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## Clues to lymphoma's cellular origin

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platelet activation. The work of Rauova and colleagues will no doubt stimulate further investigations into the role of platelet-associated PF4 in influencing the clinical expression of HIT. ■

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during mononucleosis and where it persists subsequently.

This hypothesis concerning the cellular origin of Hodgkin disease subsequently received support from studies showing that mediastinal B-cell lymphoma (a tumor arising from thymic asteroid B cells) is closer in terms of gene expression profile to classical Hodgkin disease than to diffuse large B-cell lymphoma.<sup>2,3</sup> It was suggested therefore that asteroid B cells in the thymus may give rise, through different secondary genetic alterations, either to Hodgkin disease or to mediastinal B-cell lymphoma.<sup>2</sup> If interfollicular dendritic B cells are indeed the peripheral equivalent of thymic asteroid cells, these gene expression studies would strengthen the idea that they are the cell of origin of classical Hodgkin disease arising in lymph nodes. It may be added that AID expression has been reported in mediastinal B-cell lymphoma<sup>4</sup>; it is apparently usually absent from Reed-Sternberg cells,<sup>5</sup> but this may reflect the down-regulation of many B-cell genes that is well documented in Hodgkin disease.

In the light of the findings outlined here it would be of interest to isolate asteroid B cells from the thymus in sufficient numbers for

## ● ● ● IMMUNOBIOLOGY

Comment on Moldenhauer et al, page 2470

# Clues to lymphoma's cellular origin

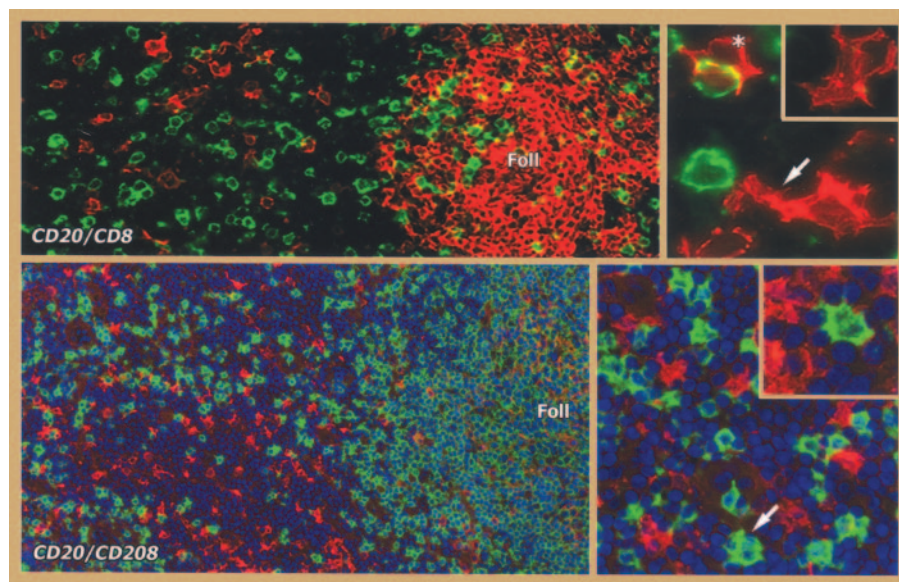
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Moldenhauer and colleagues show that a key enzyme in germinal center cells is also found in a population of interfollicular B cells. Are these cells relevant to Hodgkin disease?

**B**-cell maturation looks straightforward in textbooks, but it can still be surprisingly difficult to fit some of the cell types recognized by the hematopathologist into the neat schemes drawn by immunologists. An example is found in a paper by Marafioti et al<sup>1</sup> from 2003 that drew attention to a novel population of B cells, often carrying dendritic surface processes, that are scattered through T-cell-rich interfollicular areas in peripheral lymphoid tissue (see figure). These B cells are probably closely related to "asteroid" B cells in the medulla of the thymus, but neither cell type appears in any immunologic text. In this issue of *Blood*, Moldenhauer and colleagues report that a proportion of these interfollicular B cells, and also their thymic counterparts, contain activation-induced cytidine deaminase (AID), a key enzyme for immunoglobulin (Ig) heavy-chain class switch recombination and somatic hypermutation in germinal centers. This could indicate that they have only recently exited from the germinal center, although it is also possible that they represent B cells that undergo Ig recombination without entering the germinal center.

