p57Kip2. B. Cell adhesion molecules regulate both the anchoring of HSCs to the niche and cell cycle quiescence of HSCs in the niche. C. Myc negatively regulates cell adhesion molecules, therefore, Myc may be a negative mediator downstream of cytokine signaling. D. Accumulation of ROS in HSCs negatively affects cell adhesion and reduced quiescence.

expressed in the quiescent population in LT-HSCs. Concurrently, Qian et al. showed that p57Kip2 was dramatically down-regulated in Thpo−/− HSCs. This reduction of p57Kip2 expression in HSCs by AMM2 treatment is consistent with the data of Thpo−/− HSCs (Qian et al., 2007).

These observations indicate that simultaneous stimulation and suspension in a G0 state are critical for maintenance of the HSC pool. Czechowicz et al. (2007) have recently found that HSCs can be functionally displaced from their niches by in vivo treatment with anti-c-kit antibody. We also found that treatment of mice with anti-Mpl antibody reduced the number of quiescent LT-HSCs, and allowed exogenous HSC engraftment without myeloablation, indicating that Mpl/THPO signaling was involved in the maintenance of HSC-niche interaction (Yoshihara et al., 2007).

Wnt/β-catenin signaling

Wnt ligands have previously been identified as a key-signaling pathway in stem cell self-renewal (Reya et al., 2003). Wnt ligands activate a β-catenin-dependent pathway, (canonical pathway) or β-catenin-independent (non-canonical) pathway, such as the Wnt/planar cell polarity pathway and Wnt/Ca2+ pathway. Wnt protein binds to a receptor complex consisting of a member of the Frizzled family of seven transmembrane proteins and the LDL-receptor-related proteins LRP-5 or -6 (Clevers, 2006). In the canonical Wnt/β-catenin pathway, receptor activation leads to the stabilization of β-catenin, which accumulates and translocates into the nucleus to activate target gene expression in concert with transcription factors such as Tcf and Lef.

Although Wnt/β-catenin signaling can induce the expansion of HSCs, constitutively active nuclear β-catenin signaling reduces quiescence of HSCs and blocks HSC differentiation (Kirstetter et al., 2006; Scheller et al., 2006),...
indicating that Wnt/β-catenin signaling negatively affects quiescence of adult stem cells. Indeed, in the hair follicle bulge region, the inhibition of Wnt signaling by Wnt inhibitors such as dickkopf3 (Dkk3), secreted frizzled-related protein 1 (Sfrp1), and disabled homolog 2 (Dab2) is likely to promote stem cell quiescence (Nishikawa and Osawa, 2007). Moreover, melanocyte stem cells themselves show increased expression of Wnt inhibitors such as Wnt inhibitory factor 1 (Wif1), Sfrp1, Dab2, and Dkk4. Recently, Fleming et al. (2008) report that Wnt-inhibited microenvironments created by the osteoblast-specific overexpression of Dkk1 resulted in the increase of the number of proliferating HSCs and the reduction in the ability to reconstitute the hematopoietic system of irradiated recipient mice, indicating that microenvironment-related Wnt/β-catenin activity is crucial for the maintenance of HSC quiescence. Therefore, the fine-tuning of Wnt/β-catenin activity might be crucial for the long-term maintenance of stem cell quiescence (Suda and Arai, 2008).

**Cell adhesion molecules**

It is possible that the physical interaction between stem cells and their niche components may participate in stem cell regulation through processes such as contact dependent inhibition of proliferation. Cell adhesion molecules such as N-cadherin, β1-integrin, and osteopontin might not only be required for HSC anchoring to the niche, but also involved in the regulation of cell cycle status of HSCs. In addition, cadherin-mediated cell adhesion also regulates asymmetric cell division in *Drosophila* germ line stem cells (Yamashita et al., 2003).

