inside blood

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LYMPHOID NEOPLASIA

Comment on Chu et al, page 3907

Antigens in CLL: themes and variations

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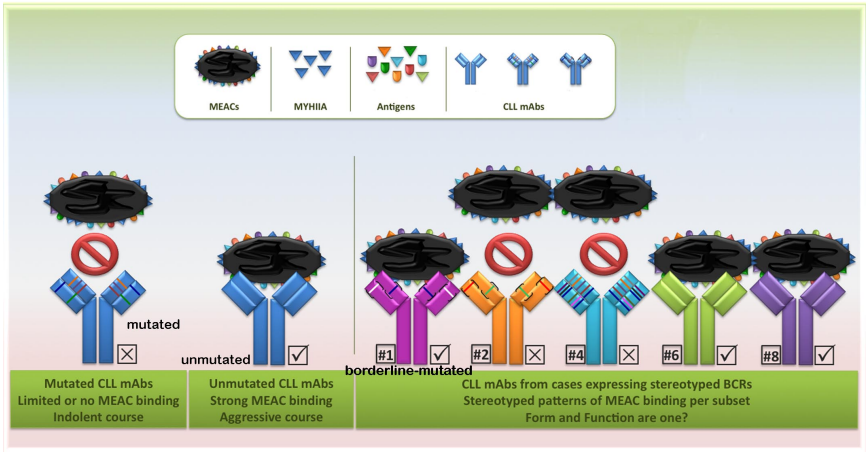
In this issue of *Blood*, Chu and colleagues report that reactivity with a particular type of apoptotic cells is a common feature of CLL, especially of the unmutated subtype.[1] Intriguingly, high binding to such apoptotic cells significantly correlated with inferior outcome, thereby providing a functional interpretation for the prognostic implications of BcR structure in CLL.



The functional antigen reactivity underlies the biological and clinical behavior of the CLL clone. Chu and colleagues report that several CLL monoclonal antibodies (mAbs) can bind MYHIIA-exposed apoptotic cells (MEACs), although not all recognize MYHIIA (ie, the molecular targets of different CLL mAbs may be other autoantigens exposed on MEACs during apoptosis). MEAC binding was essentially a property of CLL monoclonal antibodies (mAbs) with unmutated IGHV genes. Intriguingly, MEAC binding was identified as a stronger predictor of survival than *IGHV* gene mutational status. This might imply that the functional antigen reactivity profile rather than the presumed antigen-binding site structure shaped by somatic hypermutation underlies the biological behavior of the CLL clone, eventually determining patient prognosis. MEAC binding was also found to be consistent between CLL mAbs from cases in subsets with stereotyped IGs, strongly indicating that clustering of CLL cases into distinct subsets based on stereotyped primary IG gene sequences is functionally relevant. MEACs indicates MYHIIA-exposed apoptotic cells; MYHIIA, non-muscle myosin heavy chain IIA; antigens, vimentin, filamin B, oxidized epitopes, etc; ☒, no MEACs binding; ☑, MEACs binding; #, number of stereotyped subset.

The critical role of the B-cell receptor (BcR) in chronic lymphocytic leukemia (CLL) is underscored by the biased immunoglobulin heavy variable (*IGHV*) gene repertoire and the categorization of patients into subtypes with markedly different prognosis on the basis of *IGHV* gene mutational status.[2] However, the most compelling immunogenetic piece of evidence is the fact that almost 30% of CLL patients share BcRs with restricted, quasi-identical IG sequences.[3] This might justifiably be taken as a convincing hint of restriction also in terms of the antigens selecting CLL progenitors. Elucidation of the identity of the respective antigens combined with knowledge about the actual structure of CLL BcRs should aid in understanding the functional interplay between CLL cells and the (micro)environment, eventually paving the way to the design of rational, individualized treatment.[4]

Despite this and other evidence in support of the notion that all CLL cells are antigen experienced, meaningful insight into the shadowy world of antigens selecting CLL leukemic clones has only started to emerge. In fact, recent studies, mainly from the Chiorazzi and Rosen laboratories, have conclusively demonstrated that several CLL monoclonal antibodies (mAbs) react with molecular structures present on apoptotic cells and bacteria,[5-7] similar to natural Ab reactivities described in autoimmune diseases and in clearance of senescent cells and microbial pathogens.

A significant contribution to this field had been previously reported by Chu and colleagues, who showed that nonmuscle myosin heavy chain IIA (MYHIIA) is the antigenic target of CLL antibodies clustered in a subset with stereotyped *IGHV1-69/IGHD3-16/IGHJ3* rearrangements (referred to as subset no. 6).[5] MYHIIA normally resides in the cytoplasm as part of molecular motors involved in cell morphogenesis and locomotion. During apoptosis, it structurally rearranges and becomes exposed on the cell surface, thus allowing interaction with CLL subset no. 6 mAbs.[5]

In support of this idea, in this issue of *Blood*, Chu et al report that CLL subset no. 6 mAbs in vitro recognize a distinctive subset of apoptotic cells with exposed MYHIIA, which they termed MYHIIA-exposed apoptotic cells (MEACs), and not apoptotic cells without exposed MYHIIA or live cells.[1] They also show that MEACs could derive from multiple sources, includinLL cell turnover, normal cell turnover, or induction of damage in vivo. Furthermore, prompted by the finding that recognition of apoptotic cells and autoantigens can also be exposed during apoptosis is a relatively common property of CLL cells, they have examined for MEAC binding a number of non–subset no. 6 CLL mAbs. Their endeavor was rewarded with success: the majority of CLL mAbs tested (16 of 26) were found to bind MEACs! This does not necessarily imply that the determinant of MEAC binding is MYHIIA.

