REVIEW

Arch. Immunol. Ther. Exp., 2008, **56**, 245–255
PL ISSN 0004-069X

DOI 10.1007/s00005-008-0028-z

Host immune response in B-cell lymphomas: friend or foe?

Przemysław Juszczyński[1], Jacek Nowak[2] and Krzysztof Warzocha[2]

[1] Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA
[2] Institute of Hematology and Transfusion Medicine, Warsaw, Poland

Received: 2008.04.07, **Accepted:** 2008.06.30, **Published online first:** 2008.07.29

Abstract

The interaction of B-cell malignancies with the host immune system is a dynamic and bilateral process. Certain lymphomas more commonly arise within a background of autoimmunity or chronic infection. Initiation of these tumors is commonly reliant on antigenic stimulation and/or T-cell help. Apart from its tumor-fueling role, the host immune response plays a critical role in cancer immunosurveillance and immunoediting. The concept of immunoediting holds that the immune system sculpts the tumor's immunogenicity in a dynamic process that involves three essential phases: elimination, equilibrium, and escape. Data obtained by studying gene-targeted animals and human lymphomas that support the critical role of the immune response in the initiation, progression, and immunoediting of lymphoid malignancies are summarized here. A thorough understanding of this interaction will lead to the identification of more rational treatment targets and improved immunotherapies in B-cell lymphomas.

Key words: lymphoma, immune escape, immunoediting.

Corresponding author: Przemysław Juszczyński, M.D. Ph.D., Department of Medical Oncology, Dana Farber Cancer Institute, 44 Binney Street, Room M515, Boston, MA 02115, USA, e-mail: przemyslaw_juszczynski@dfci.harvard.edu

INTRODUCTION

Interaction between tumor and the reactive infiltrate was originally conceived as the process leading to tumor elimination and/or control of its progression. Recent studies have extensively redefined the role of the interaction between the host immune response and tumor, demonstrating that it is a bilateral and multistep process playing a more complex role in the etiology and progression of cancer. According to these findings, the host immune response shapes the immunogenicity of spontaneous or carcinogen-induced solid tumors, leading to the emergence and outgrowth of more aggressive, less immunogenic clones [21–24, 78]. This dynamic process, known as immunoediting, involves three essential phases: elimination, equilibrium, and escape. In the elimination phase the newly transformed cells are recognized and eliminated by the innate and adaptive immune responses. Incomplete elimination leads to a subclinical equilibrium phase in which tumor persists, but is restrained by the host immune pressure, ultimately leading to the emergence of less immunogenic clones. The expansion of these clones and subsequent acquisition of additional lesions tilts the balance toward the tumor, which enters the escape phase.

B-cell lymphomas present as tumors with a variable inflammatory infiltrate that includes effector and regulatory T cells, macrophages, and dendritic cells. Recent studies demonstrate that the dual role of the host immune response leading from immunosurveillance to immune escape is not limited to solid tumors only, but also shapes the biological behavior of B-cell lymphomas. However, the interactions between host immune response and lymphoma involve additional levels of complexity, as the emergence of these tumors is often associated with certain underlying chronic inflammatory disorders. In this review, the role of the host immune response in the pathogenesis of B-cell tumors will be discussed. First, the role of chronic inflammation and associated molecular mechanisms leading to the initiation of lymphomagenesis will be addressed. The following sections will focus on the role of the immune response and key effector molecules in the progression of the established lymphoma from immune surveillance to immune escape.