Zhang et al. (2003) showed that N-cadherin is present at the interface between HSCs and a sub-population of osteoblastic cells. We previously reported that Tie2/Ang-1 signaling induced β1-integrin and N-cadherin dependent HSC adhesion (Arai et al., 2004). Mpl/THPO signaling also up-regulates β1-integrin in LT-HSCs (Yoshihara et al., 2007). Therefore, it thought that β1-integrin and N-cadherin are key downstream targets of Tie2/Ang-1 and Mpl/THPO signaling in HSCs. It has been shown that the conditional inactivation of c-Myc induces excessive expression of integrins and N-cadherin in HSCs, and Myc-deficient HSCs are not able to proliferate and detach from the niche due to uncontrollable cell adhesion (Wilson et al., 2004). Osteopontin negatively regulates HSC number in the BM niche. Two studies of Osteopontin deficient mice show that the lack of Osteopontin results in an increase in the number of HSCs (Nilsson et al., 2005; Stier et al., 2005). These data suggest cell adhesion molecules not only contribute to the anchoring of HSCs to the niche, but also regulate cell cycle quiescence of HSCs in the niche (see Figure 2).

Although we and other groups have shown that HSCs residing in the osteoblastic niche have higher level of N-cadherin than those in the vascular niche (Haug et al., 2008; Hosokawa et al., 2007; Jang and Sharkis, 2007; Zhang et al., 2003), Kiel et al. (2007b) showed no expression of N-cadherin in CD150+CD48−CD41− HSCs. Since CD150+CD48−CD41− HSCs are predominantly located in the vascular niche (Kiel et al., 2005), we hypothesize that N-cadherin expression levels regulate the localization of HSCs between the osteoblastic and vascular niche. Indeed, we previously reported that during the late stage of myelosuppression, HSCs left the niche following the downregulation of N-cadherin in HSCs and then the HSCs re-enter the cell cycle (Hosokawa et al., 2007).

**4. Metabolism of quiescent stem cells**

Generally, stem cells show low oxidative phosphorylation and high glycolytic activity to synthesize ATP. Thus, stem cells favor enzymatic pathways synthesizing ATP anaerobically. This observation suggests that stem cells in a hypoxic condition are metabolically different from progenitor cells.

Niches or niche cells for quiescent stem cells are located in hypoxic regions of tissues not rich in vasculature, such as the trabecular zone for HSCs and bulges for pigmented stem cells (Jang and Sharkis, 2007). Lower organisms such as *C. elegans* (Golden and Riddle, 1984; Lee et al., 2003) and bacteria (Cho and Eagon, 1967) enter a resting phase characterized by suppressed metabolism and decreased cell cycling in response to the environmental influences of low-temperature or low-nutrients. This adaptation is crucial for their survival. Recently, an evolutionarily conserved mechanism regulating the resting phase of mammalian HSCs is being established through the analysis of mice deficient in FOXO transcription factors (Miyamoto et al., 2007; Tothova et al., 2007), homologues of DAF-16, the gene regulating the resting phase of *C. elegans* (Lee et al., 2003). These results show that spontaneous quiescence of HSCs can be initiated by environmental factors in a way similar to *C. elegans* and bacteria. Therefore, it is likely that stem cell quiescence is regulated in a passive as well as an active manner. Histological localization of label-retaining cells in the bone marrow indicating that most slow-cycling cells reside in hypoxic area distant from capillaries also supports this notion (Kubota et al., 2008).
We demonstrated that ataxia telangiectasia mutated (ATM) regulates the self-renewal capacity of LT-HSCs, but not their proliferation or differentiation into progenitors (Ito et al., 2004). ATM protein maintains genomic stability by activating a key cell cycle checkpoint in response to DNA damage, telomeric instability or oxidative stress. $Atm^{-/-}$ mice over the age of 24 weeks show progressive BM failure due to a defect in HSC function associated with elevated ROS. Elevated ROS induces up-regulation of the cyclin-dependent kinase (CDK) inhibitors $p16^{Ink4a}$ and retinoblastoma ($Rb$) gene in $Atm^{-/-}$ HSCs. Treatment with anti-oxidative reagents restored the long-term reconstitution capacity of $Atm^{-/-}$ HSCs. These data demonstrate that the prevention of HSC senescence depends on ATM-mediated inhibition of oxidative stress.

