Cutting the head off chemokines

Chemokines are small secreted proteins that attract leukocyte migration. Chemokines play essential roles in the normal immune response against invading pathogens. Unfortunately, in an unregulated state they can also mediate abnormal leukocyte infiltration in ARDS, postinfarction damage, and multiple auto-immune diseases. In addition, chemokines or their receptors have also been subverted for nefarious purposes by viruses as diverse as KHSV and HIV.

Since abnormal expression of chemokines can produce so many diseases of leukocyte tissue destruction, a major issue in chemokine research is how the effect of chemokines is down-regulated. Such down-regulation after proper leukocyte tissue infiltration is important to prevent inappropriate flooding of adjacent normal tissue with activated leukocytes.

It has recently been shown that some chemokines can have their amino terminus cleaved off by extracellular proteases. Since the amino terminus mediates receptor activation, this creates truncated chemokines that can bind to but not activate their cognate receptors. Specific mechanisms for this have not been completely defined.

The report by McQuibban and colleagues in this issue (page 1160) provides a fascinating insight into the down-regulation of one subset of chemokines, the monocyte chemoattractants MCP-1, MCP-2, MCP-3, and MCP-4. They found that several matrix metalloproteinases (MMPs), which are secreted during the inflammatory response, can specifically cleave the amino termini of many of the MCPs. Intriguingly, MMP-2, secreted and activated late in the inflammatory response, uniquely cleaves MCP-3. This cleaved MCP-3 functions as a potent antagonist to macrophage chemotaxis both in vitro and in vivo. Indeed, cleaved MCP-3 not only had the capability of blocking the initiation of an in vivo inflammatory response but also completely abrogated prior inflammation.

These data have significant implications. First, this study provides a detailed mechanism by which chemokine activity is immediately down-regulated at a specific stage in the inflammatory response. Second, the cleaved MCP-3 may be clinically useful in preventing tissue damage in septic shock, viral infections, ARDS, or a number of diseases of abnormal macrophage infiltration. Third, since MMPs are important in many types of tissue remodeling from embryonic development to wound healing to cancer metastasis, it is tempting to speculate that this mechanism may be important in terminating local macrophage function during such tissue remodeling.

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HbE heterozygote RBCs inhibit P falciparum invasion, but does HbE have other tricks up its sleeve?

P falciparum malaria has modified the human genome considerably in endemic regions of the world. Most of the genes selected by malaria are hereditary red cell defects, as the sickle gene, the thalassemias, HbC, G-6PD deficiency, Southeast Asia ovalocytosis, and HbE. The last one might be the most frequent malaria-related genetic red cell defect in the world. In recent times, this mutation has appeared in nonendemic regions, including this country, by virtue of gene flow.

Chotivanich and colleagues (page 1172) describe an interesting finding: red cells of heterozygotes for HbE (AE) reduce the P falciparum invasion fourfold compared with AA cells and threefold compared with other red cell mutations, affording the host innate resistance. This finding places AE red cells in the same category as Southeast Asia ovalocytosis. In both, red cell membrane abnormalities appear to interfere with the complex dance involved in merozoite red cell invasion: lateral adherence, followed by apical adherence, then penetration, and finally release into the cytosol. AE red cell membrane defect could interfere with the process of invasion in one or several of these steps.

The paper also stimulates new questions. It is puzzling that HbE/β thalassemia (a severe disease) and homozygote EE red cells, a mild clinical condition, exhibit only a small invasion barrier. The case of HbE/β thalassemia is particularly puzzling, since β-thalassemia intermedia is known to damage the red cell cytoskeleton.

Moreover, the data in this paper and the previous findings by others of the partial inhibition of parasite growth in EE red cells suggest that EE and HbE/β thalassemia might represent an alternative, anti-P falciparum strategies yet to be elucidated. A new chapter seems to be unfolding in the genome’s quest for providing the host, if not with protection against acquiring malaria, at least from dying of malaria.

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B-CLL: is the enigma of disease heterogeneity about to be revealed?

B-chronic lymphocytic leukemia (B-CLL) can be a relatively easy management problem since a majority of these patients initially come to the hematologist with minimal-to-low tumor burden. But there is a compelling need for accurate prognostic parameters because at least 20%-30% of these patients will ultimately progress and require therapy. We are now in an era where exciting therapeutic options exist for the B-CLL patient. Thus, there is a therapeutic advantage to more accurately predict patients who are high risk and which early stage patients will progress quickly. Current accepted prognostic features include classification in the Rai or Binet staging system, lymphocyte-doubling time, marrow infiltration patterns, and select cytogenetic abnormalities. While these have proved useful,
they remain imperfect for use in an individual patient. Two recent pivotal papers by the Hamblin and Chiorazzi groups have defined immunoglobulin (Ig) mutational status and CD38 expression level as 2 new important prognostic markers. In this issue, 3 papers studying relatively large cohorts of B-CLL patients further study the association of these 2 novel biologic parameters with other biologic features to further our understanding of critical prognostic elements in B-CLL. In summary, these articles (1) affirm the value of Ig mutation status as an independent prognostic factor for B-CLL, (2) demonstrate that the incidence of high-risk genetic aberrations is significantly higher in patient tumor cells that express unmutated IgVH region genes than in those that express mutated Ig genes, and (3) identify 17p− and/or mutant p53 as a new independent prognostic factor in multivariate analysis.