In the earlier paper, Marafioti et al proposed that interfollicular dendritic B cells and asteroid B cells might represent the elusive cell of origin of classical Hodgkin disease (arising respectively in lymph nodes and thymus). Features in common include their dendritic surface morphology, their location (early

nodal Hodgkin disease shows a predilection for interfollicular areas), and their mutated Ig gene status. It is also notable that the interfollicular area is the region where Epstein-Barr virus (present in 50% of classical Hodgkin but rarely in other lymphomas) proliferates



**Double immunofluorescence labeling of lymphoid tissue to show interfollicular B cells.** Top panel: The low-power view (left) shows B cells (labeled in red for CD20) and CD8<sup>+</sup> T cells (green). Scattered B cells are present in the interfollicular area adjacent to a B cell follicle (Foll). The high-power view (right) shows dendritic processes extending from several of these interfollicular B cells (arrow) and a single example of an interfollicular B cell (asterisk) in intimate contact with a CD8 cell. Bottom panel: Double immunofluorescence labeling for CD20 (green) and the dendritic cell marker CD208/DC-LAMP (red) shows that these 2 cell populations are clearly distinct. In the high-power view (right), typical interfollicular dendritic B cells are seen (eg, in the inset and as indicated by an arrow). Adapted from Marfioi et al<sup>1</sup> (used with permission).

gene expression and/or proteomic profiling, looking for similarities to nodal interfollicular B cells and to Reed–Sternberg cells. It might also be worth exploring the possibility that occasional cases of nodal diffuse large B–cell lymphomas arise from these cells (ie, are the peripheral equivalent of mediastinal B–cell lymphoma). ■

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topoietic hierarchy mirrors quantitative differences in the ability to efflux dyes, perhaps suggesting a similar gradient in transporter pump expression levels. Importantly, all bone marrow cells that are HSCs express high EPCR levels, and it appears that the converse is true as well. The availability of an explicit set of HSC markers will facilitate answers to a number of outstanding questions in HSC biology. First, these markers should facilitate a more precise definition of the bone marrow niches within which HSCs reside. Second, it should be possible to dissect the regulatory mechanisms that ensure a high level of EPCR expression in HSCs and progressively lower expression as more committed progeny are produced. Third, the actual role of EPCR in HSC biology is likely to be interesting. Fourth, the ability to isolate HSCs to near homogeneity using a single marker will certainly be a significant advantage. Recently, specific combinatorial expression patterns of the signaling lymphocytic activation molecule (SLAM) receptor family members have also defined distinct stages in the HSC and progenitor cell hierarchy.<sup>1</sup> It will be interesting to use these together with EPCR in efforts to further define and understand hematopoietic development. ■

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## ● ● ● HEMATOPOIESIS

Comment on Balazs et al, page 2317

# Hematopoietic stem cells, explicitly

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A study by Balazs and colleagues in this issue of *Blood* begins to fill a significant gap in our abilities to analyze the biology of hematopoietic stem cells.

Stem cells in mammalian tissues such as gut, epidermis, and blood are responsible for the robust generation of mature cells throughout adult life, requiring an ability to correctly balance self-renewal and differentiation cell fate choices, a process that is poorly understood. Unraveling stem cell regulatory mechanisms depends on the ability to identify these rare cells and to isolate them for functional analyses. Alternatively, as in the gut and epidermal systems, the positions of stem cells within complex tissue architectures have provided a “roadmap” for mechanistic studies. In the hematopoietic system, this has been difficult, although the hematopoietic stem cells (HSCs) can be isolated to near homogeneity using a variety of flow cytometric approaches. However, essentially all of these strategies require complex combinations of cell-surface (or other) markers, none of which are specific to HSCs. An “explicit” HSC marker has, to date, eluded identification. Building on results from HSC gene expression analyses, Balazs and colleagues show that endothelial protein C receptor (EPCR) is an “explicit” marker that can be used alone to isolate HSC from murine bone marrow. EPCR expression is quantitatively distributed in a small subset of bone marrow cells. The authors show that the very highest levels of expression correlate with the ability of the purified cells to reconstitute he-

matopoiesis after transplantation into radiation-ablated recipient animals. Furthermore, this population is not enriched for the more numerous committed progenitor cells that can produce myeloid and erythroid progeny in vitro. These progenitors are, however, enriched in populations that express intermediate levels of EPCR. Such a quantitative distribution of this molecule within the hema-

## ● ● ● NEOPLASIA

Comment on Aneja et al, page 2486

# Microtubules, leukemia, and cough syrup

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In this issue of *Blood*, Aneja and colleagues continue their interesting work on a novel class of antimicrotubule, anticancer, opioid drugs by showing that a synthetic derivative shows promise for leukemia treatment.

The natural opioid is noscapine, used for decades almost exclusively as an antitussive, and which even now may have new applications as cough syrup.<sup>1</sup> Joshi’s group has shown that noscapine and derivatives have interesting antimicrotubule properties that differ from the other 2 principal classes of anticancer drugs that target microtubules. Vinca alkaloids (eg, vinblastine) and taxanes (eg, paclitaxel [Taxol]) are widely used chemo-

therapeutic agents. But both are relatively toxic at effective doses, killing other dividing cells, including normal blood cells, and damaging peripheral axons, which are tightly packed with microtubules. Development of peripheral neuropathy is an important factor limiting vinca and taxane dosing.<sup>2</sup> Further, leukemic cells often become resistant to these drugs via the multidrug resistance (MDR) phenotype.<sup>3</sup> Aneja and colleagues now report