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MYELOID NEOPLASIA

Comment on Gerber et al, page 3571

ALDH marks leukemia stem cell

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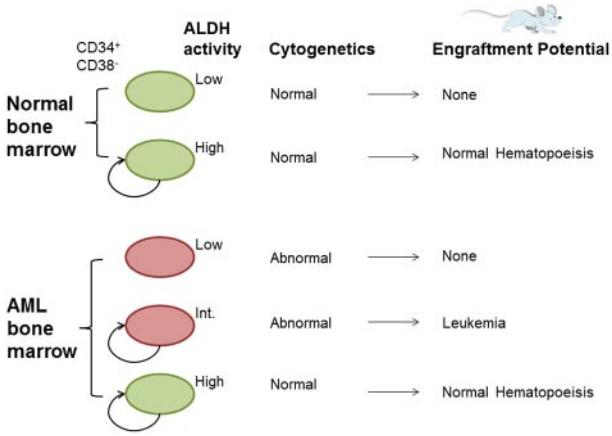
In this issue of *Blood*, Gerber et al use aldehyde dehydrogenase (ALDH) activity to further subdivide the $CD34^+CD38^-$ compartment in the bone marrow of acute myeloid leukemia (AML) patients. They identify a unique population with intermediate ALDH activity ($ALDH^{int}$) that contains leukemia stem cells (LSCs). Moreover, persistence of this population after therapy is a marker of clinically significant minimal residual disease.[1]



Normal bone marrow $CD34^+CD38^-$ cells can be divided into 2 distinct populations based on ALDH activity (high and low), with the ability to engraft immunodeficient mice restricted to the $ALDH^{high}$ population. AML patient bone marrow contains an additional subpopulation with intermediate ALDH activity ($ALDH^{int}$); this population contains cells that bear the diagnostic leukemic cytogenetic marker and transplant leukemia into immunodeficient mice.

ALDH activity has been touted as a marker for normal and malignant stem cells, not only in the hematopoietic system[2-5] but also in solid organs such as breast,[6] colon,[7] and ovary.[8] Normal bone marrow $CD34^+CD38^-$ cells can be subdivided into 2 nonoverlapping populations based on ALDH staining (high and low), with the ability to engraft immunodeficient mice restricted to the $ALDH^{high}$ population. Gerber et al now demonstrate that AML patient bone marrow contains an additional subpopulation with intermediate ALDH activity ($ALDH^{int}$; see figure).[1] This population is absent in normal control bone marrow. It is important to note that the $ALDH^{int}$ population is not necessarily a ubiquitous feature of AML; it was not present in 4 of the 20 newly diagnosed AML patients studied.

The $ALDH^{int}$ population fits the bill for the LSC compartment: as few as 1000 cells engraft leukemia into immunodeficient mice. The $ALDH^{int}$ population is uniformly positive for the clonal leukemic cytogenetic marker. Like the $ALDH^{int}$ population, cells within the $ALDH^{low}$ population also contain the diagnostic leukemia cytogenetic marker, but in contrast to $ALDH^{int}$ cells cannot engraft immunodeficient mice. This suggests that cells contained within the $ALDH^{low}$ population are the leukemic progeny of the $ALDH^{int}$ population.

The $ALDH^{high}$ population in AML patients is a reservoir of "normal" hematopoietic stem cells. This population is devoid of cytogenetic abnormalities and as few as 1000 cells engraft normal, nonleukemic hematopoiesis into immunodeficient mice, similar to the $ALDH^{high}$ population of normal bone marrow. Theoretically, on the basis of ALDH activity one could delicately separate out and collect normal hematopoietic stem cells amid a sea of leukemic cells.

Perhaps the most clinically relevant finding is that persistence of the aberrant $ALDH^{int}$ population after therapy was highly predictive of subsequent relapse. The authors followed 11 AML patients who achieved morphologic complete remission (CR) after induction chemotherapy. Of the 7 patients who consistently lacked the aberrant $ALDH^{int}$ population, none have relapsed (average duration of follow-up 509 days). In contrast, of 4 patients in whom the $ALDH^{int}$ population was detected, all 4 have subsequently relapsed. Perhaps detection of this aberrant population could be exploited as a measure of residual disease and could potentially be used to guide therapy.

ALDH activity has also been applied to investigate the ontogeny of the $JAK2^{V617F}$ clone in chronic myeloproliferative neoplasms (MPNs).[9] In all 9 $JAK2^{V617F}$-positive patients investigated, the $ALDH^{high}$ population was composed of cells bearing the $JAK2^{V617F}$ mutation, demonstrating that the mutation arises in a primitive hematopoietic progenitor. In the chronic phase of the disease the $ALDH^{int}$ population was absent, but subsequently appeared coincident with transformation to acute leukemia in 2 patients. This data further support the specificity of the $ALDH^{int}$ population to AML and its appearance as a herald of acute leukemia.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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● ● ● PLATELETS & THROMBOPOIESIS

