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The role of the marrow microenvironment in hematopoietic stem cell transplantation

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Abstract

The success of hematopoietic stem cell transplantation depends on the engraftment of pluripotent hematopoietic stem cells and the regulated proliferation and maturation of committed progenitor cells. It is generally agreed that these processes cannot occur without an appropriate milieu provided by a competent marrow microenvironment (ME). The ME is composed of both non-hematopoietic and hematopoietic stem cell derived cells and consequently is chimeric following allogeneic stem cell transplantation, containing recipient stromal cells and donor macrophages.

Keywords: hematopoietic microenvironment, stromal cell, transplantation, stem cell niche, ME units, monocyte/macrophage

Early studies

Some of the most compelling evidence for the absolute requirement of a competent microenvironment (ME) to support engraftment comes from early studies in mutant mice. In particular, unequivocal studies show that both the SL/SL, or "Steel" mutant mouse which dies of anemia spontaneously, and the more viable SL/SL^d mouse, which succumbs following very low doses of irradiation, cannot be rescued with an infusion of normal bone marrow cells [38]. However, the animals could be rescued by transplantation of intact spleen tissue, which becomes the site of hematopoiesis [29]. These studies not only established the importance of the ME for stem cell engraftment, but also advanced the concept that at least some components of the ME cannot be transplanted by an intra-venous infusion of aspirated marrow cells. More recently the mutated gene product that gives rise to the Steel phenotype was shown to be kit ligand, also known as "stem cell factor" (SCF) expressed by stromal cells [12, 19].

Early seminal work by Wolf and Trentin illustrated that the ME is also critical for inducing lineage commitment. In these experiments, a section of bone with intact marrow was implanted within the spleen of a mouse prior to irradiation. After stem cell transplantation, the resulting spleen colonies that bridged the two different MEs were mixed such that there was mostly erythroid differentiation on the splenic side while myeloid differentiation predominated on the marrow side [51].

Although these early studies highlighted the important role of the ME in normal hematopoiesis, identifying the cells and secreted products that are involved in this process remains unfinished work. Specifically, the components that can support the expansion of stem cells without loss of their potential have not been defined. This may be due in part to the fact that more than one cell type and gene product participate in this regulation. In addition, even though the hematopoietic system is a liquid tissue, some ME components appear to be „fixed" stromal elements that contribute to the architecture and may have critical spatial relationships with each other that are difficult to reproduce in vitro.

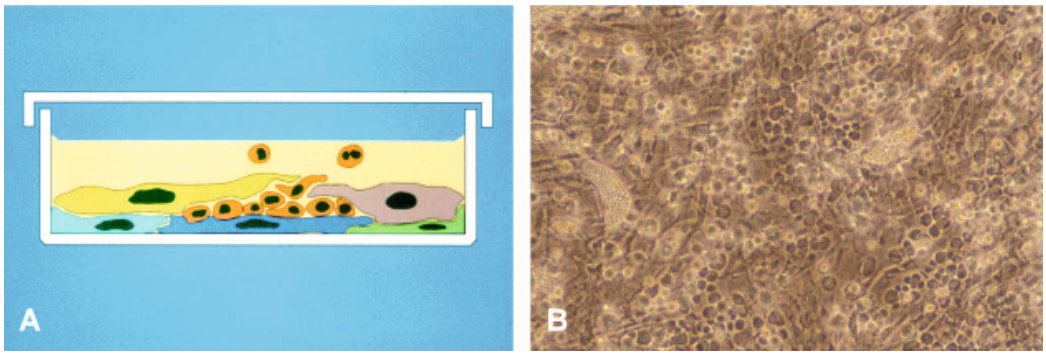

Figure 1: Dexter Long-Term Culture (LTC): **Panel A** depicts a schematic representation of a typical LTC. A complex adherent layer composed of fibroblasts, endothelium, adipocytes, and macrophages which supports the production of hematopoietic cells. As hematopoietic cells mature, they are released from the adherent layer into the media. **Panel B** depicts a phase-contrast photomicrograph of a typical human LTC.

The adherent stromal layer in the LTC consists of fibroblasts, endothelial cells, macrophages, adipocytes, osteoclasts, and extracellular matrix. LTC, if done properly, appear to approximate the in vivo ME since the functional ramifications of the Steel defect are apparent in cultures established from SL/SL^{d} marrow [14]. However there are limitations to this system as myeloid cell production is generally favored over erythroid, and the ever-increasing proportion of monocyte-derived macrophages, is eventually associated with the termination of cell production [10].

