approximately 40 patients entered on the IRIS trial and treated with imatinib. Approximately 40% of the subgroup of patients entered on the IRIS trial who had serial molecular analyses achieved this end point by 12 months and all remained without disease progression with an event-free survival of approximately 90% with long-term follow-up (see figure). Certainly, this is reassuring for this group of patients and therefore clinically helpful, but, only if one can measure MMR reliably. Q-PCR assays can be fickle and as documented by Branford et al, values can vary widely among different molecular laboratories. These same authors demonstrated that with exchange of clinical material, results could become relatively standardized on what is termed the “International Scale” (IS; in which 100% is the baseline value, with < 0.1% as an MMR and < 1% roughly corresponding to CCyR). However, they also emphasize the need for continued recalibration to maintain consistency of results.

And, the molecular assays are not perfect, even in the hands of experts. Hughes et al mention 6 patients apparently in MMR by molecular analyses who had the Philadelphia chromosome detected by cytogenetic assays done simultaneously. Indeed, assessment of MMR is not available in most molecular laboratories in the United States because they have not calculated the correction factor needed to correlate their results with the IS. It remains unclear how often the absence of this information adversely affects clinical management of individual patients.

Much of this uncertainty could be alleviated by the development of internal BCR-ABL “standards” which could be used to create a reference curve to generate the Q-PCR results. Efforts to create such a standard reagent from K562 cells are in progress. A minority of patients become completely Q-PCR “negative” and a recent study, with short follow-up, has suggested that perhaps a third of patients who are repeatedly PCR negative using sensitive assays may not have disease recurrence after imatinib side effects. As these newer agents are used more routinely as first-line therapy, long-term follow-up of molecular outcomes analogous to the study by Hughes et al will be needed because the kinetics of response are more rapid with the newer agents. Thus, we can expect an amplification of the number of articles documenting (and debating) the clinical merits of molecular quantification in the future.

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Comment on Sabado et al, page 3839

HIV and DC: hate at first sight

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In this issue of Blood, Sabado and colleagues report on the dynamics of DCs during the early phases of primary HIV infection, showing that changes in DC numbers and function which may play pivotal roles in the immunopathogenesis of chronic HIV infection, can in fact be observed even during the early stages of the disease. DC endritic cells (DCs) can be regarded as gatekeepers for the immune system. They provide the initial sparkle to ignite immune reactions against pathogens, but also shape and regulate the activity of effector immune cells and preserve the vital equilibrium.
The finding that, despite their reduction in number during primary HIV infection, both mDCs and pDCs retain the ability to stimulate T-cell responses—at least as alloantigens—and conserve or increase their responsiveness to direct stimulation with HIV or TLR7/8 ligands is noteworthy. This is substantiated by the authors’ finding that the expression of molecules involved in the signaling cascade of DC activation, such as TLR7 and IRF7, is increased in DCs from patients with primary HIV infection. These observations confirm that DCs can react—or overreact—to stimuli and elicit T-cell activation, preserving their role as master regulators of immune responses. This is a central issue in HIV pathogenesis. Thus, activated mDCs and pDCs that have transferred to lymphoid tissues may directly contribute to triggering chronic T-cell activation and exhaustion, as well as release inflammatory mediators that sustain pathogenic immune activation. Consistent with this view, the authors report the increased expression of interferon-stimulated genes in total leukocytes as well as remarkable differences in the gene expression profiles of both DC types from primary HIV-infected patients compared with controls.

The classic view of HIV disease as a chronic and relatively slow progressing condition has been reviewed in recent years, and increasing evidence suggests that the virologic and immunologic events that occur during primary HIV infection irremediably damage the immune system, which is left incapable of recovery and condemned to gradually fail. Rapid and irreversible loss of CD4 T lymphocytes from the gut mucosa occurs during acute HIV infection of humans and simian immunodeficiency virus (SIV) infection of macaques, leading to disruption of the mucosal barrier and microbial translocation, a chain of events that triggers and promotes pathogenic immune activation during the course of the disease. Furthermore, recent evidence shows that the up-regulation of interferon-stimulated genes is transient and limited to the acute phase in nonpathogenic SIV infection of natural host nonhuman primates. In contrast, the burst of these responses does not cease after the peak of viremia in pathogenic SIV infection of macaques, and correlates with chronic immune activation and disease progression.

The current study places the dysregulation of
CD56 dim NK cells

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NK cells are an important component of innate immunity. Their best-characterized function is the capability to kill virus-infected or tumor cells and to release proinflammatory cytokines. 1,2 NK-cell function is primarily regulated by several activating and inhibitory receptors, some of which recognize major histocompatibility complex (MHC) class I molecules and play a fundamental role in the capability of NK cells to discriminate between normal and aberrant target cells. 3-5

Human mature natural killer (NK) cells are generally divided into 2 subsets based on the relative surface density of CD56 antigen: CD56bright cells, predominant in secondary lymphoid tissues, and CD56dim cells, predominant in peripheral blood (PB). CD56bright cells have been shown to derive from CD34+ hematopoietic stem cells (HSC) via phenotypically identified stages. 6,7 In turn, CD56bright PB NK cells are thought to give rise to CD56dim cells because they appear first after HSC transplantation and in cytokine-driven models of NK-cell in vitro differentiation. 7,8 In addition, they have longer telomeres than CD56dim cells. 9 In agreement with these concepts, recent studies revealed that the density of surface expression of CD94 or of CD62L identifies functional intermediaries between CD56bright and CD56dim human NK-cell subsets. 10 These data support the notion that, in vivo, human CD56bright NK cells may undergo progressive differentiation ending with a CD94−CD62L−CD56dim phenotype.

Notably, it was commonly accepted that CD56bright NK cells are the main source of cytokine production, while CD56dim are

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Model of human CD56dim NK-cell differentiation. Different experimental evidence supports the notion that peripheral blood CD56bright cells give rise to CD56dim NK cells. These 2 subsets differ in proliferative potential, cytolytic activity, and capability of secreting IFN-γ or TNF-α upon cytokine stimulation. With respect to cytokine secretion, however, recent studies revealed that CD56dim are capable of rapid secretion upon cell triggering via activating receptors (Fauriat et al. and A. De Maria et al., personal communication). Two independent articles showed that CD56dim cells can be further fractionated into different cell subsets on the basis of their surface markers and function. As depicted in this schematic figure, the progression of CD56dim toward putative terminally differentiated NK cells is accompanied by the progressive loss of their proliferative capacity and the acquisition of more efficient cytolytic activity. Different maturational stages can be identified on the basis of the progressive down-regulation of CD94 and the expression of (1 or more) KIRs and of CD16. CD62L expression is acquired at later stages and marks terminally differentiated cells with high cytolytic activity but very low proliferative potential.

Dissecting CD56dim human NK cells

Comment on Björkström et al, page 3853, and on Lopez-Vergès et al, page 3865

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Proliferative potential

CD56bright

CD94***

KIR*

CD16+

perforin*

CD56dim

CD94**

KIR*

CD16±

perforin**

CD56**

KIR+

CD16−

perforin***

Cytolytic activity

CD56dim

CD94***

KIR*

CD16+

perforin*

CD56dim

CD94**

KIR*

CD16±

perforin**

CD56dim

CD94*

KIR*

CD16±

perforin*

CD56dim

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