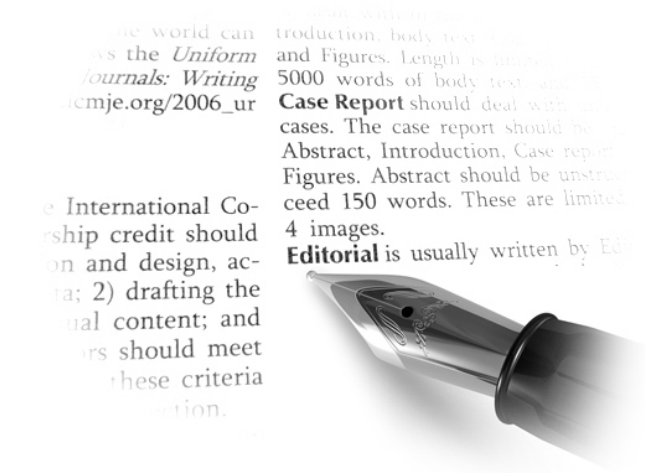

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Editorial

Mesenchymal niche: the sensor and effector of leukemogenesis

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Mesenchymal stromal cells (MSCs) are nonhematopoietic adherent cell populations in the bone marrow (BM) that exhibit multilineage differentiation potential towards diverse types of tissues. These MSCs are widely used for cell-therapy applications to stimulate injured tissues regeneration. The therapeutic effects of MSCs are primarily exerted through their paracrine secretion of various factors that can stimulate the regenerative potential of endogenous stem cells, promote angiogenesis, and inhibit apoptosis [1].

While *ex-vivo* expanded MSCs have been widely used for cell-therapy trials, the *in vivo* identity of these MSCs has been suggested to be a subset of pericytes, and they were demonstrated to be able to reconstitute both endosteal and the perivascular niche in heterologous implantation studies [2]. While geographically distinct, the perivascular and endosteal niche in BM exhibit both distinct and common characteristics in cellular entities and cross-talk molecules, comprising primarily of MSCs, endothelial cells, and some cells with neuronal origin [3]. Moreover, recent studies have further identified complex heterogeneity in the cellular entity of the mesenchymal niche. For example, studies have identified early-stage osteoblastic cells expressing runt-related transcription factor 2 (runx2), subsets of MSCs in perivascular regions expressing nestin and leptin-receptor, and primitive (prx-1+) mesenchymal cells expressing C-X-C motif chemokine 12 (CXCL-12) as key functional cells in the niche. These niche cells express cross-talk molecules such as Jagged-1, CXCL-12, and angiopoietin-1 in order to interact with hematopoietic stem cells (HSCs). Thus, fine orchestration of this microenvironmental cross-talk exerts a key influence on HSCs, controlling their self-renewal, quiescence, and mobilization.

While accumulating studies have established the functional impact of the mesenchymal cell niche in regulating normal HSCs, emerging interest is now focusing on its significance for leukemia stem cells (LSCs), the malignant counterpart of normal HSCs. The key question being addressed is whether the niche is affected under leukemic conditions and, in turn, whether the niche executes any functions in the leukemogenic process itself.

The possible involvement of the niche in leukemogenesis was first suggested by the observation that LSCs, when transplanted into mice, engraft in BM and competes with normal HSCs [4]. Moreover, leukemia cells transplanted into mice create an abnormal niche in BM to usurp the transplanted normal HSCs into a tumor niche [5], suggesting the functional impact of leukemia cells on the niche.

Recently, studies have shown that leukemia cells can alter the condition of the mesenchymal niche in an animal leukemia model, i.e., a transgenic model of chronic myeloid leukemia exhibits defective homing and retention of HSCs in the niche because of decreased CXCL12 in BM MSCs [6]. Similarly, studies on bcr-abl-transformed leukemia revealed alterations of MSCs and osteoblastic cells during the leukemogenesis [7]. Thus, it appears that the mesenchymal niche is certainly influenced, under the leukemogenic conditions, to bring about new concept of the "leukemic niche" that is established by alteration of the normal mesenchymal niche.

On the other hand, several experimental studies also

raised the possibility that the mesenchymal niche itself contributes to the leukemogenic process. For example, a higher incidence of myeloproliferative disease was observed in mice when the BM stroma was disrupted with retinoic acid-γ [8] or retinoblastoma [9]. Although these animal models have not clarified a molecular basis for developing and/or expanding the leukemic cells, these observations, at least, present the possibility that the microenvironment could also be a driving force in the leukemogenic process.

Of note, while most insight was obtained from a series of animal leukemia models, recent studies by our group and others revealed that clinical models of human leukemia exhibit similar alterations in the mesenchymal niche [10]. This study shows that the mesenchymal niche in leukemic patients undergoes extensive functional and transcriptomic alteration accompanied by the alteration in cross-talk molecules. The altered leukemic niche had a functional impact on the BM microenvironment, leading to selective expansion of leukemia cells while suppressing normal HSCs. Thus, the emerging insights into the leukemic niche indicate that leukemia cells reprogram the mesenchymal niche to reinforce their own leukemogenesis, leading to the clonal dominance of leukemic cells over the normal hematopoietic process.

Interestingly, the study by Kim *et al.* [10] recently demonstrated that the heterogeneity in microenvironmental remodeling can be a parameter for heterogeneous clinical courses in acute myeloid leukemia patients, suggesting that the stromal patterns in leukemia BM can serve as a predictor of prognosis. Based on these collective insights, it appears that MSCs are the responding cells being targeted under the leukemic conditions, but also take up a role as active effectors in the leukemogenic process. Accordingly, the mesenchymal niche represents an attractive target for therapy against various hematological diseases. Microenvironment-based therapeutic planning will broaden the horizon for more personalized, biological approaches to efficient leukemia treatment by targeting the specific leukemogenic process in the niche.

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