Stromal component of the ME

There has been considerable debate concerning the origin of the ME stromal cells. Many reports have suggested that hematopoietic cells and stromal cells have a common precursor, and in agreement with this, several reports have claimed that stromal fibroblasts as well as hematopoietic cells are replaced by donor cells after hematopoietic stem cell transplantation [23, 43]. However, many of these studies typically looked at LTC established from sex mismatched transplants and detected donor cells using standard cytogenetics or fluorescent in-situ hybridization (FISH) for sex chromatin [23]. While it is clear that adherent cells of donor origin were detected in these LTC, these reports were flawed, as they did not properly account for the macrophage component of the adherent layer. This is an important consideration, since studies have shown that even after weekly passage of adherent cells, macrophages can represent a significant proportion of the cells in a 12 week LTC (see Table 1) [5]. Using histochemistry to identify and exclude the donor-derived macrophage component, our lab has determined that even after decades following successful stem cell transplantation, with 100% donor-derived hematopoietic cells, the stromal cells detected in an LTC from a transplanted patient remain of host origin, as predicted by the Steel mouse [5, 42].

The stromal component of the ME remains relatively constant and is quite resistant to currently used conditioning regimens. Therefore, after transplantation, the ME as a whole becomes chimeric; the stromal fibroblasts and endothelial cells remain host-derived while the macrophages are donor-derived [42, 48]. There are several possible explanations for this: First, unlike hematopoietic cells, the stromal fibroblasts and endothelial cells that are harvested from marrow and detectable in the transplanted product are not equipped with the surface molecules needed for trans-migrating the endothelium and homing to the ME. Pre-clinical animal studies suggest that when stromal cells are infused intravenously, they get trapped primarily in the lung and spleen (M. Mielcarek, personal communication). Second, because stromal cells are relatively resistant to chemotherapy and irradiation, the stromal cell compartment is not depleted by standard conditioning; as a result there may not be a demand for stromal cell replacement.

ME niches

After conditioning, the resident stromal cells express or secrete molecules that attract hematopoietic stem and progenitor cells, provide cell surface receptors which allow for the attachment of these cells, and secrete activities for the induction and support of various cell fates. Recently there has been

	Weeks in culture					
	2wk	4 wk	6wk	8wk	10wk	12wk
Donor						
1	**15.5**	**17.7**	**44.0**	**28.0**	**23.0**	**8.2**
2	**13.9**	**24.9**	**17.4**	**5.8**	**2.1**	**1.9**
3	**32.8**	**22.3**	**29.6**	**31.7**	**29.5**	**22.0**
4	**25.1**	**21.4**	**27.6**	**41.1**	**16.5**	**3.3**

NSE=nonspecific esterase; LTC=long term culture

LTCs were established from 4 normal donors and evaluated at various time points for the presence of monocytes/macrophages using NSE staining. As shown in the table, even after 12 weeks there can be a considerable proportion of macrophages in LTC.

Table 1: Percentage of NSE + cells in LTC of normal donors

considerable interest in identifying the specific cellular components that make up the stem cell niche, the specific ME unit where the hematopoietic stem cell resides and self-renews. Over the past two decades, the mouse model has been used to identify various chemokines, cell surface adhesion molecules, and cell types that contribute to this niche. There is general agreement that a number of signaling pathways including c-kit/SCF, CXCR4/CXCL12, VCAM1/VLA-4, Tie2/angipoietin, c-mpl/thrombopoietin, notch/jagged-1, and osteopontin play important roles in maintaining the stem cell niche [6, 30, 3, 16, 22, 32, 4, 27, 31, 44, 25, 35, 52, 9]. However, there is less agreement on the exact identity of the cells that make up the stem cell niche.

Compelling evidence from mouse studies suggest that the endosteal region is critical for the maintenance of hematopoietic stem and precursor cells. One prevalent model proposes that stem cell maintenance critically depends on N-cadherin-mediated binding to osteoblasts [9, 53]. This "osteoblastic niche" model was based on experiments which showed that N-cadherin-positive cells in the endosteal region are associated with cells expressing stem cell markers [9] . However, there are also reports that ablation of osteoblasts does not result in an immediate loss of stem cells, suggesting that while the stem cells may be spatially associated with osteoblasts, the osteoblasts may not be playing a significant role in their support [50, 54]. Furthermore, a recent study demonstrated that only CD146-positive mesenchymal progenitors and not osteoblasts can transfer a ME when transplanted into immunodeficient mice [39] .

