Immunoproteasomes are constitutively expressed in immune tissues and are expressed at much lower levels in other cell types. Immunoproteasomes play a major role in antigen presentation on MHC class I. These proteasomes, while of similar efficiency to the standard or constitutive proteasome, have different cleavage preferences so that the spectrum of antigenic peptides produced differs from that seen with the standard proteasome in other cells. These uniquely generated peptides influence CD8+ T-cell responses. While we are only now beginning to understand the role the immunoproteasome plays in normal cells, mounting evidence is beginning to suggest its dysregulation may play a role in diverse diseases including Huntington disease, macular degeneration, and inflammatory bowel disease. With this biology in hand and the experience of bortezomib alongside them, Kuhn and colleagues have identified a series of immunoproteasome-specific inhibitors (IPSIs), using an in vitro screen. Using purified preparations of standard (or constitutive) proteasomes and immunoproteasomes, they screened a rationally designed series of peptidyl-aldehydes, identifying one with unique specificity for the immunoproteasome. IPSI-001 preferentially targeted the β1i subunit, inducing accumulation of a host of varied proteins including ubiquitin–protein conjugates and proapoptotic proteins. Kuhn et al demonstrate that targeting the immunoproteasome in multiple myeloma cell lines and patient specimens with IPSI-001 produced a concentration dependent cytotoxicity. What is equally as interesting, and similar to the constitutive proteasome inhibitor experience, is that the IPSIs appear to overcome the acquired drug resistance phenotype in malignant cells.

Clearly, there is much to be learned about the differential functions of constitutive and immunoproteasomes. The demonstration that relatively unique inhibitors could be developed for one form of proteasome over another is remarkable and shows how a clearer understanding of even subtle differences in biology can lead to new hypotheses about treatment. While it will be years before we can declare this exercise a therapeutic success, it is abundantly clear that our ability to both understand and potentially manipulate the biology represents an exciting scientific advance.

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LYMPHOID NEOPLASIA

Comment on McCann et al, page 4677

Primary central nervous system lymphoma: coming or going?

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PCNSL is a rare disease, affecting about 1200 people each year in the United States. Its very name highlights its most unique feature: a diffuse, large B-cell lymphoma limited to the CNS. It may involve the brain, cerebrospinal fluid, spinal cord, or the eyes which are actually neural tissue. How does such a malignancy arise in the only organ system of the body that is devoid of lymph nodes and lymphatics?

A small number of predominately T lymphocytes traffic in and out of the nervous system normally, and can be attracted to the central nervous system (CNS) by a wide variety of pathologic processes including infection. Normal B cells can also move into the CNS, but are less prominent than T cells. They can also be attracted by pathologic processes, such as multiple sclerosis, where the initiating insult is unknown. So how does primary central nervous system lymphoma (PCNSL) develop? Does a B cell become transformed during its excursion through the brain and get trapped there, or does a cell transformed in the periphery find its way into the CNS where it lodges and proliferates?

Clinical data give a few hints but no real answers to this question. Fewer than 10% of patients with presumed PCNSL have an identifiable site of systemic involvement at diagnosis, and often the search for that single site of extra-CNS disease must be meticulous or it is missed. Because these sites are often small and involve a single extranodal area, it is unclear whether they represent the initial site of tumor that then spreads to the CNS, or if the direction of the tumor spread is in the opposite direction. Furthermore, about 10% of patients with PCNSL ultimately relapse with clinically apparent systemic disease, although more than 25% have systemic sites detected by (18)F-fluorodeoxyglucose PET imaging when they develop CNS relapse. This may occur years after their initial diagnosis and apparently successful therapy. However, the 25% estimate is lower than expected if one postulates a systemic source of tumor cells, present at diagnosis, and treated only by a CNS-directed chemotherapy regimen, which is usually inadequate to eradicate systemic disease. The source of these cells and their biology has clinical as well as academic relevance. Understanding the origin of this disease and its potential triggers may hold an important key to improved therapies which are sorely needed.

In this spirit, the work of McCann and colleagues makes a valuable contribution. They demonstrated restricted Vγ1 gene usage, particularly asymmetric usage of the Vγ4 family, favoring the V4-34 gene in the tumor tissue of 12 patients with PCNSL. These findings expand previous data in a disease where securing tumor tissue can be particularly challenging. In addition, they also had blood and bone marrow specimens taken at diagnosis from 3 patients and were able to demonstrate a tumor-related subclone in the peripheral specimens of all three. They could also show that the subclones identified in the periphery were not present in the brain specimen and that continued diversification occurred in the
Comment on Liuba et al, page 4790

Intrauterine transplantation

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In this issue of Blood, Liuba and colleagues provide important results in support of intrauterine transplantation for fetuses with X-SCID.

Using a congenic mouse model, Liuba and colleagues show that lymphoid–primed multipotent progenitors are superior to hematopoietic stem cells in providing rapid lymphoid reconstitution following intrauterine transplantation, with sustained polyclonal B-cell production. Furthermore, they clearly demonstrate that in this model, intrauterine transplantation results in superior B-cell and T-cell reconstitution of X-linked severe combined immunodeficiency (X-SCID) patients as compared to delaying transplantation until the neonatal or adolescent age range. Although caution must be executed when extrapolating these data to humans, the study is very interesting and important in regard to the potential for providing a cure for these children before birth.

Since Touraine et al published the first instance of intrauterine transplantation in a human fetus affected by bare lymphocyte syndrome (BLS) in 1989, we are aware of 4 X-SCID intrauterine transplantation cases. All these fetuses survived and were chimeric at birth. Despite favorable results, the intrauterine approach was criticized by several authorities in this field who claimed that this approach did not offer any advantage over postnatal transplantation. The main arguments against intrauterine transplantation were that the fetal invasive procedure carried a certain additional risk, and if the mother was used as a donor, there might be an increased risk for graft-versus-host disease (GVHD), a condition which cannot be treated prenatally. Conversely, promoters of intrauterine transplantation claimed that reconstitution of the immune system before birth results in reduced susceptibility to infections in the neonatal period, and to an improved psychosocial situation for the family. Other potential advantages for an intrauterine approach include cost savings and a reduced risk of GVHD in the fetal environment.

Not surprisingly, these varied opinions on the risk–benefit balance of intrauterine transplantation were expressed by representatives from different fields of medicine. Those arguing against are usually transplantation clinicians comfortable with postnatal transplantation procedures, and those arguing in favor of intrauterine transplantation usually represent specialists in fetal medicine and fetal surgery. Thus, a consensus has been difficult to reach and fetal transplantation has not been widely adopted, despite the fact that cases treated in utero had outcomes comparable with the best reported with postnatal transplantation.

So far, 46 cases of intrauterine human transplantation for various indications have been reported. In 1 case, the fetus did not survive the procedure. A % complication rate is in agreement with the risk calculation performed by Liuba et al. Likely, the complication rate can be reduced further using a 22-gauge needle and modern ultrasonic guidance.

The lack of relevant animal models allowing direct comparisons between prenatal and postnatal transplantation has hampered further development in this field. The work by Liuba et al adds important information. It seems that the earlier the reconstitution of the immunologic system takes place, the better the results. This needs to be considered by those involved in the care of mothers carrying fetuses potentially affected by X-SCID.

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