Wiskott-Aldrich syndrome is caused by mutations in the WASP gene, which affects the function of most hematopoietic cells and leads to immunodeficiency. In this issue of Blood, Morales-Tirado and colleagues show that T helper cells lacking WASp have a selective deficiency in their memory response.

The Wiskott-Aldrich syndrome protein (WASp) is a crucial regulator of actin polymerization. Its gene is located on the X chromosome and when mutated, it leads to thrombocytopenia, immunodeficiency, and eczema. WASp is expressed in hematopoietic cells and in its absence, migration, adhesion, activation, and antigen uptake malfunction. It has previously been shown that WASp plays a role in T-cell activation, being important for the regulation of the so-called immunologic synapse. This membrane structure, crucial for activation of T cells, is formed between T cells and antigen-presenting cells and is composed of clusters of T-cell receptor, adhesion molecules, and signaling molecules. It has also been suggested that WASp can regulate transcriptional activation in T cells independent of its role in actin polymerization.

Th1 cells secrete IL-2 and IFN-γ, which are particularly important for cell-mediated responses, whereas Th2 cells secrete IL-4, IL-5, and IL-13, which play important roles in humoral immunity and atopic allergy. There are also more newly discovered CD4+ cell populations such as Th17 cells, T follicular helper cells, and Treg cells.

In this issue of Blood, Morales-Tirado et al show that cytokine secretion from activated primed T helper cells is affected in the absence of WASp. They demonstrate that absence of WASp leads to lower IFN-γ and IL-4 secretion in primed, in vitro--activated Th1 and Th2 cells, respectively. Secretion of IFN-γ can be rescued by signals from antigen-presenting cells, whereas secretion of IL-4 cannot. Levels of other Th2 cytokines, such as IL-5, IL-10, and IL-13, were also lower in the absence of WASp. Early events in Th2 differentiation are not affected by the absence of WASp and there is no measurable defect in transcriptional activation of the il4 gene in the memory response. Thus, there is an uncoupling of IL-4 protein production and transcription in Th2 effector function. Morales-Tirado et al give evidence that this effect could be due to a deficiency in activation of the signaling molecule ERK, which might regulate translation or protein stability.

In their experiment, Morales-Tirado et al went on to analyze T helper cell function in parasite responses in vivo, studying WASp-deficient T cells in a WASp-sufficient environment. They found that T cells mediated protective immunity and parasite clearance in a Th1 response, but were unable to support a Th2 response to the nematode *Nippostrongylus brasiliensis*. Thus, there was a significant delay in parasite clearance, which seemed to be due to lower IL-4 and IL-13 levels as well as reduced recruitment of innate effectors to infected tissue.
The experiments performed by Morales-Tirado et al are puzzling in view of the elevated IgE levels in WAS patients, considering that IgE production is dependent on IL-4. If Th2 cells are deficient in IL-4 secretion, where does IL-4 come from? Morales-Tirado et al show that basophils and the minor T-cell subpopulation γδ T cells can produce IL-4 in a manner independent of WASp. They propose that these cells are responsible for IL-4 production in WAS patients.

The paper by Morales-Tirado et al puts forward new aspects of WASP regulation in T cells. Their findings are interesting but do not always agree with previous data. More studies are needed to fully understand why there is reduced cytokine production in WASP-deficient T helper cells. Whereas Morales-Tirado et al measured steady-state levels of cytokine protein or mRNA, it would be interesting to determine rates of synthesis or degradation. Furthermore, it will be very important to confirm their findings using T cells from WAS patients. The paper by Morales-Tirado et al gives further insights into the immunodeficiency in WAS patients and puts additional focus on the T cells. This could be helpful in finding better treatments for the disease.

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

REFERENCES

Comment on Klingebiel et al, page 3437

Haploidentical transplantation in children

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In this issue of Blood, Klingebiel and colleagues present a summary of the outcomes of children and adolescents treated with a T cell–depleted haploidentical HCT for ALL. This paper presents one of the largest experiences to date that describes the outcome of 127 children receiving a haploidentical HCT’s using the EBMT registry from 36 pediatric centers.

A constant challenge for pediatric hematopoietic cell transplantation (HCT) centers is finding an acceptable donor for a child with very high-risk acute lymphoblastic leukemia (ALL) in first complete remission (CR1) or relapsed ALL. When no acceptable sibling donor is found, most centers attempt to find an HLA–identical unrelated adult marrow donor or umbilical cord blood (UCB). Unfortunately, initial searches frequently fail to identify acceptable HLA-matched unrelated donors, leading the center to 1 of 2 options. These are either a T cell–depleted haploidentical parent donor or a 4-of-6 HLA–matched unrelated UCB. The chance of finding a parent donor, as long as the parents are in good health, is 100%, and that of a 4-of-6 HLA–matched unrelated umbilical cord blood is as high as 98%. Thus, the availability of an acceptable donor from the 2 sources is essentially identical for a pediatric HCT center.

In this study in this issue of Blood, Klingebiel and colleagues found that smaller pediatric centers performing a T cell–depleted haploidentical HCT had a poorer outcome than did larger centers. Significant differences included a higher rate of cytomegavirus positivity in donor and recipient, greater use of the Isolex T-cell depletion, less total body irradiation, and more antithymocyte globulin or antilymphocyte globulin as part of the conditioning regimen at the smaller centers. Adjustment for these variables still supported the conclusion that the leukemia-free survival was higher and the relapse incidence was lower at larger pediatric transplantation centers.

Although between 20% to 25% of all allogeneic HCT performed worldwide are in the pediatric population, pediatric HCT centers are predominantly smaller centers. The outcomes of a 4-of-6 HLA–matched UCB transplantation have been evaluated in relatively large series by both the CIBMTR and Eurocord. In the CIBMTR study, Eapen et al evaluated 267 children with ALL who received a 4-of-6 HLA–matched UCB transplant. The 5-year event-free survival (EFS) for these patients was 33% with a transplantation-related mortality of 46% and relapse rate of 19%. Similarly in Eurocord, Roche et al evaluated 290 children receiving an unrelated UCB transplant for ALL with a 2-year EFS of 65% for CR1, 43% for CR2, and 22% for CR3 patients. They also compared outcomes with 118 children receiving a haploidentical transplant and found that, although the children receiving a UCB transplant had a higher graft failure rate and acute GVHD rate, they had a lower relapse rate. The transplantation-related mortality and disease survival rates were similar. The results from these studies evaluating unrelated UCB transplants is almost identical to the outcomes quoted in a recent review of T cell–depleted haploidentical transplants of 3-year disease-free survival of 22% to 48%.

The findings in the Klingebiel paper suggest that medium-sized and small pediatric HCT centers should focus on the use of unrelated UCB transplants rather than attempting the more technologically dependent approach of T cell–depleted haploidentical transplants. One potential option that has not been rigorously evaluated in the pediatric setting is the use of a lower technology–dependent haploidentical donor transplant approach such as post-HCT cyclophosphamide without any ex vivo T-cell depletion. The additional advantage of this approach is that it could potentially be applied to countries outside of Europe and North America where access to UCB is limited and the parents are immediately available.

The other concern raised by the Klingebiel study is the very poor outcome for ALL in...
When T cells cannot help

Eva Severinson