Oscier and colleagues (page 1177) have added important new information regarding survivorship of B-CLL patients in relation-ship to the mutational status of the leukemic B-cell clone. Specifically, they have determined that unmutated IgVH genes are associated with trisomy 12 and deletion 11q23, 2 previously known unfavorable genetic alterations. Conversely, they showed that clones with mutated IgVH genes were associated with the more favorable genetic defect 13q14.

Kröber and colleagues (page 1410) present from a large cohort convincing data, which demonstrate that the high-risk 17p− and 11q− genomic aberrations were seen almost exclusively in patients with unmutated IgVH genes. Conversely and consistent with work by Oscier and colleagues, the clinically favorable 13q− abnormality was over represented in the patients with mutated Ig genes. These data continue to affirm the growing body of information that IgVH mutational status of the CLL B-cell clone is linked to disease outcome. In addition, the finding of more frequent deleterious genetic defects in the unmutated IgVH type clones suggests that these clones are more likely to undergo critical genetic trans-formation events. Future analysis of gene methylation patterns and chromosomal stability parameters in sequential fashion in these clones will be of interest. This latter study may lend insight into CLL B cell clones that are prone to undergo clonal evolution.

All 3 papers, using different approaches, affirm the unfavorable clinical outcome for patients with 17p/p53 mutation and/or loss. Using an alternative assay of p53 function, that is, responsiveness to ionizing radiation, Lin and colleagues (page 1404) demonstrated that all of the patients studied with dysfunctional p53 belonged to the unmutated IgVH subgroup. Moreover, dysfunctional p53 was a highly significant predictor of poor outcome. Of interest, when patients with functional p53 were studied, the prognostic power of Ig mutation status was lost. If the clinical use of this test is indeed feasible, there may be a powerful prognostic test now available.

The association of CD38 expression levels with genetic aberrations and Ig mutation status and its utility as a prognostic factor was also evaluated in the 3 papers. All 3 groups confirm the association between CD38 expression and relative lack of IgVH region mutations. Lin and colleagues were able to demonstrate that patients with more than 20% CD38+ leukemic cells exhibited significant shorter survival times than those with fewer than 20% CD38+ cells. But Oscier et al using a cutoff of 30% CD38 and Kröber et al using a cutoff of 7% failed to demonstrate that CD38 had independent prognostic significance. Since we know that CD38 levels on leukemic B cell clones may change with time and that mixed levels of CD38 expression are commonly observed in leukemic cells (Kröber et al), understanding the precise role that this molecule plays in this disease is problematic. Nevertheless, the association with Ig mutation status and prior reports in the literature demonstrating prognostic value for CD38 in B-CLL validates further functional studies (ie, adhesion, signaling capacity) of this molecule.

We are now blessed with a surfeit of laboratory tools to more accurately dissect the transformed programs in B-CLL clones. This collection of papers substantiates that, by further understanding critical features of CLL B cell clones, we can further discern disease outcome in B-CLL. This of course is not the final answer to the puzzle of disease heterogeneity but encourages us to keep trying.

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Platelet formation: a link between apoptosis and differentiation

Proteases of the caspase family represent the central executors of the apoptotic process. Many recent observations suggest that caspases, beyond their well known main role in cell death, exert important functions in other cellular processes, including cell differentiation and control of T-cell proliferation and cell-cycle progression. Concerning the role of caspases in cell differentiation, recent studies suggest that caspase activation is required for normal keratinocyte differentiation (Weil et al, Current Biol. 1999;9:361-364), for lens fiber differentiation (Ishizaki et al, J Cell Biol. 1998;140:153-158), and for erythroid maturation (Zermati et al, J Exp Med. 2001;193: 247-254).

De Botton and colleagues (page 1310) elegantly demonstrate that caspase activation within megakaryocytes is required for platelet production. They present evidence that in vitro–grown megakaryocytes exhibit during their terminal stages of maturation the activation of caspases 3 and 9. Two lines of evidence suggest that this spontaneous caspase activation observed under physiologic conditions is required for platelet production. They present evidence that in vitro–grown megakaryocytes exhibit during their terminal stages of maturation the activation of caspases 3 and 9. Two lines of evidence suggest that this spontaneous caspase activation observed under physiologic conditions is required for platelet production: (1) caspase inhibitors markedly decrease proplatelet formation, and (2) megakaryocytic cells overexpressing the antiapoptotic protein Bcl-2 exhibited reduced proplatelet formation. The most interesting and intriguing finding of this study, however, consisted in the observation...
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