Comment on Pascale et al, page 3595

Overcoming "aspirin resistance" in MPN

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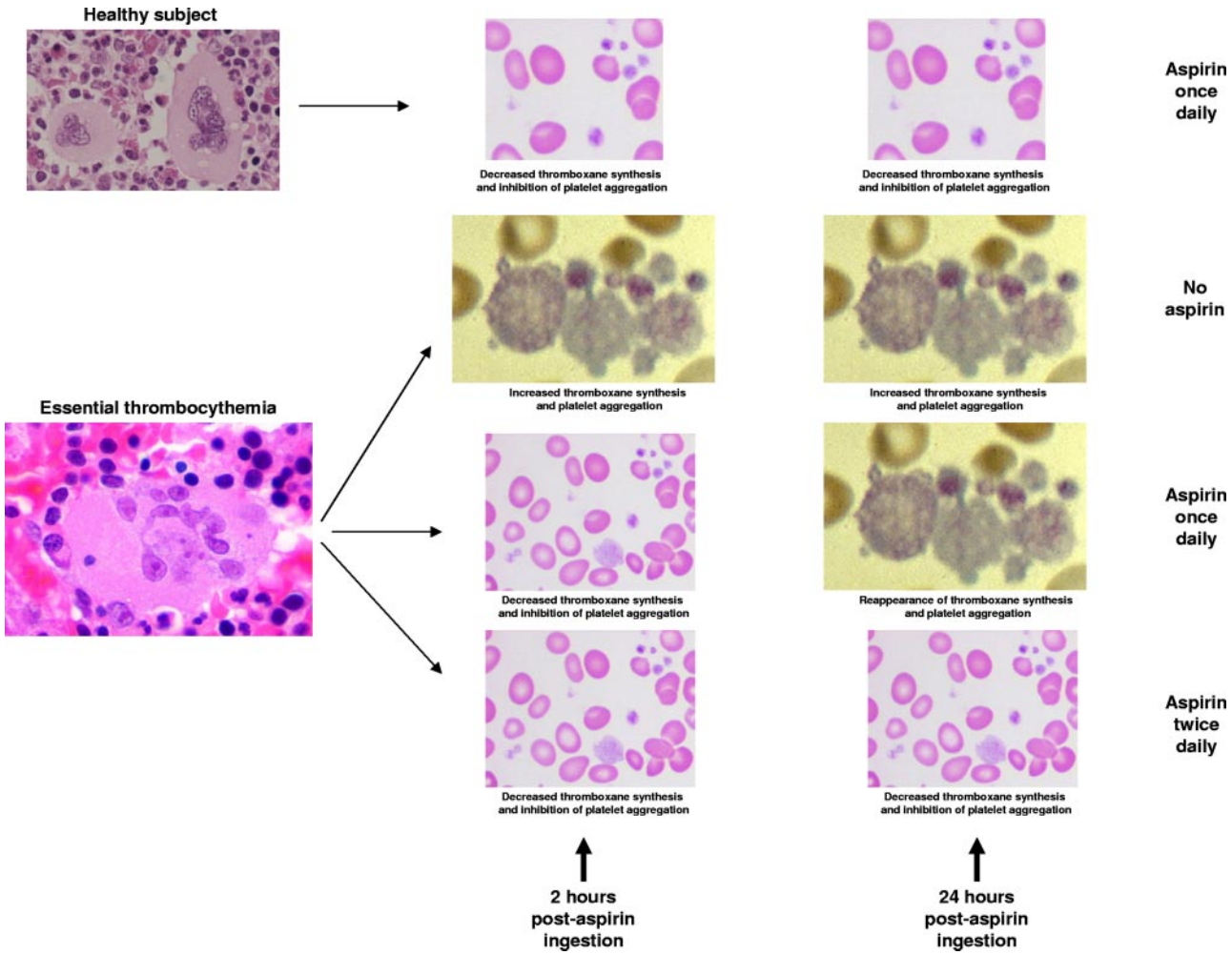
In this issue of *Blood*, Pascale and colleagues show that biochemical resistance to aspirin in patients with essential thrombocythemia (ET) can be reversed by twice-daily dosing.[1]

The cardiovascular protective effect of aspirin is ascribed to its ability to irreversibly inactivate cyclo-oxygenase (COX)–1 and consequently suppress platelet thromboxane A_2 (TXA_2) synthesis. Despite a short circulation half-life (~ 20 minutes), the biologic effect of a single aspirin dose in healthy subjects lasts for approximately 3 days because of the time needed by aspirin-naive megakaryocytes to replenish the body with new platelets; the daily platelet regeneration rate is estimated at 10%. In vivo aspirin effect is gauged by a number of biochemical and functional assays, including measurements of serum TXB_2 (the more stable but inactive metabolite of TXA_2) and antiplatelet aggregation response to aspirin. However, it is important to recognize the limitations and inconsistency of such assays in accurately depicting in vivo aspirin effect.

In healthy, nonsmoking subjects, once-daily aspirin produces > 95% suppression



In vivo aspirin effect at peak and trough time points in healthy subjects and in patients with essential thrombocythemia receiving aspirin once or twice daily.