IMMUNE RESPONSE AND LYMPHOMAGENESIS: THE ROLE OF INFECTIOUS AGENTS AND CHRONIC INFLAMMATION

Chronic activation of the lymphoid system and sustained proliferation of lymphocytes can be observed in several infectious and autoimmune diseases which are associated with the more common B-cell malignancies [26, 45, 74]. Lymphomagenesis associated with chronic infections by pathogens that are not lymphotropic and not directly oncogenic or with autoimmunity involves chronic stimulation of effector B-cells by pathogen-derived antigens or autoantigens. Lymphomas that arise according to this model commonly appear to originate from marginal-zone B cells [3, 17]. Chronic inflammation either at the site of infection or at the site of the autoimmune response elicits a polyclonal B-cell response and leads to the formation of extranodal lymphoid tissue, which is a prerequisite for lymphomagenesis (Fig. 1) [62]. Suggestive of antigen-driven selection, B cells in these lesions commonly exhibit a biased immunoglobulin (Ig) V gene usage and somatic hypermutation (SHM) [7, 16, 19, 20, 52, 56, 89]. Consistently, in mucosa-associated lymphoid tissue (MALT) lymphomas arising within the background of these lesions, CDR3 sequences of Ig receptor genes suggest a common specificity of surface B-cell receptors to the relevant pathogen or to autoantigens [7, 15]. For sustained B-cell proliferation, costimulatory signals and cytokines are provided by primed T cells and/or by dendritic cells. T cells from patients with gastric MALT lymphomas are able to support the proliferation of autologous B cells in the presence of *Helicobacter pylori* (*H. pylori*) extracts in a CD40-dependent manner, underscoring their pathogenic role [35]. A critical role of chronic T-cell help was also suggested in mouse models. *H. pylori* does not induce gastritis in SCID mice, but gastritis is induced by adoptive transfer of naïve $CD4^+$ T cells to these mice [25]. *H. pylori* elimination is also impaired in MHC class II-deficient mice, underscoring the role of $CD4^+$ T helper cells [69]. Consistently, inherited genetic polymorphisms in the *CTLA4* gene are associated with increased risk of gastric MALT lymphoma in patients with *H. pylori* infection, suggesting that a defective negative signal and prolonged T-cell activation may be a predisposing factor for this malignancy [10].

Most lymphomas, however, develop in the absence of any known chronic antigenic stimulation. An alternative signal recruiting T cells fueling chronic lymphoproliferation can be elicited by superantigens. Several mouse strains that harbor endogenous retroviruses encoding superantigens develop tumors resembling human lymphomas. These tumors fail to grow in γ-irradiated or athymic mice except when simultaneously injected with normal syngeneic lymphoid cells, suggesting their dependence on T cell-derived costimulation [41, 51]. This costimulatory signal is obtained from activated interleukin (IL)-5-secreting superantigen-specific $CD4^+V\beta16^+$ T cells [46, 90, 91]. A superantigen-dependent mechanism may also be involved in human Epstein-Barr virus (EBV)-related lymphomas. EBV transactivates superantigen encoded by the human endogenous retrovirus K18, which strongly and rapidly stimulates T cells [33, 88]. The response is initiated by oligoclonal superantigen-specific T-cell receptor (TCR) Vβ13 T cells [33, 88]. Since $CD4^+$ T cells greatly increase the development of EBV lymphomas, this mechanism may play at least a partial role in EBV-induced lymphomagenesis.

In a recent study, Zangani et al. [99] have shown that B cell-unique variable-region-derived idiotypic (Id) peptides presented in the context of MHC II to T cells may serve as a chronic antigenic stimulus promoting lymphomagenesis [63, 99]. Transgenic Id^+ B cells chronically helped by Id-specific Th2 cells developed into diffuse large B-cell lymphomas (DLBCLs). The phenotype of the lymphoma cells suggested that they were selected for potent interaction with T cells. They expressed high levels of MHC class II as well as costimulatory