The macrophage component of the ME

It is obvious that in vivo, stromal cells do not function in isolation, but do so in the context of other cells. One cell type that is clearly conspicuous both in vivo and in vitro (see Figure 2) is the monocyte-derived macrophage [34, 33] .

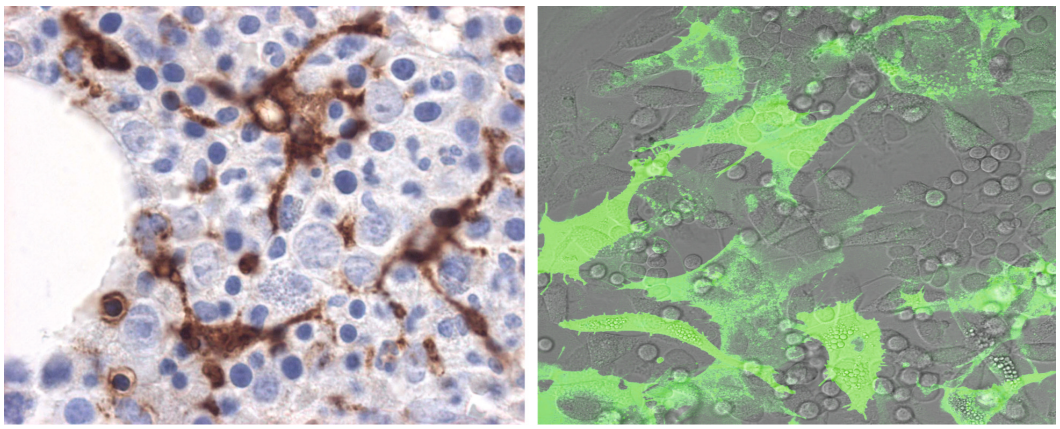

Figure 2: Panel A shows a normal human bone marrow biopsy stained with macrophage-specific CD68 antibody. Panel B depicts a marrow LTC from an inducible transgenic mouse where GFP is under the control of the human CD68 promoter and is expressed exclusively in macrophages. As illustrated in the photomicrographs, CD68 positive macrophages have a significant presence in the marrow and have numerous cell processes which interact with many cell types, suggesting a crucial role in the regulation of hematopoiesis.

In vivo, monocytes are recruited from the circulation into tissues, where they can differentiate into macrophages and perform functions that are relevant to that particular tissue ME. It has long been known that macrophages play a critical role in hematopoiesis. Bessis first described the "nurse cell", a specialized macrophage that is an important component of the erythroblast island, thought to provide structure and nutrients to developing erythroid cells [7, 11]. Osteoclasts, another specialized type of monocyte-derived macrophages, are critical in Ca+ homeostasis in the bone, which is also important for the maintenance of hematopoietic stem cells [1]. However, there is little known or even speculated about the role macrophages may play in the stem cell niche.

Available data suggest that stromal cells play a direct role in the stem cell niche by influencing cell fate decisions through the expression of proteins, such as SDF1 and Jagged, which bind progenitor surface determinants CXCR4 and Notch, respectively. While SDF1 facilitates homing and retention of cells in the marrow, Jagged transduces a signal through Notch that renders early progenitors resistant to differentiation signals [30, 3, 27, 9]. However, since the stromal cell compartment appears constant, with little turnover, it is unclear how interactions between stroma and stem cells can be modulated to allow for the dynamic range of cell production that is characteristic of hematopoiesis. In particular, the mechanisms that regulate gene expression in stromal cells have not been well defined. However, in theory the influence of a constant level of a stroma-expressed genes, e.g. Jagged, could be modulated to some extent indirectly, by down-regulating the level of its receptor, Notch, expressed by progenitors. In vitro studies using cloned human stromal cell lines suggest that this may occur.

Recent data from our laboratory indicates that functionally distinct stromal cell lines isolated from the same LTC can induce different gene expression profiles in monocytes. Specifically, the cloned stromal cell line HS27a, which expresses a number of genes associated with the stem cell niche including CXCL12, angiopoietin, Jagged 1, VCAM, induces the secretion of osteopontin by monocytes [37, 15, 20]. The osteopontin in turn down-regulates Notch expression on progenitors. It is reasonable to conclude that the reduced expression of Notch on progenitors can limit Jagged-Notch signaling, thereby making the progenitors more responsive to differentiation signals [20]. Interestingly, we also showed that the second functionally distinct stromal line, designated HS5, secretes activities that increase the production of matrix metalloproteinase 9 (MMP9) by monocytes, which would facilitate egress of the newly matured cells [21]. Since monocytes circulate and can be recruited from the blood, changes in their number and gene expression within an ME could significantly modulate stromal function.

