development and trials are currently under way investigating Syk inhibition in a wide range of disorders from chronic immune disorders such as immune thrombocytopenic purpura to malignancies such as retinoblastoma. Given their general safety in these initial trials, a case can be made for a clinical translational trial of a Syk TKI in malaria.

But there is a potential for other uses of Syk inhibition in hematology. Many red cell membrane disorders involve band 3, from hereditary spherocytosis and glucose-6-phosphate dehydrogenase favism to *Streptococcus*-mediated hemolysis.[6-9] Indeed, many of the pathologies of sickle cell anemia involve band 3 and there might be benefit from therapies that decrease band 3 clustering and allow for membrane stabilization, decreased microparticle formation, and decreased free hemoglobin.[10]

Given the high frequency of both sickle cell anemia and malaria in Africa, Syk inhibition has the intriguing potential for benefit (in combination with currently accepted effective therapies) on many levels for several disease processes.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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TRANSPLANTATION

Comment on Hill et al, page 1062

Chromosomally integrated HHV-6: a new piece of the puzzle

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In this issue of *Blood*, Hill et al address the issue of the role of inherited chromosomally integrated human herpesvirus 6 (iciHHV-6) for complications, especially acute graft-versus-host disease (GVHD) occurring after allogeneic hematopoietic cell transplantation (HCT).[1]

The importance of human herpesvirus 6 (HHV-6) for severe complications after allogeneic HCT has remained unclear despite it being 1 of the most ubiquitous viruses, with almost everybody being infected by the age of 18 months. There are several reasons for this. One reason is that we in fact are dealing with not 1 but 2 viruses: HHV-6A and HHV-6B, with HHV-6B being the most frequent. Another reason is that the clinical consequences despite several studies performed over the last decades have not been fully appreciated. It is now recognized that HHV-6B is the most common cause of viral encephalitis after allogeneic hematopoietic stem cell transplantation (HSCT),[2] and there is emerging evidence associating HHV-6B with acute GVHD and other complications to allogeneic HSCT.[3] A third reason is that there is no antiviral agent with specific efficacy against HHV-6, making treatment studies to confirm the impact of the virus impossible. Finally, HHV-6A and HHV-6B have the unique, although uncommon, capacity to integrate into the human genome, allowing vertical transmission and also transmission of the integrated virus from the donor to the recipient through the HSCT itself. For many years, this was seen mostly as a nuisance, making the diagnosis of "true" HHV-6 reactivation more difficult to assess.[4] However, more recently evidence has emerged showing that iciHHV-6 can reactivate and can have important consequences.[5]

Hill et al used a large sample repository consisting of >4000 donor-recipient pairs using an ingenious screening algorithm to identify patients and donors with iciHHV-6 with the aim of assessing if integrated virus conferred an increased risk of complications. The frequencies of individuals with iciHHV-6 were as expected from previous reports, ~1% to 1.5%, resulting in 100 cases where the recipient, the donor, or both had integrated virus. By multivariate analysis, Hill et al found that iciHHV-6 in either the recipient or the donor was associated with an increased risk for acute GVHD grades II-IV. Furthermore, the frequency of cytomegalovirus reactivations was increased in recipients carrying iciHHV-6. There were no other statistically significant associations with any analyzed outcome variable.

How can these associations be explained? HHV-6 reactivation has also been associated with increased risks for acute GVHD and cytomegalovirus reactivations, and the findings would indicate that also the integrated genome could influence the likelihood for these complications. In addition, it is suggested due to the ubiquitous presence of HHV-6B in the population and high rate of reactivation in HSCT recipients that the risk is increased beyond what is mediated by HHV-6 replication itself. It is possible that in the setting of severe immunosuppression, such as after an allogeneic HCT, that the likelihood for gene expression and possibly viral replication from iciHHV-6

is increased. The effect by iciHHV-6 could then be through influence on the immune reconstitution or direct antiviral T-cell activity after an allogeneic HSCT. Strenger et al showed that individuals with iciHHV-6 have functionally active T-cell immunity with more virus-specific $CD8^+$ cells than those without iciHHV-6.[6] Because of the retrospective nature of the study, it was not possible to assess whether the integrated virus contributed to HHV-6 replication in recipients who either had iciHHV-6 or had integrated virus transferred from the stem cell donor.

One question that is not addressed is the mechanism that increases the risk for grade II-IV acute GVHD to a similar range irrespective of iciHHV-6 source (donor or recipient). The underlying immunological situation is different because iciHHV-6 can be detected in all somatic cells. Thus, the recipient would have iciHHV-6 in all target tissues for acute GVHD and in the residual hematopoietic cells, making all these cells potential targets for donor T cells. On the other hand, the donor's transferred hematopoietic cells would have iciHHV-6, and it is unclear how this would result in an increased risk for acute GVHD. Thus, there are uncertainties about the underlying mechanism.

Where do we go from here? The authors suggest in their conclusions that iciHHV-6 status could be incorporated into donor selection algorithms or patient management strategies. This interpretation seems a bit premature at this time. Prospective studies are clearly needed to verify and extend their findings, including identifying the possible mechanism involved in iciHHV-6 complications. The relatively low number of donors and recipients positive for iciHHV-6 in the population will require multicenter collaboration to perform such studies.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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