

The Role of the Bone Marrow Niche in Leukemia Stem Cell Maintenance and Leukemia Cell Progression

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論文名： Leukemia Stem Cells Maintain Self-Renewal by Restructuring the Bone Marrow Niche through TGF- β Activation of ALCAM⁺ Bone-Lining Cells

(白血病幹細胞の維持と白血病の進行における骨髓ニッチの役割)

区 分： 甲

論 文 内 容 の 要 旨

Leukemia stem cells (LSCs) are characterized by their stem cell-like properties and are widely recognized as the origin of leukemia cells. These cells reside within a specialized microenvironment in the bone marrow (BM) known as the "niche", which provides crucial support for their survival, proliferation, and drug resistance through distinct interactions compared to normal hematopoietic stem cells (HSCs). Our research revealed significant heterogeneity among LSC populations based on their spatial distribution within the BM. LSCs located in the endosteal region demonstrated higher expression of quiescence-associated genes, such as p21 and p57, and exhibited a more quiescent state compared to their counterparts in the perivascular region. These quiescent LSCs were found in close proximity to Alcam⁺ bone lining cells (BLCs), which are predominantly localized in the endosteal region. As leukemia progressed, we observed a dynamic shift in the cellular composition of the BM niche, characterized by a decrease in Alcam⁺ BLCs in the endosteal region and an increase in CD51⁺CD140a⁺ perivascular mesenchymal stem cells (MSCs) in the central BM region.

This suggests distinct roles for different niches, with Alcam⁺ BLCs in the endosteal niche potentially maintaining LSC quiescence and CD51⁺CD140a⁺ MSCs in the vascular niche supporting LSC proliferation. Furthermore, we identified a novel mechanism of niche remodeling involving LSC-secreted TGF- β 1, which stimulates osteopontin (OPN) production in Alcam⁺ BLCs. The secreted OPN subsequently anchors LSCs to the endosteal region and promotes their quiescence, demonstrating the active role of LSCs in modifying their microenvironment to create a favorable niche. These insights into the dynamic and complex interactions between LSCs and the BM niche enhance our understanding of leukemia progression and open up new avenues for developing more effective treatment strategies targeting the LSC-niche interactions.