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 chemotactic proteins 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 off the amino termini of most 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,
HbE heterozygote RBCs inhibit *P. falciparum* invasion, but does HbE have other tricks up its sleeve?

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