As emphasized by the authors, it is equally possible that the molecular targets of different CLL mAbs are other uncharacterized autoantigens exposed during apoptosis (eg, vimentin, filamin B, or oxidized epitopes).

In-depth investigation into the patterns of MEAC binding enabled Chu et al to identify interesting associations with far-reaching implications.[1] First, MEAC binding inversely correlated with *IGHV* gene mutational status. Indeed, 15 of 16 MEAC-reactive CLL mAbs carried unmutated *IGHV* genes. Second, high binding to MEACs significantly correlated with poor patient survival. This suggests that it is the functional antigen reactivity profile rather than the presumed antigen-binding site structure shaped by somatic hypermutation that underlies the biological behavior of the CLL clone, eventually determining patient prognosis. Third, most (14 of 16) MEAC-binders derived from cases in subsets with stereotyped IGs. More importantly, however, CLL mAbs from the same stereotyped subsets bound with similar effectiveness to MEACs, further evidence that the clustering of CLL cases into distinct subsets based on stereotyped primary IG gene sequences is functionally relevant.

The final part of the study hinges on CLL ontogeny, in particular, the still elusive normal cell counterpart of CLL. Given that binding to apoptotic cells is a property of natural Abs, the authors have tested serum Abs from healthy persons for the ability to bind MEACs. Their results indicate that a large number of natural Abs can bind epitopes present on MEACs well and, in some cases, at a level comparable with strong MEAC-binding CLL mAbs. On these grounds, Chu et al propose that at least a large subset of CLL could derive from the human counterparts of mouse B-1 cells or other subsets producing natural Abs.

Does all this mean that "form and function are one" in CLL? Or perhaps emphasis on form will eventually be superseded by insight into functional responses triggered by certain antigenic reactivities and variations thereof? Only the future will tell; however, on the available evidence, it seems reasonable to argue that neo/self-antigen/apoptotic cells acting in synergy with microbial pathogens may drive CLL progenitors or even the malignant cells themselves by continuously triggering BcRs with distinctive structural features.

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● ● ● CLINICAL TRIALS

Comment on Warren et al, page 3869

Combating cancer with allogeneic T cells

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Clinical phase 1/2 studies exploring the efficacy and toxicity of adoptive transfer of mHAg-specific T cells are essential to evaluate the applicability, potential risks, and benefits of specific cellular immunotherapy in the context of allogeneic stem cell transplantation for the treatment of hematologic cancers.

Cellular immunotherapy with donor-derived T cells recognizing specific antigens on the malignant cells from the patient is one of the major advantages of allogeneic hematopoietic stem cell transplantation over autologous stem cell transplantation in the treatment of hematologic cancers. Treatment of patients who relapse with leukemia, lymphoma, or multiple myeloma after allogeneic transplantation with donor T cells has illustrated that cellular immunotherapy can lead to complete eradication of cancer cells, resulting in cure of the disease.[1]

In the nontransplantation situation, an immune response from donor T cells recognizing alloantigens on hematopoietic cells from the patient will lead to destruction of the patient's hematopoietic system. If the malignant counterpart of these cells also expresses these alloantigens on their cell membrane, this immune response will also eradicate hematopoietic cancer cells. In contrast, donor-derived hematopoiesis after transplantation will be left unharmed, because donor-derived T cells have been educated in the donor to recognize donor hematopoiesis as "self" tissue. This graft-versus-leukemia/lymphoma (GVL) or graft-versus-tumor (GVT) reactivity is the major beneficial effect of allogeneic stem cell transplantation. Characterization of hematopoiesis-restricted alloantigens that can be targeted in GVL reactivity may allow more specific and effective cellular immunotherapy.

After HLA-matched stem cell transplantation, donor-derived T cells can recognize polymorphic peptides presented in the context of (self-)HLA molecules as foreign antigens. Because the human genome contains a broad variety of single nucleotide polymorphisms (SNP) resulting in small differences in amino acid sequences of many proteins, processing of these polymorphic stretches of amino acids that differ between the donor and recipient can lead to strong immune responses. Polymorphic peptides that can be recognized in the context of (self-)HLA molecules are defined as minor histocompatibility antigens (mHAgs).[2] From an evolutionary standpoint, this mHAg-specific immune response mimics the recognition of virus-derived foreign peptides presented in the context of self-HLA molecules and this provides a clear rationale for the strong avidity of T cells for these antigens. Donor-derived T cells recognizing mHAgs on recipient malignant cells are capable of mediating a strong GVL response.[3] Unfortunately, donor T cells recognizing polymorphic peptides presented on normal nonhematopoietic tissues from the recipient can also mediate graft-versus-host disease (GVHD), which is the main cause of morbidity and mortality after transplantation.[2,4] Treatment of patients with unmodified donor lymphocyte infusion (DLI) after transplantation may lead to cure of