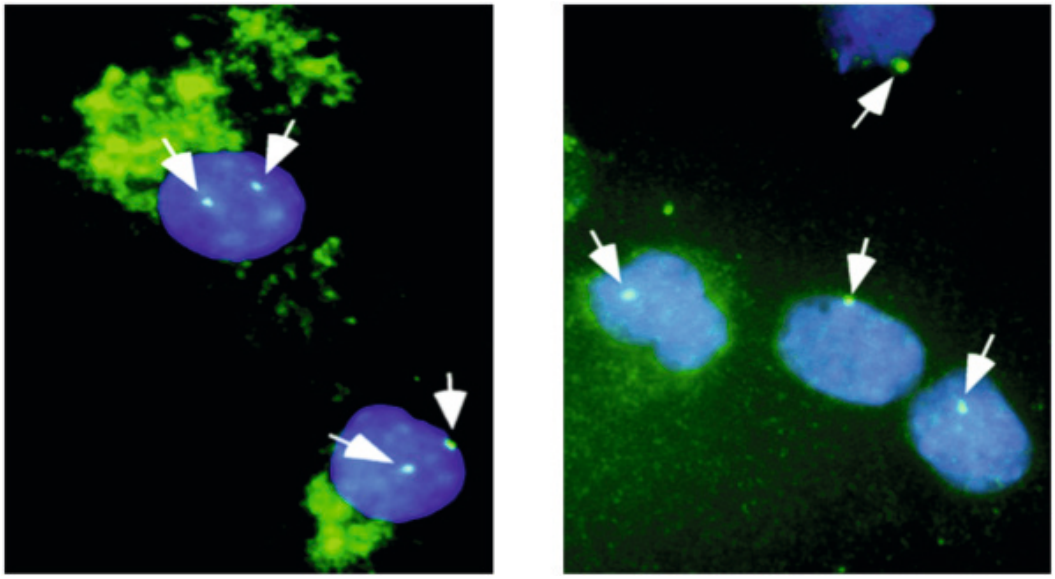

Figure 3. Combined Immunohistochemistry for MMP-9 and FISH for chromosome 7. Monocytes from a healthy donor and from an MDS patient with monosomy seven were isolated and exposed to stromal signals. Cytospins were prepared and IHC for MMP-9 and FISH for chromosome 7 were performed. **Panel A** depicts monocytes from a healthy control which upregulate MMP-9 expression in response to stromal signals (green cytoplasmic staining) and have two copies of chromosome 7 detected by FISH (see white arrows). **Panel B** depicts clonal MDS monocytes identified by monosomy 7 which fail to upregulate MMP-9 expression in response to stromal signals.

The potential clinical relevance of this finding was suggested by a significant negative correlation between the proportion of abnormal monocytes and degree of marrow cellularity [21]. Given the role of MMP-9 in facilitating the egress of cells from marrow, it is reasonable to conclude that as the proportion of non-responsive monocytes increases, inducible levels of MMP-9 decline, resulting in hypercellularity. We also determined that the stromal signal from HS5 that induced MMP-9 is most likely MCP-1; however, we have not as yet identified the compromised monocyte signaling pathway that fails to respond [21]. Clearly a better delineation of signaling pathways that are responsible for normal responses between stromal cells and monocytes as well as the activities that trigger these pathways are needed.

These data suggest that macrophages can play a significant role in altering the hematopoietic ME to support the malignant/dysplastic process. This has clear implications for the success of hematopoietic stem cell transplantation, especially with the introduction of reduced intensity and so-called non-myeloablative conditioning regimens. Most of these conditioning regimens are of insufficient intensity to eliminate residual clonal host macrophages. Thus, when allogeneic stem cells are infused, they encounter a ME that remains dysregulated. This may explain the high rates of graft rejection and relapse seen in MDS patients after reduced intensity and non-myeloablative transplantation [21, 2, 28, 40, 26].

