thrombosis. Alternatively, the interaction between the monoclonal cell population and the host may be more intense shortly after initiation of the clonal plasma cell expansion. Thereafter, contra-regulatory mechanisms may dampen the stimulatory activity and thereby reduce, but not efface, the thrombotic risk.

Only patients with an IgG or IgA isotype, but not those with an IgM paraproteinemia, were at increased risk for thrombosis. This is an important observation pinpointing a substantial difference in the underlying biological processes in patients with different paraprotein isotypes. However, most likely not the paraprotein itself but rather the clonal cells and their interactions with the components of the host account for all or most of the different biological and clinical sequels.

Patients with MGUS had an almost 2-fold increased risk of arterial thrombosis compared with matched controls, an observation not reported before, although its explanation needs still to be elucidated. The analysis in patients with myeloma revealed for the first time also an increased risk for arterial thrombosis, of similar magnitude as in MGUS. These latter findings are substantiated by a prospective cohort study of the HOVON group, which included patients receiving induction therapy either with TAD (thalidomide-adriamycin-dexamethasone), PAD (bortezomib-adriamycin-dexamethasone), or VAD (vincristine-adriamycin-dexamethasone), followed by stem cell transplantation. These authors observed arterial thrombosis in 11 of 195 patients (5.6%) followed for 522 patient-years. The incidence of arterial thrombosis was not different in the 3 treatment cohorts (VAD: 5.9%, TAD: 4.5%, PAD: 6.4%), with 5 of the 11 events occurring during induction therapy. In this study, multivariate analysis revealed increased factor VIII levels, together with hypertension and smoking as critical risk factors for arterial thrombosis. Importantly, 4 patients developed arterial thrombosis while on therapy with vitamin K antagonists, and 2 despite low-molecular-weight heparin prophylaxis, indicating that platelet inhibitory treatment might be more effective and appropriate in reducing the incidence of arterial thrombosis.

What are the consequences for clinical management? For MGUS patients, applying the widely accepted guidelines for antithrombotic prophylaxis should suffice, therefore restricting therapy only to persons with additional risk factors for thrombosis. In multiple myeloma, the situation is more complex because the thrombotic risk depends not only on disease-related and conventional risk factors, but even more on the type of antimalkyoma therapy applied. Thalidomide, high-dose dexamethasone, doxorubicin, etrypoietins, and lenalidomide all increase the risk for thrombosis. Guidelines for prophylactic interventions have been published, but several of the recommendations are based on expert opinions rather than on solid clinical data. In the future, we should aim at elucidating the underlying causes of increased thrombosis risk in greater detail, establish more precise risk models for patient selection for prophylactic treatment, and elucidate the value of novel oral antithrombin and antifactor Xa inhibitors in this setting.

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immunobiology

Comment on Isnardi et al, page 5026

The anergic B cell

Sarah F. Andrews and Patrick C. Wilson UNIVERSITY OF CHICAGO

In this issue of Blood, Isnardi and colleagues describe a phenotypically distinct population of autoreactive B cells that have become functionally limited upon stimulation, or “anergic.” Importantly, these cells are found at increased frequency in some rheumatoid arthritis patients and in patients with autoimmune-associated CVID.

The concept of clonal anergy was first proposed by Beverly Pike and Gustov Nossal in 1982 when they found that B-cell precursors cultured with high levels of antibody against surface IgM (anti- 

Cμ) impeded any B-cell development. In contrast, low concentrations of anti-Cμ resulted in normal numbers of B cells. However, unlike B cells that emerged in the absence of any anti-Cμ, these cells could no longer be activated by polyclonal stimulation to proliferate or to secrete antibody. Clonal anergy was proposed as a way to inactivate B cells stimulated early in development when only autoantigens would be presented. Experiments by the Goodnow group elegantly demonstrated clonal anergy in vivo using mice with transgenic B-cell receptors (BCR) against hen-egg lysozyme (HEL). When crossed to mice expressing a soluble form of HEL, the transgenic B cells became anergic. In the more than 20 years since these first papers were published, there have been many informative studies describing anergic B cells in unmanipulated and various transgenic mouse models, but only now are we beginning to characterize anergic B cells in humans.
The anergic B cells described by Isnardi et al in this issue of Blood were naive-like B cells identified primarily by down-regulation of cell-surface complement receptor 2 (or CD21<sup>lo</sup>).1 Because chronic infection and other autoimmune diseases such as lupus have been previously reported to also cause a CD21<sup>lo</sup> (in some instances, anergic) phenotype, Isnardi et al propose that this phenotype results from the common feature of being chronically stimulated by B-cell receptor engagement leading to an eventual reduction in signaling capacity1 (see figure). Induction of anergy may also depend on the context of BCR stimulation invoking the long-held central theory of 2-signal stimulation for immunity versus single-signal induction of tolerance first proposed by Bretscher and Cohn some 40 years ago.3 In modern terms, the chronic stimulation likely occurs without sufficient costimulation via T-cell help or pattern-recognition receptors (ie, Toll-like receptor engagement). In the absence of sufficient costimulation, high BCR cross-linkage leads to clonal deletion whereas low BCR cross-linkage results in anergy (see figure).

