

Fighting against the CNS Invasion of Pediatric Leukemia

Seiji Fukuda*

Department of Pediatrics, Shimane University School of Medicine, Japan

One of the major complications that negatively influence prognoses in leukemia patients is extramedullary infiltration or dissemination of leukemia cells, in particular, infiltration into the central nervous system (CNS). For instance, CNS relapses are common in patients with childhood T-ALL [1]. However, intensified intrathecal chemotherapy and cranial irradiation as prophylaxis of CNS relapse can lead to serious adverse side effects, particularly secondary tumors, bone marrow suppression, growth impairment and endocrine complications [1], indicating that more selective therapeutic strategies are warranted. Leukemia cells are believed to emerge in the bone marrow from hematopoietic stem progenitor cells as a consequence of accumulation of oncogenic mutations. They subsequently move into the blood circulation and home to other organs or different sites within the marrow. Leukemia cells occupy normal hematopoietic niches and impair the production of functionally normal blood cells, demonstrating that the dissemination of acute leukemia cells is a crucial step in leukemic progression. However, the current chemotherapies and specific molecule-targeting drugs were designed to kill leukemia cells, but none of them is able to antagonize leukemia cell movement and trafficking. Blocking leukemia cell invasion and migration may represent a rational alternative strategy to minimize treatment-associated mortality and serious adverse effects.

Although little is known about the mechanisms responsible for CNS invasion by leukemia cells, recent studies indicate that chemokines and their receptors are involved in this dissemination process. The chemokine CCL19, which is expressed in the CNS, serves as a chemo-attractant for T-ALL cells harboring CCR7. CCR7 is a receptor for CCL19 and is up-regulated by oncogenic Notch1 signaling, which is frequently activated in T-ALL. In an animal model, antagonizing CCR7 and CCL19 inhibited CNS infiltration by T-ALL [2]. Meanwhile, the over expression of CCR7 successfully recruited T-ALL cells to the CNS [2]. These data indicate that CCL19/CCR7 signaling that is activated by oncogenic Notch1 regulates the CNS infiltration of T-ALL. Therefore, targeting the CCR7 pathway may represent a novel therapeutic strategy for the prophylaxis of CNS invasion by T-ALL [2]. Mixed lineage leukemia (MLL), which is frequently found in infant ALL, is associated with poor outcome with relatively high frequency of central nervous involvement [3]. A recent report indicates that MEF2C regulates the homing and invasiveness of MLL/ENL leukemia cells and the expression of the chemokine receptors CXCR4, CCR2 and CCR5 and chemokines such as CCL2, CCL3, CCL4 and CCL6 [4]. These data suggest that the invasion of MLL leukemia into CNS may be mediated through MEF2C by affecting the expression of chemokines and their receptors.

Another potential strategy to eradicate CNS leukemia is to antagonize selective signaling components that are provided from the CNS niche to leukemia cells. One major bone marrow niche factor for hematopoietic stem cells is SDF1, a chemokine that is expressed on osteoblastic cells. SDF1 attracts HSCs to the bone marrow niche and provide survival cues to HSCs. Recent studies have suggested that marrow niches serve as a shelter for leukemia cells, especially leukemia stem cells, protecting them from intensive cytoreductive treatments. Similarly, a CNS niche that provides an optimal environment and serves as a shelter for leukemia cells may exist. Once the leukemia cells colonize the CNS niche, they presumably become more resistant to chemotherapy because they were exposed to the survival cues provided by the niches. The functional interaction between niche signaling and

oncoproteins in the leukemia cells in the niche would cause aberrant signals that are qualitatively distinct from those located outside the niche. For instance, chemokine signaling and oncogenes interact functionally and cause molecular events that are qualitatively distinct from those of oncogene signaling or chemokine signaling alone [5,6]. If the resistant phenotype depends on the components created by the niche, antagonizing interactions between leukemia cells and the CNS niche will help to eradicate refractory and residual leukemia cells. Therefore, understanding the signaling components created by this niche is crucial for the development of effective treatment strategies.

Although numerous cells that have invaded the CNS may settle in this niche, some of them fail to survive, while others may opt to hibernate in the unfavorable environment until they are ready to grow. The quiescent and metabolically inactive state of those cells may be beneficial for them, allowing them to survive without expending any energy for an extended period of time. These cells are most likely to be dormant in the cell cycle that promotes the leukemia stem cell phenotype. Alternatively, some cells may adapt to the unfavorable environment or remodel undesired surrounding cells into favorable niches for leukemia cells.

What are the survival cues that are delivered from the CNS niche? How do leukemia cells find and colonize their niche? The specific questions that must be addressed include the molecular consequences of the functional interaction between the signals created by the niche and the oncoproteins in the leukemia cells and the mechanism through which leukemia cells find or create new niches in the CNS. Finding the mechanisms by which leukemia cells are recruited to the CNS niche and discovering cross talk between CNS niche and leukemia cells are important steps toward potential breakthroughs in novel therapeutic strategies for children suffering from CNS leukemia.

References

1. Pui CH, Howard SC (2008) Current management and challenges of malignant disease in the CNS in paediatric leukaemia. *Lancet Oncol* 9: 257-268.
2. Buonamici S, Trimarchi T, Ruocco MG, Reavie L, Cathelin S, et al. (2009) CCR7 signalling as an essential regulator of CNS infiltration in T-cell leukaemia. *Nature* 459: 1000-1004.
3. Pieters R (2009) Infant acute lymphoblastic leukemia: Lessons learned and future directions. *Curr Hematol Malig Rep* 4: 167-174.
4. Schwieger M, Schüler A, Forster M, Engelmann A, Arnold MA, et al. (2009) Homing and invasiveness of MLL/ENL leukemic cells is regulated by MEF2C. *Blood* 114: 2476-2488.
5. Fukuda S, Broxmeyer HE, Pelus LM (2005) Flt3 ligand and the Flt3 receptor regulate hematopoietic cell migration by modulating the SDF-1alpha(CXCL12)/CXCR4 axis. *Blood* 105: 3117-3126.
6. Fukuda S, Onishi C, Pelus LM (2011) Trafficking of Acute Leukemia Cells: Chemokine Receptor Pathways that Modulate Leukemia Cell Dissemination. *Acute Leukemia* 137-156.

*Corresponding author: Seiji Fukuda, Department of Pediatrics, Shimane University School of Medicine, Japan, E-mail: sfukuda@med.shimane-u.ac.jp

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