Finally, appreciating the critical role that monocyte-derived macrophages may play in the hematopoietic ME sheds new light on the "seed versus soil" debate as to the cause of hematopoietic dysplasias and aplasias, as well as graft failures. Clearly, the ME (soil) may appear abnormal, yet the defect may reside in the hematopoietic stem cell (seed)- derived monocyte, which upon entering the ME, fails to respond appropriately to stromal signals and thereby contributes to abnormal ME function. This would explain why "defective" MEs appear to be corrected by transplantation; the transplant is actually replacing the abnormal monocytes, not the stromal cells. This is not to suggest that primary stromal failures do not exist. Two examples of such failures have been observed following transplantation: one involves CMV infection and destruction of stromal cells [41, 47, 36, 46, 8], the other involves GVH-mediated anti-stroma activities [49, 18, 17]. In both cases the recipients could not be rescued by the infusion of additional stem cells, even after the anti-stroma mechanism had been eliminated.

Summary

Over the past several decades, studies have revealed the hematopoietic ME to be a complex tissue that consists of both hematopoietic and non-hematopoietic cells, extra-cellular matrix, as well as soluble and membrane bound factors, all of which act in concert to support normal hematopoiesis.

- The ME consists of both hematopoietic stem cell derived and non-hematopoietic cells.
- A viable host ME is required for successful stem cell transplantation.
- Graft failure ensues when the ME is damaged/destroyed.
- After transplantation, the ME becomes chimeric. The stromal elements of the ME remain host-derived, whereas the monocyte/macrophage component is replaced by donor cells.
- Distinct niches or "ME units" exist that are responsible for the regulation of stem cell quiescence as well as differentiation.
- The hematopoietic stem cell derived monocyte/macrophage is a critical component of the ME.
- Stromal cells activate monocytes to assume different fates, which subsequently secrete activities that regulate hematopoiesis.

- In hematologic malignancies, clonally derived monocytes contribute to the dysregulation of the ME.

Data from our lab suggest that monocyte-derived macrophages play a significant role within the ME, and that abnormal monocytes derived from a clone of malignant hematopoietic cells, can compromise ME function. Importantly, following reduced intensity conditioning, recipient macrophages can be retained, and the dysregulated ME can persist and fail to support engraftment. Clearly, further investigation is necessary to completely understand how stroma and monocytes interact to regulate normal hematopoiesis, and how these pathways are altered by abnormal cells. As our knowledge increases we will be able to develop strategies to identify and correct abnormal signaling within the ME.

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References

1. Adams, G. B., K. T. Chabner, I. R. Alley, D. P. Olson, Z. M. Szczepiorkowski, M. C. Poznansky, C. H. Kos, M. R. Pollak, E. M. Brown, and D. T. Scadden. 2006. Stem cell engraftment at the endosteal niche is specified by the calcium-sensing receptor. Nature 439, (7076) (Feb 2): 599-603.

2. Alyea, E. P., H. T. Kim, V. Ho, C. Cutler, D. J. DeAngelo, R. Stone, J. Ritz, J. H. Antin, and R. J. Soiffer. 2006. Impact of conditioning regimen intensity on outcome of allogeneic hematopoietic cell transplantation for advanced acute myelogenous leukemia and myelodysplastic syndrome. Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation 12, (10) (Oct):1047-55.

3. Ara, T., K. Tokoyoda, T. Sugiyama, T. Egawa, K. Kawabata, and T. Nagasawa. 2003. Long-term hematopoietic stem cells require stromal cell-derived factor-1 for colonizing bone marrow during ontogeny. Immunity 19, (2) (Aug):257-67.

4. Arai, F., A. Hirao, M. Ohmura, H. Sato, S. Matsuoka, K. Takubo, K. Ito, G. Y. Koh, and T. Suda. 2004. Tie2/angiopoietin-1 signaling regulates hematopoietic stem cell quiescence in the bone marrow niche. Cell 118, (2) (Jul 23):149-61.

5. Awaya, N., K. Rupert, E. Bryant, and B. Torok-Storb. 2002. Failure of adult marrow-derived stem cells to generate marrow stroma after successful hematopoietic stem cell transplantation. Experimental Hematology 30, (8) (Aug): 937-42.

6. Barker, J. E. 1994. Sl/Sld hematopoietic progenitors are deficient in situ. Experimental Hematology 22, (2) (Feb):174-7.

7. Bessis, M. 1958. Erythroblastic island, functional unity of bone marrow. Revue d'Hematologie 13, (1) (Jan-Mar):8-11.

8. Boeckh, M., C. Hoy, and B. Torok-Storb. 1998. Occult cytomegalovirus infection of marrow stroma. Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America 26, (1) (Jan): 209-10.

9. Calvi, L. M., G. B. Adams, K. W. Weibrecht, J. M. Weber, D. P. Olson, M. C. Knight, R. P. Martin, et al. 2003. Osteoblastic cells regulate the haematopoietic stem cell niche. Nature 425, (6960) (Oct 23):841-6.

