An unexpected link between HCV and platelets

Neither the cellular binding sites nor the extrahepatic reservoirs for the hepatitis C virus (HCV) are well understood. The study of Hamaia and colleagues (page 2293) investigates the characteristics of HCV binding to platelets and 2 mononuclear cell lines. Among the interesting findings of this study: (1) Most HCV (95%) circulates bound to IgG; only 1% of circulating virus is cell bound. (2) HCV binds efficiently to platelets. (3) The mechanism of HCV binding to platelets is different than to mononuclear cells in that platelets bind free and complexed HCV equally well and that platelet binding does not reach a saturation limit; platelet binding may represent simple absorption. (4) Although CD81 has been proposed as a major receptor for HCV absorption, HCV binds equally to CD81 and complexed HCV equally well and that mononuclear cells in that platelets bind free and antibody to CD81 does not block HCV binding. Thus, CD81-independent binding sites must exist. (5) The hypervariable region 1 (HVR1) of HCV appears to play an important role in viral attachment. (6) The binding characteristics of recombinant HCV envelope (rE2) are different than those of native HCV, suggesting that studies that employ rE2 may not be fully representative of natural infection.

The implications of this study are that platelets as well as mononuclear cells may serve to transport HCV to sites of immune recognition or alternately to sequester virions from such recognition. In addition, these hematopoietic cells may serve as important reservoirs of HCV that account for the almost universal infection of HCV-naive livers following liver transplantation. This study also indicates that HCV binding is not dependent on the postulated HCV receptor, CD81, and that HVR1 serves as an important attachment site of the virion. HVR1 is also the region presumed to be the target for neutralizing antibody against HCV and the region that under immune pressure mutates to create the vast HCV quasi species.

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Leukemia stem cells and constitutive activation of NF-κB

It has been clear for many years that leukemic cells from most patients with AML are organized into a hierarchy reminiscent of normal hematopoiesis. The disease is thought to originate in leukemic stem cells, characterized by an immature phenotype and possessing self-renewal capacity. This hierarchy was probably first appreciated when it was discovered that only a small subset of AML cells can form colonies in vitro, and later more elegantly documented by showing that only leukemic cells with a primitive immunophenotype can generate leukemia upon transfer into NOD/SCID mice. Since these stem cells, like normal stem cells, are relatively quiescent, it has been thought that they contribute substantially to drug resistance and thus to relapse. Therefore, in this era of targeted therapy, identification of biochemical and molecular features that distinguish leukemic stem cells from normal stem cells may be important in the design of the next generation of AML therapies.

Guzman and colleagues (page 2301) show that cells with a “stem cell phenotype” from the blood of patients with AML have constitutive activation of the NF-κB transcription factor complex; cells with a similar immunophenotype from normal marrow or cord blood do not. Further, leukemic, but not normal, CD34+ cells underwent apoptosis when treated with a proteasome inhibitor, MG-132, that blocks NF-κB activity (among other things). Although it has previously been reported that AML cells (and many other types of hematopoietic neoplasms) have constitutive activation of NF-κB and that AML cells are sensitive to MG-132, this is the first demonstration that activation of NF-κB is a major distinguishing characteristic between normal and leukemic stem cells. If selective killing of leukemic cells through inhibition of NF-κB can be verified in vivo, then this pathway may prove to be a fruitful one for drug discovery. Whether proteasome inhibition is the best way to inhibit NF-κB, or conversely whether the toxic effects of MG-132 are actually due to inhibition of NF-κB, remains to be determined. Other questions are also raised. Why is NF-κB activated in virtually all cases of AML? In normal cells, NF-κB is induced by diverse stimuli, such as growth factors, or as a cytoprotective response to toxic events. In leukemic cells, is increased NF-κB activity due to upstream signals from pro viability oncogenes such as ras or FLT3? Or is NF-κB induced by the cell to counteract some of the toxic effects of an oncogene such as myc? In the long run, the best way to inhibit NF-κB may well be to inhibit the activity of the oncogene that induces it. Finally, inhibition of NF-κB could have an indirect benefit in AML therapy. Inhibition of NF-κB has been shown to enhance sensitivity of several epithelial cancers to standard chemotherapy drugs, and it may therefore be possible to increase the therapeutic index of existing AML drugs without causing additional damage to normal stem cells.

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C/EBPα and the G-CSF receptor gene — partners in granulopoiesis?

The C/EBPs are a protein family with highly homologous leucine zipper domains designed to allow dimerization within the
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