What is striking is that “the anergic B cell” appears to take multiple forms. Phenotypically, the various anergic B cells found in humans are quite divergent. The RA and common variable immunodeficiency (CVID) “anergic” cells are predominantly CD21<sup>lo</sup>/IgG memory B cells that have never been involved in an immune response, whereas the anergic cells isolated from healthy people or from people with chronic infectious diseases look predominantly like CD21<sup>lo</sup>/IgM memory B cells. For example, Fc-receptor-like-4 (FCRL4)—expressing IgG memory B cells that are also CD21<sup>lo</sup>/IgM and have become functionally inert are expanded in HIV patients.6 A similar population was reported to be expanded in malaria patients2 and an IgM memory-like CD21<sup>lo</sup>B-cell population is expanded in hepatitis C virus (HCV) patients.8 In these instances of chronic infection, functional inactivation of lymphocytes is referred to as “exhaustion” rather than anergy. The Sanz laboratory reported that human B cells known to be naturally autoreactive to polyclontric glycans that can be identified by the 9G4 idiotypic antibody are anergic and strictly naive.9 Zheng et al also identified 9G4<sup>+</sup>IgM<sup>+</sup> marginal zone–like memory and plasma cells, suggesting a complex regulation of 9G4<sup>+</sup>B cells.10 In addition, Duty et al recently identified a subset of naive B cells that is common in healthy people that is anergic and naturally autoreactive to diverse self-antigens.11 Similar to the anti-HEL transgenic mouse model of anergy, these anergic B cells have down-regulated IgM on the cell surface but maintain IgD and, in contrast to the cells reported by Isnardi et al7 and exhausted memory B cells,5–8 they are CD21<sup>+</sup> and are negative for FCRL4. (S.F.A. and P.C.W., unpublished data, 2010). In mice, a number of laboratories have identified a similar diversity of B-cell phenotypes that are anergic, ranging from transitional-like to memory cell–like and with diverse self-antigen specificities (reviewed in Cambier et al1). Early on there was hope that we might identify an anergic B-cell type in humans that might be diagnostic of autoimmune diseases or targeted in some fashion for the treatment of disease. In the end, it seems that the anergic phenotype is likely a common phenomenon that can affect various types of B cells.

When B cells recognize self, induction of anergy can help to avoid autoimmune reactivity. However, there is evidence in both humans12–14 and mice1 that anergic, autoreactive B cells can become activated with sufficient stimulation. Thus, since their discovery,2 these cells have posed a risk and a conundrum: why are they maintained at all? One possibility is that anergic B cells are simply being detected as they are honed from the repertoire and therefore pose no risk. The examples of exhaustion in B cells associated with chronic infectious diseases suggests that rescue from anergy by proper stimulation may in some cases be a necessary measure to fight infections. Another intriguing possibility is that they are the precursors of regulatory B cells or are themselves able to induce tolerance of autoreactive T–cell populations via HLA–II presentation of self–peptides. Examples of regulatory B cells have been recently identified in both mice12 and humans.13 A role for anergy or a lack thereof in causing or exacerbating either autoimmune or chronic infectious disease has not been formally established, likely because of the complicated nature of this phenotype. The hope is that by furthering our understanding of the causes and function of anergy, we may manipulate this phenotype in the treatment of diseases.