10. Chabannon, C., and B. Torok-Storb. 1992. Stem cell-stromal cell interactions. Current Topics in Microbiology and Immunology 177:123-36.

11. Chasis, J. A., and N. Mohandas. 2008. Erythroblastic islands: Niches for erythropoiesis. Blood 112, (3) (Aug 1):470-8.

12. Copeland, N. G., D. J. Gilbert, B. C. Cho, P. J. Donovan, N. A. Jenkins, D. Cosman, D. Anderson, S. D. Lyman, and D. E. Williams. 1990. Mast cell growth factor maps near the steel locus on mouse chromosome 10 and is deleted in a number of steel alleles. Cell 63, (1) (Oct 5):175-83.

13. Dexter, T. M., T. D. Allen, and L. G. Lajtha. 1977. Conditions controlling the proliferation of haemopoietic stem cells in vitro. Journal of Cellular Physiology 91, (3) (Jun):335-44.

14. Dexter, T. M., and M. A. Moore. 1977. In vitro duplication and „cure" of haemopoietic defects in genetically anaemic mice. Nature 269, (5627) (Sep 29):412-4.

15. Graf, L., M. Iwata, and B. Torok-Storb. 2002. Gene expression profiling of the functionally distinct human bone marrow stromal cell lines HS-5 and HS-27a. Blood 100, (4) (Aug 15):1509-11.

16. Heissig, B., K. Hattori, S. Dias, M. Friedrich, B. Ferris, N. R. Hackett, R. G. Crystal, et al. 2002. Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand. Cell 109, (5) (May 31):625-37.

17. Hirabayashi, N. 1981. Studies on graft versus host (GvH) reactions. I. impairment of hemopoietic stroma in mice suffering from GvH disease. Experimental Hematology 9, (2) (Feb):101-10.

18. Hows, J. M. 1991. Mechanisms of graft failure after human marrow transplantation: A review. Immunology Letters 29, (1-2) (Jul):77-80.

19. Huang, E., K. Nocka, D. R. Beier, T. Y. Chu, J. Buck, H. W. Lahm, D. Wellner, P. Leder, and P. Besmer. 1990. The hematopoietic growth factor KL is encoded by the sl locus and is the ligand of the c-kit receptor, the gene product of the W locus. Cell 63, (1) (Oct 5):225-33.

20. Iwata, M., N. Awaya, L. Graf, C. Kahl, and B. Torok-Storb. 2004. Human marrow stromal cells activate monocytes to secrete osteopontin, which down-regulates Notch1 gene expression in CD34+ cells. Blood 103, (12) (Jun 15):4496-502.

21. Iwata, M., M. Pillai, A. Ramakrishnan, R. C. Hackman, H. Joachim Deeg, G. Opdenakker, and B. Torok-Storb. 2007. Reduced expression of inducible gelatinase B/matrix metalloproteinase-9 in monocytes from patients with myelodysplastic syndrome: Correlation of inducible levels with the percentage of cytogenetically marked cells and with marrow cellularity. Blood 109, (1) (Jan 1):85-92.

22. Jiang, Y., H. Bonig, T. Ulyanova, K. Chang, and T. Papayannopoulou. 2009. On the adaptation of endosteal stem cell niche function in response to stress. Blood 114, (18) (Oct 29):3773-82.

23. Keating, A., J. W. Singer, P. D. Killen, G. E. Striker, A. C. Salo, J. Sanders, E. D. Thomas, D. Thorning, and P. J. Fialkow. 1982. Donor origin of the in vitro haematopoietic microenvironment after marrow transplantation in man. Nature 298, (5871) (Jul 15):280-3.

24. Kiel, M. J., O. H. Yilmaz, T. Iwashita, O. H. Yilmaz, C. Terhorst, and S. J. Morrison. 2005. SLAM family receptors distinguish hematopoietic stem and progenitor cells and reveal endothelial niches for stem cells. Cell 121, (7) (Jul 1):1109-21.

25. Kimura, S., A. W. Roberts, D. Metcalf, and W. S. Alexander. 1998. Hematopoietic stem cell deficiencies in mice lacking c-mpl, the receptor for thrombopoietin. Proceedings of the National Academy of Sciences of the United States of America 95, (3) (Feb 3):1195-200.

