microparticles play roles beyond the vascular space was not investigated in the present study, but it might implicate leakage of the endothelial barrier, which has been described in different inflammatory contexts and enables microparticle extravasation. Furthermore, lymph, which contains platelet microparticles and drains tumors, may favor the interaction of tumor cells with microparticles. Microparticles are thought to contribute to hemostasis and the support of the coagulation cascade. Although it is unknown whether distinct populations of platelet-derived microparticles are delivered to tumors to prevent tumor growth, this important study further confirms the versatility of extracellular vesicles produced by platelets in health and disease.

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LYMPHOID NEOPLASIA

Comment on Münch et al, page 643

Targeted therapy of CNS leukemia?

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In this issue of Blood, Münch et al demonstrate that vascular endothelial growth factor (VEGF) secreted by acute lymphoblastic leukemia (ALL) cells facilitates their spread to the central nervous system (CNS). Antagonizing VEGF may therefore provide the first targeted therapy of this devastating complication of ALL.

CNS leukemia is a major clinical problem in patients with ALL. It is estimated that the majority of children with ALL have leukemic infiltration of the meninges at the time of diagnosis. Prophylactic CNS-directed chemotherapy (or radiotherapy) has reduced the rate of CNS relapse from 70% to less than 5%. However, this therapy is associated with significant long-term neurological toxicity that is especially relevant for children whose life expectancy after cure from leukemia is >70 years. Furthermore, while the majority of children with ALL are cured, up to a third of the relapses involve the CNS. Thus, more specific and less toxic drugs are urgently needed for the prevention and treatment of CNS relapse.

Leukemic cells typically grow in the cerebrospinal fluid (CSF) in the subarachnoid space (see figure panel A). By analyzing RNA derived from leukemic cells infiltrating the CNS and the bone marrow of immune-deficient mice transplanted with human ALLs, the authors identified a gene expression signature responsive to the hypoxic conditions in the subarachnoid space. VEGF was one of the most upregulated genes in CNS leukemic cells. Similar findings were recently reported in Blood by Kato et al, who also confirmed the increased expression of VEGF in ALL cells isolated from the CSF of patients with CNS leukemia. These observations complement a previous report of high levels of VEGF in the CSF from patients with CNS leukemia. VEGF regulates angiogenesis in both normal and pathological conditions. Relevant for the current discovery, VEGF increases the permeability of the brain vasculature. VEGF may also promote the survival of cancer and leukemic cells. Remarkably, both Münch et al and Kato et al observed marked reduction of CNS leukemia upon treatment with bevacizumab, an anti-VEGF antibody that is a widely used drug against various cancers (see figure panel B).

These exciting findings by 2 independent research groups raise several questions regarding both the role of VEGF in CNS leukemia and the therapeutic potential of anti-VEGF therapy:

1. Does VEGF have a role in the entrance of leukemic cells into the CNS? In both studies, VEGF was upregulated in leukemic cells isolated from the CNS compared with cells isolated from bone marrow. If indeed VEGF is induced in leukemic cells only after they have already penetrated the CNS, how could it affect their CNS migration? One possibility is that only a small subpopulation of ALL cells that express VEGF in the bone marrow reaches the CNS. It is also possible that VEGF secreted by blasts that successfully entered the CNS locally facilitates entrance of additional leukemic cells (see figure panel A).

2. Does VEGF have a role in enhancing the survival of leukemic cells in the CNS? Münch et al did not observe any effects of VEGF on survival and proliferation of leukemic cells in culture under optimal conditions. However, based on previous studies (reviewed in Goel and Mercurio) and the apoptosis observed by Kato et al in CNS leukemic cells after treatment with bevacizumab, it is likely that VEGF supports the survival of ALL cells in the hypoxic growth inhibitory environment in the subarachnoid compartment. Indeed, this may be its more important function in CNS leukemia.

3. What is the therapeutic potential of VEGF against CNS leukemia? Prevention of trafficking of leukemic cells into the CNS is likely to have only a limited therapeutic role, because at the time of diagnosis, the CNS is already infiltrated with leukemic cells in the...
majority of the patients. Furthermore, CNS relapses are hypothesized to rise from dormant residual leukemic cells in the subarachnoid space. However, if VEGF has a major role in enhancing the survival of ALL cells in the subarachnoid space, then VEGF antagonists could be the first targeted and less toxic therapy for CNS leukemia and for the prevention of CNS relapses. Because bevacizumab is an approved drug and has been used for the treatment of brain tumors, a clinical trial in refractory CNS relapse of ALL may be warranted.

After the CNS, the testis is the most frequent nonhematopoietic extramedullary site in pediatric ALL. Approximately half of all boys with an extramedullary involvement have a testicular relapse. The mechanisms of leukemic cell migration and survival in the testis are unknown. As hypoxia may be present within the testicular leukemic mass, it is tempting to speculate that leukemic secretion of VEGF may have a role in both the CNS and the testis, the 2 major sites of extramedullary ALL (see figure panel C).

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**Comment on Hu et al, page 666**

**Zebrafish factor 10 and the life aquatic**

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In this issue of Blood, Hu et al demonstrate that homozygous factor 10 gene ablation (f10−/−) in the zebrafish does not result in either embryonic lethality or vascular developmental abnormalities.

The f10−/− phenotype maintains the expected Mendelian ratios during early development, before exhibiting delayed mortality between 16 and 120 days postfertilization (dpf) as a result of spontaneous bleeding (see figure). These results contrast with murine gene ablation studies for the common pathway coagulation factors (F10, F5, and prothrombin), which demonstrate a mixture of embryonic lethality and fatal perinatal bleeding.

F10 deficiency in humans is a rare autosomal recessive bleeding disorder in which the majority of reported genetic defects are either homozygous or compound heterozygous
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