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Comment on O’Donnell et al, page 5097

First do no harm

Bronwen E. Shaw ANTHONY NOLAN TRUST AND ROYAL MARSDEN HOSPITAL

Can a physician caring for a patient who requires a transplant make an unbiased assessment of the suitability of that patient’s relative to be the donor? In this issue of Blood, O’Donnell et al highlight this important question in their article reporting practice patterns for related donor care in the United States.1

A real or potential conflict of interest exists when a transplant recipient and the intended donor are assessed by the same physician. This is important as trust among physician, donor, and/or patient could break down, and there is a possibility that medical and psychosocial risks to the donor may be underplayed or not objectively considered.

Both in solid organ transplantation and in unrelated donor hematopoietic cell transplantation (HCT), regulations state that the donor must be (medically) assessed by a physician who is not a member of the team caring for the recipient.2,3 Conversely, regulations concerning related donors of hematopoietic stem cells (HSC) are sparse. Although the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee of International Society for Cellular Therapy and European Group for Blood and Marrow Transplantation (FACT–JACIE) recommends that “an independent physician be utilized for evaluating donor suitability” for all donors, it does not have an explicit standard addressing all aspects of related donor management.4

In view of this absence of clear regulations for related donors, O’Donnell et al hypothesized that overlapping care teams may be a common practice. To address this, they performed a large survey of transplantation centers in the United States to assess practice patterns for evaluation and care of related donors. The survey addresses 2 main questions: what type of health care provider is involved in the medical clearance, informed consent, and medical management of the related donor, and what is the relationship of that provider to the transplant recipient. The survey was sent to 222 transplantation teams with an overall response rate of 40%. Importantly, the majority of centers that did respond were FACT-accredited. In almost all cases (>80%), a transplant physician performed the medical care and consent. The key finding in this study confirms the hypothesis, as more than 70% of centers replied that the same physician caring for the donor had (or might have) simultaneous responsibility for the care of the recipient. Interestingly, the larger the transplant, the less likely that the donor’s and recipient’s physicians would be the same—which may be as a result of staffing issues in smaller centers and the emphasis on the transplantation expertise in assessing the donors. Clare et al report very similar findings in a survey of practice patterns in related donor care in Europe.5 More than half of the donors were consented by the transplant physician and in only a quarter of centers was donor assessment performed by a physician not connected to the transplantation team.

Is it necessary that a transplant physician do the donor assessment? Non–transplant providers could easily be trained to understand relevant transplantation and donation issues. Independent assessors or advocates who may be geographically separate, and possibly part of a network associated with nearby centers, could be used. The need for an independent advocate may be especially important in the case of pediatric donors, where there may be an inherent conflict of interest because of the requirement for a consenting parent/guardian.

This report is timely, especially with regard to pediatric donors. The American Academy of Pediatrics has this year published a policy statement for children as (related) hematopoietic cell donors in which it states that a donor advocate should be appointed and that the advocate must be independent of the team responsible for the direct care of the recipient.6 The requirement for an independent accredited assessor (guardian/advocate) distinct from the recipient’s care team is already entrenched in European Union law (Tissues and Cells Directive 2004/23/EC; http://www.dh.gov.uk/en/Publichealth/ScientificDevelopmentGeneticsandBioethics/Tissue/TissueRegulatoryInformation/DH_4136920. Accessed May 5, 2010).

There is strong justification for bringing related HCT donor care in line with that of unrelated donors and addressing additional issues, such as adverse events reporting and donor follow-up. Van Walraven et al7 on behalf of the World Marrow Donor Association, which regulates all aspects of unrelated HCT donor care and management,1 have recently published recommendations in this regard.

We need to recognize, however, that there are obvious differences between related and unrelated donors—for example, age and ethical and psychosocial concerns. The psychosocial risks and benefits to the donor are important and data in related donors are very limited and/or relatively outdated. The assumption that a related donor should be, or is, willing to accept a greater degree of risk in view of the his or her potential emotional benefit of helping a sick relative is unsubstantiated and controversial. In addition, it is not clear whether related donors feel that long-term follow-up is desirable, particularly if the donor’s relative has died. Some European countries already have a legal requirement to perform regular follow-up of related donors, similar to that in unrelated donors. It is hoped that an ambitious study currently recruiting in the United States—RDSafe (related donor safety study): a Multi-Institutional Study of HSC Donor Safety and Quality Life by Pulsipher and Switzer (http://www.researchgrantdatabase.com/g/1R01HL085707) will...
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