26. Laport, G. G., B. M. Sandmaier, B. E. Storer, B. L. Scott, M. J. Stuart, T. Lange, M. B. Maris, et al. 2008. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. Biology of Blood and Marrow Transplantation : Journal of the American Society for Blood and Marrow Transplantation 14, (2) (Feb):246-55.

27. Li, L., L. A. Milner, Y. Deng, M. Iwata, A. Banta, L. Graf, S. Marcovina, et al. 1998. The human homolog of rat Jagged1 expressed by marrow stroma inhibits differentiation of 32D cells through interaction with Notch1. Immunity 8, (1) (Jan):43-55.

28. Martino, R., S. Iacobelli, R. Brand, T. Jansen, A. van Biezen, J. Finke, A. Bacigalupo, et al. 2006. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. Blood 108, (3) (Aug 1):836-46.

29. McCulloch, E. A., L. Siminovitch, J. E. Till, E. S. Russell, and S. E. Bernstein. 1965. The cellular basis of the genetically determined hemopoietic defect in anemic mice of genotype sl-sld. Blood 26, (4) (Oct): 399-410.

30. Nagasawa, T. 2000. A chemokine, SDF-1/PBSF, and its receptor, CXC chemokine receptor 4, as mediators of hematopoiesis. International Journal of Hematology 72, (4) (Dec):408-11.

31. Nilsson, S. K., H. M. Johnston, G. A. Whitty, B. Williams, R. J. Webb, D. T. Denhardt, I. Bertoncello, L. J. Bendall, P. J. Simmons, and D. N. Haylock. 2005. Osteopontin, a key component of the hematopoietic stem cell niche and regulator of primitive hematopoietic progenitor cells. Blood 106, (4) (Aug 15):1232-9.

32. Papayannopoulou, T., C. Craddock, B. Nakamoto, G. V. Priestley, and N. S. Wolf. 1995. The VLA4/VCAM-1 adhesion pathway defines contrasting mechanisms of lodgement of transplanted murine hemopoietic progenitors between bone marrow and spleen. Proceedings of the National Academy of Sciences of the United States of America 92, (21) (Oct 10):9647-51.

33. Pillai, M. M., B. Hayes, and B. Torok-Storb. 2009. Inducible transgenes under the control of the hCD68 promoter identifies mouse macrophages with a distribution that differs from the F4/80 - and CSF-1R-expressing populations. Experimental Hematology 37, (12) (Dec):1387-92.

34. Pillai, M. M., M. Iwata, N. Awaya, L. Graf, and B. Torok-Storb. 2006. Monocyte-derived CXCL7 peptides in the marrow microenvironment. Blood 107, (9) (May 1):3520-6.

35. Qian, H., N. Buza-Vidas, C. D. Hyland, C. T. Jensen, J. Antonchuk, R. Mansson, L. A. Thoren, M. Ekblom, W. S. Alexander, and S. E. Jacobsen. 2007. Critical role of thrombopoietin in maintaining adult quiescent hematopoietic stem cells. Cell Stem Cell 1, (6) (Dec 13):671-84.

36. Randolph-Habecker, J., M. Iwata, and B. Torok-Storb. 2002. Cytomegalovirus mediated myelosuppression. Journal of Clinical Virology : The Official Publication of the Pan American Society for Clinical Virology 25 Suppl 2, (Aug):S51-6.

37. Roecklein, B. A., and B. Torok-Storb. 1995. Functionally distinct human marrow stromal cell lines immortalized by transduction with the human papilloma virus E6/E7 genes. Blood 85, (4) (Feb 15):997-1005.

38. Russell, E. S. 1979. Hereditary anemias of the mouse: A review for geneticists. Advances in Genetics 20:357-459.

39. Sacchetti, B., A. Funari, S. Michienzi, S. Di Cesare, S. Piersanti, I. Saggio, E. Tagliafico, et al. 2007. Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. Cell 131, (2) (Oct 19):324-36.

40. Scott, B. L., B. M. Sandmaier, B. Storer, M. B. Maris, M. L. Sorror, D. G. Maloney, T. R. Chauncey, R. Storb, and H. J. Deeg. 2006. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: A retrospective analysis. Leukemia : Official Journal of the Leukemia Society of America, Leukemia Research Fund, U.K 20, (1) (Jan):128-35.

41. Simmons, P., K. Kaushansky, and B. Torok-Storb. 1990. Mechanisms of cytomegalovirus-mediated myelosuppression: Perturbation of stromal cell function versus direct infection of myeloid cells. Proceedings of the National Academy of Sciences of the United States of America 87, (4) (Feb):1386-90.

