The silent war against CMV in CLL

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In this issue of Blood, Pourghesari and colleagues demonstrate that there is a highly exaggerated expansion of CMV-specific CD4⁺ T cells in CMV-seropositive compared with CMV-seronegative CLL patients, particularly after chemotherapy. Despite this, patient survival is reduced by almost 4 years in the CMV⁺ cohort. However, as CMV⁺ CLL individuals do not exhibit symptoms of CMV-induced disease, the negative impact of CMV infection on survival may occur by indirect mechanisms.

Persistent cytomegalovirus (CMV) infection drives the accumulation of CMV-specific T cells (both CD4⁺ and CD8⁺), especially in older humans. This accumulation of CMV-specific T cells is even more marked in patients with chronic lymphocytic leukemia (CLL) compared with age-matched controls. These patients do not experience severe problems like pneumonitis, uveitis, and colitis that can be caused in immunocompromised individuals by this virus. Therefore, the anti-CMV T-cell response in CLL patients is sufficient to prevent CMV-induced disease. Although an intense, but asymptomatic, secret battle between CMV and the host also takes place in healthy subjects, CMV seropositivity and the associated large expansion of specific effector T cells also predict decreased survival in older subjects (> 80 years of age). Thus, there is a striking parallel between CMV infection in older humans and in CLL patients where infection with this virus in both groups may shorten life expectancy (see figure). However, it is not clear whether the decreased survival is directly due to episodes of CMV reactivation, which seems to be well controlled by specific T cells, or to an indirect effect possibly exerted by the large population of CMV-specific T cells themselves.

Pourghesari et al speculate that the immunosuppression associated with CLL triggers subclinical viremia that in turn activates and expands CMV-specific T-cell populations. In addition, they suggest that chemotherapy may induce increased immune suppression that leads to greater viral reactivation and further expansion of CMV-specific T cells. They were not able to detect CMV reactivation in the blood of CLL patients by polymerase chain reaction, suggesting that viral replication is controlled effectively. However, the blood may not be the best place to detect viral reactivation because CMV DNA can be detected in the urine, but not the blood, of older, but not younger, CMV-seropositive subjects. Whether CMV DNA is also detectable in the urine of CLL patients remains to be determined. Nevertheless, the reactivation of the virus itself does not seem to be the problem because CLL patients do not exhibit any signs of CMV-induced disease.

CMV-specific CD4⁺ and CD8⁺ T-cell populations are both increased in seropositive CLL patients. One study noted that CMV-specific T cells are driven toward replicative exhaustion suggesting that defects in these cells may develop as a result of continuous viral reactivation. Perhaps the expanded cells themselves have the negative impact. The expanded CMV-specific T-cell pool can constitute over 40% of the total CD4⁺ T-cell repertoire of CLL patients receiving chemotherapy; circumstantial evidence indicates that such expanded T-cell populations can have adverse consequences for immunity. In mice, for example, specific T-cell expansions have been shown to inhibit the function of other antigen-specific T-cell populations and cause disease. Furthermore, expanded CMV-specific T cells may inhibit the expansion of Epstein-Barr virus–specific T cells in the same
individuals. Therefore, there is a possibility that the detrimental effect of CMV infection in CLL patients results from the constriction of the total T-cell repertoire by the overwhelmingly increased numbers of the CMV-specific T-cell population (see figure) because of the competition for essential growth factors and/or overcrowding of tissue niches that support memory T-cell survival. Such an effect would lead to the loss of certain essential memory T-cell populations directed towards other microorganisms. The increased reactivation of latent pathogens (ie, Varicella zoster virus [VZV]) that occurs in CMV-seropositive CLL patients supports this possibility. A similar situation may be at work during the aging of healthy CMV-seropositive humans, where accumulation of CMV-specific cells may occlude VZV-specific cells from tissue niches thus leading to the increased incidence of VZV reactivation (shingles) in older humans (see figure). A crucial point that requires further investigation is whether the expanded CMV-specific T-cell populations in CLL patients may restrict the quality of the T-cell response to the leukemic cells themselves.

Thus, the study of Pourgheysari et al provides interesting insight into the dominant role that CMV infection has on shaping the T-cell repertoire in CLL patients. Although the exact cause for the negative association of CMV seropositivity and survival in these patients is not currently clear, determining whether targeting the virus itself—or the T-cell expansions that it induces—may improve the survival of both CLL patients and older humans.

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REFERENCES

Comment on Kapitsinou et al, page 3039

Dual control: the HIF-2 regulator

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Identification of the specific roles of individual members of the hypoxia-inducible factor (HIF) family of transcriptional activators provides insights into the pathogenesis of anemia and erythrocytosis that may enable the development of novel therapies for these disorders. In this issue of Blood, Kapitsinou and colleagues1 use conditional ablation of Hif-2α in the murine kidney to establish that hypoxic induction of erythropoietin (Epo) is completely dependent on Hif-2α and that in the absence of renal Hif-2, hepatic Hif-2 becomes the main regulator of serum Epo.

Toward the end of the 19th century, 3 Frenchmen—Paul Bert, Denis Jourgadan, and Francois-Gilbert Viault—established a theory of the relationship between reduced oxygen pressure and increased circulating red blood cells (RBCs) based on their work on altitude in Mexico and the Peruvian Andes.2 In 1992, interest in understanding the physiologic and molecular basis of this adaptation to hypoxia led to the discovery of EPO and the HIF family of transcriptional activators.

During human fetal development EPO is produced mainly in the liver but its primary site of production changes to the kidney during late gestation. Although the adult liver does not normally produce EPO under normoxic conditions, it retains the capacity to produce EPO in the event of renal impairment. In the 1990s, in vitro studies by Gregg Semenza and colleagues identified a novel transcription factor, HIF-1, which was widely assumed to be responsible for the hypoxia-induced increase in EPO found in Hep3B cells, based on its binding to an 18-nucleotide fragment of the oxygen-sensitive 3′ EPO regulatory element.3,4 However, recent genetic studies in mice5-7 and investigations of patients with familial erythrocytosis8-10 have provided strong evidence that HIF-2α, not HIF-1α, is the prevalent regulator of circulating EPO levels.

In an elegant study, Kapitsinou and colleagues inactivate Hif-2α specifically in the kidney by Cre-loxP recombination enabling the contribution of renal Hif-2 signaling to Epo homeostasis to be determined directly (see figure). Loss of renal Hif-2α resulted in hypoproliferative anemia with RBCs and hematocrit (HCT) reduced to half of the normal levels, due to significantly lower circulating serum Epo levels in the mutant mice. The mutant mice also had increased levels of renal Hif-1α protein and increased expression of the Hif target genes Glut1, Pfk, Lha, and Phd3, but not Epo production, providing further evidence that hypoxic regulation of Epo in the kidney is not dependent on Hif-1α.

To investigate the role of hepatocyte-derived Hif-2, the authors generated double mutants lacking or substantially reducing Hif-2α in the kidney and liver (see figure). These animals had significantly reduced serum Epo levels compared with their renal Hif-2-deficient, single mutant littermates indicating that hepatic Hif-2 plays a role in Epo regulation of the single mutants under baseline conditions. When further challenged by phlebotomy the double mutants had a 70% reduction in serum Epo levels compared with their single mutant counterparts. This suggests that in this scenario, at least 70% of serum
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