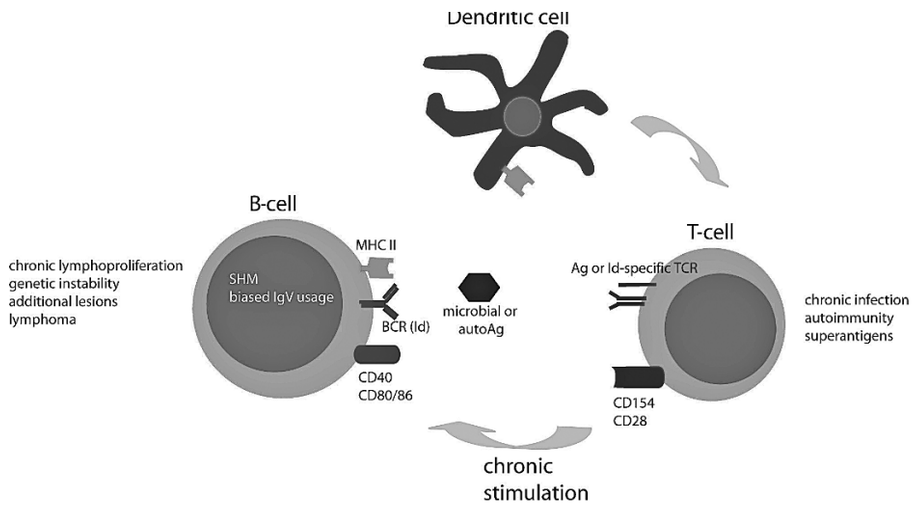

Fig. 1. Role of chronic stimulation in the initiation of lymphomagenesis. Polyclonal B cells specific to certain microbial or autoantigens are chronically helped by activated T cells and undergo prolonged activation, proliferation and form extranodal lymphoid tissue. B cells in these lesions exhibit a biased immunoglobulin V gene (IgV) usage and somatic hypermutation (SHM). Protracted antigen-dependent lymphoproliferation, sustained by costimulatory signals may lead to acquisition of additional lesions, genetic instability that renders B cells lymphoproliferation antigen-independent. See text for further details.

CD80/CD86 molecules and the λ2 Id^+ light-chain antigen [99]. These cells also expressed high levels of CD40, suggesting their dependence on activated T cell-derived signals. These results suggest that chronic Id-driven collaboration between T and B cells could represent a novel mechanism for lymphomagenesis. However, when Id^+ B cells were transferred to transgenic mice expressing Id-specific TCR, lymphomas were uniformly rejected, likely due to the mounting of an anti-Id Th1 response, suggesting a dual role of the immune response in Id-mediated lymphomagenesis [54, 55]. These observations suggest that, apart from a tumor-fueling role in certain B-cell lymphomas, the host immune response plays a critical role in cancer immunosurveillance and immunoediting.

EPIDEMIOLOGIC EVIDENCE FOR LYMPHOMA IMMUNE SURVEILLANCE IN HUMANS

Indirect evidence suggesting that the host immune response is involved in lymphomagenesis is provided by population and epidemiologic studies demonstrating that lymphoid malignancies arise more frequently in immunocompromised individuals. In a recent meta-analysis of human immunodeficiency virus (HIV)--infected patients (n=444,172) and transplant recipients (n=31,977), the incidences of both non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL) were highly elevated [30]. Consistently, patients with certain congenital immune deficiency syndromes with loss of T-cell control (Wiskott-Aldrich syndrome) or abnormal T/B-cell interactions (hyper-IgM syndrome) are also at risk of developing lymphoma [26]. The clinical features shared by the majority of immunodeficiency-related lymphomas are DLBCL histology, aggressive clinical course, and an association with EBV or human herpesvirus 8 (HHV-8). These data suggest that in the absence of an effective immune response and lack of infection control, infected B cells are more likely to persist, expand, and acquire additional lesions. However, EBV- and HHV-8-negative lymphomas also occur in transplant recipients and patients with HIV, suggesting that factors other than uncontrolled infection account for the higher risk of lymphoma in these cases.

MOUSE MODELS OF LYMPHOMA IMMUNOEDITION

The hypothesis of cancer immune surveillance and immunoedition was rigorously examined and validated using gene-knockout mouse lymphoma models. Interferon (IFN)-γ sensitivity is crucial for successful immmunoelimination of spontaneous or carcinogen--induced solid tumors and thus established the paradigm of immune surveillance and immunoediting [58, 78, 87]. Subsequent studies raised the role of this cytokine in immunoedition of lymphoid tumors as well. IFN-γ and granulocyte-macrophage colony-stimulating factor double-deficient mice developed spontaneous lymphomas within a background of persistent infection and inflammation, highlighting the synergism between chronic inflammation and impaired immune surveillance [28]. Tumor formation was delayed or prevented by antimicrobial therapy, demonstrating that the interplay of infectious agents with cytokine-mediated regulation of immune homeostasis is an important determinant of lymphomagenesis [28].

A similar mechanism, involving ineffective elimination of chronically activated/transformed cells, was proposed for *lpr*/*lpr* or *gld*/*gld* mice [103]. These mice, mutant in *Fas* (CD95) or *Fas* ligand (CD95L), respectively, accumulate memory-like B cells and plasma cells [11, 14]. FAS is a proapoptotic protein expressed within germinal centers where it plays an important role in the negative selection of B cells [64]. FAS ligand cross-links the transmembrane FAS death receptor, leading to the assembly of a death-inducing signaling complex and initiating caspase-mediated apoptosis. FAS ligand-receptor system mutations greatly increase the risk of B-cell malignancies arising within the background of systemic immunity in both mice and humans. Dysregulation of the FAS system may also occur due to physiological or aberrant SHM [64], which likely extends the lifespan of B cells, increasing the likelihood of secondary genetic abnormalities and/or favor the outgrowth of lymphomas not susceptible to FAS ligand-mediated apoptosis [14, 85].