42. Simmons, P. J., D. Przepiorka, E. D. Thomas, and B. Torok-Storb. 1987. Host origin of marrow stromal cells following allogeneic bone marrow transplantation. Nature 328, (6129) (Jul 30-Aug 5):429-32.

43. Singer, J. W., A. Keating, J. Cuttner, A. M. Gown, R. Jacobson, P. D. Killen, J. W. Moohr, V. Najfeld, J. Powell, and J. Sanders. 1984. Evidence for a stem cell common to hematopoiesis and its in vitro microenvironment: Studies of patients with clonal hematopoietic neoplasia. Leukemia Research 8, (4):535-45.

44. Stier, S., Y. Ko, R. Forkert, C. Lutz, T. Neuhaus, E. Grunewald, T. Cheng, et al. 2005. Osteopontin is a hematopoietic stem cell niche component that negatively regulates stem cell pool size. The Journal of Experimental Medicine 201, (11) (Jun 6):1781-91.

45. Sugiyama, T., H. Kohara, M. Noda, and T. Nagasawa. 2006. Maintenance of the hematopoietic stem cell pool by CXCL12-CXCR4 chemokine signaling in bone marrow stromal cell niches. Immunity 25, (6) (Dec):977-88.

46. Torok-Storb, B., M. Boeckh, C. Hoy, W. Leisenring, D. Myerson, and T. Gooley. 1997. Association of specific cytomegalovirus genotypes with death from myelosuppression after marrow transplantation. Blood 90, (5) (Sep 1):2097-102.

47. Torok-Storb, B., L. Bolles, M. Iwata, K. Doney, G. E. Sale, T. A. Gooley, and R. Storb. 2001. Increased prevalence of CMV gB3 in marrow of patients with aplastic anemia. Blood 98, (3) (Aug 1):891-2.

48. Torok-Storb, B., and L. Holmberg. 1994. Role of marrow microenvironment in engraftment and maintenance of allogeneic hematopoietic stem cells. Bone Marrow Transplantation 14 Suppl 4:S71-3.

49. Torok-Storb, B., P. Simmons, and D. Przepiorka. 1987. Impairment of hemopoiesis in human allografts. Transplantation Proceedings 19, (6 Suppl 7) (Dec):33-7.

50. Visnjic, D., Z. Kalajzic, D. W. Rowe, V. Katavic, J. Lorenzo, and H. L. Aguila. 2004. Hematopoiesis is severely altered in mice with an induced osteoblast deficiency. Blood 103, (9) (May 1):3258-64.

51. Wolf, N. S., and J. J. Trentin. 1968. Hemopoietic colony studies. V. effect of hemopoietic organ stroma on differentiation of pluripotent stem cells. The Journal of Experimental Medicine 127, (1) (Jan 1):205-14.

52. Yoshihara, H., F. Arai, K. Hosokawa, T. Hagiwara, K. Takubo, Y. Nakamura, Y. Gomei, et al. 2007. Thrombopoietin/MPL signaling regulates hematopoietic stem cell quiescence and interaction with the osteoblastic niche. Cell Stem Cell 1, (6) (Dec 13):685-97.

53. Zhang, J., C. Niu, L. Ye, H. Huang, X. He, W. G. Tong, J. Ross, et al. 2003. Identification of the haematopoietic stem cell niche and

control of the niche size. Nature 425, (6960) (Oct 23):836-41.

54. Zhu, J., R. Garrett, Y. Jung, Y. Zhang, N. Kim, J. Wang, G. J. Joe, et al. 2007. Osteoblasts support B-lymphocyte commitment and differentiation from hematopoietic stem cells. Blood 109, (9) (May 1):3706-12.

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Роль микроокружения костного мозга в трансплантации гемопоэтических стволовых клеток

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Резюме

Успешность трансплантации гемопоэтических стволовых клеток зависит от приживления плюрипотентных гемопоэтических стволовых клеток (ГСК) и регулируемой пролиферации и созревания коммитированных родоначальных клеток. В целом, существует согласие в том, что эти процессы не могут возникать без соответствующей среды, которую обеспечивает компетентное микроокружение костного мозга. Оно состоит как из негемопоэтических клеток, так и клеток гемопоэтического происхождения, и впоследствии, после аллогенной трансплантации ГСК, становится химерным, содержащим стромальные клетки реципиента и макрофаги донора.

Ключевые слова: гемопоэтическое микроокружение, стромальные клетки, трансплантация, ниша стволовых клеток, единицы микроокружения, моноцит/макрофаг