Most proliferating stem cells appear more susceptible to radiation than other cells, while quiescent stem cells are likely more resistant to such damage due to expression of repair, antioxidant, and anti-apoptotic machinery. ATM is preferentially expressed in cycling stem cell fractions (Ito et al., 2004), but quiescent stem cells are not detected in ATM-deficient mouse bone marrow cells (Ito et al., 2006). It has been suggested that non-cycling stem cells are depleted after the decrease of cycling HSCs. Alternatively, the production of ROS caused by ATM-deficiency may directly affect the interaction of quiescent stem cells and osteoblasts. It remains to be determined whether stem cell functions are changed outside the niche, since ROS may destroy cell adhesion of the niche.

5. Biological Function of Quiescence in HSCs

Defects in quiescence of HSCs observed in the p21 $Cip1$ deficient mouse leads to failure in the maintenance of long-term repopulating activity (Cheng et al., 2000), suggesting that maintaining cell cycle quiescence is directly linked to the preservation of self-renewal activity of HSCs.

We hypothesize that cell cycle regulation by the niche is critical for the fate of HSCs (Suda et al., 2005). Treatment with anti-cancer drugs or cytokines makes quiescent stem cells enter the cell cycle and proliferate. Cycling HSCs are mobilized to the peripheral blood, suggesting that a change in environment leads to the transition between quiescent and cycling HSCs. Indeed, the disruption of the osteoblastic niche induces the proliferation of HSCs and the transition of the HSC to the vascular niche area (Visnjic et al., 2004; Walkley et al., 2007a; Walkley et al., 2007b), which sometimes results in myeloproliferative disease (Walkley et al., 2007a; Walkley et al., 2007b). Moreover, in the case of a massive loss of hematopoietic cells (e.g., by treatment with anti-cancer drugs or irradiation), surviving HSCs must enter the cell cycle and proliferate to supply progenitors giving rise to differentiated cells. However, HSCs tend to exit the cell cycle once the hematopoietic cells have been compensated for.

Why does cell cycle quiescence lead to maintenance of stem cell capacity? Every cell division must shorten the telomere length in HSCs. Hematopoietic progenitors have a high replicative potential and express telomerase to protect the ends of their chromosomes. As animals age, telomeres undergo erosion. HSCs can also undergo telomere shortening. Accelerated telomere erosion reduces the long-term repopulating capacity of HSCs in mutant mice (Allsopp et al., 2003). The period of quiescence prevents telomere erosion. Alternatively, cell proliferation may increase the level of ROS. Indeed, quiescent HSCs are metabolically inactive, therefore the generation of endogenous free radicals and ROS is relatively lower compared to the cycling cells (Tothova et al., 2007). Then, the cell cycle quiescence could potentially reduce the frequency of the replicative error or DNA damage in stem cells. However, on the other hand, HSC quiescence might contribute to the accumulation of DNA damage as aging proceeds (Rossi et al., 2008; Rossi et al., 2007b). In the progenitor cells, DNA damaged cells are eliminated by apoptosis or growth arrest during their rapid cell cycling. Meanwhile, DNA damage is accumulated in quiescent stem cells during aging. Indeed, quiescent HSCs purified from aged mice showed the accumulation of the gH2AX foci (Rossi et al., 2007a). In addition, aged HSCs showed functional deficiency, including homing, mobilization, and repopulation ability (Kim et al., 2003; Morrison et al., 1996; Rossi et al., 2007a). These findings indicate that the cell cycle quiescence have biphasic function in the protection of the HSCs.

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7. References


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