Defects in another death-inducing molecule, TNF--related apoptosis-inducing ligand (TRAIL) are also associated with increased incidence of late onset murine B-cell lymphomas [102]. Consistently, deletions of the chromosome 8p21.3 region including the TRAIL receptor 1 and 2 loci are a recurrent genetic abnormality in human B-cell NHL associated with the down-regulation of either receptor expression and impaired TRAIL--induced apoptosis [75].

Increased incidence of spontaneous B-cell lymphomas was also noted in perforin ($pfp^{-/-}$) mice and was further enhanced upon crossing with $Ifng^{-/-}$, β2--microglobulin ($\beta 2m)^{-/-}$, or $p53^{-/-}$ animals [81, 86, 87]. Perforin is a pore-forming protein expressed exclusively by natural killer (NK) and cytotoxic T lymphocytes (CTLs) and is essential for NK- and CTL-mediated cytolytic activity [42, 80]. When transplanted to wild--type recipients, B-cell lymphomas formed in $pfp^{-/-}p53^{-/-}$ mice were rejected in a CTL-mediated manner but grew progressively when transplanted to $pfp^{-/-}$ mice, suggesting that loss of perforin resulted in an "unedited", highly immunogenic phenotype [81]. Similarly, lymphomas formed in $pfp^{-/-}\beta 2m^{-/-}$ mice effectively primed cell-mediated cytotoxicity in an NK/γδTCR^+-dependent fashion and were rejected when transplanted to syngeneic control wild-type mice, but not by $pfp^{-/-}$ animals [86]. Of note, lymphomas arising in mice with isolated IFN-γ deficiency were nonimmunogenic, suggesting weaker immunoselection pressure by IFN-γ [87].

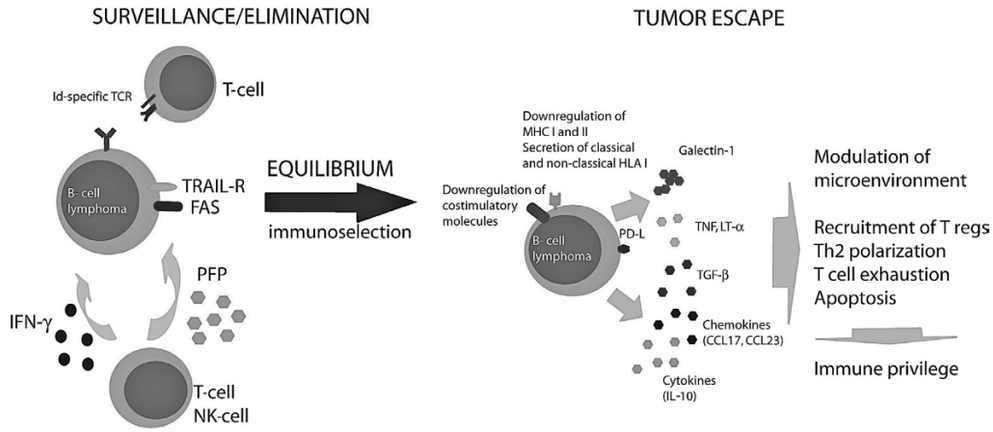

Fig. 2. Proposed scenario of immunoedition of B-cell lymphomas. During the elimination phase, the newly transformed cells are recognized and eliminated by the innate and adaptive immune responses. Tumor formation is facilitated by experimental gene targeting (*Ifng*$^{-/-}$, *Pfp*$^{-/-}$, *Fas*$^{-/-}$, *Fasl*$^{-/-}$) or spontaneous mutations/deletions or SHMs occurring in humans (FAS, TRAIL-R). Incomplete elimination leads to a subclinical equilibrium phase in which tumor persists, but is it restrained by the host immune pressure, ultimately leading to the emergence of less immunogenic clones. The expansion of these clones and subsequent acquisition of additional lesions tilts the balance toward the tumor, which enters the escape phase. In the escape phase, cells utilize potent mechanisms to evade recognition (abnormalities in MHC expression, downregulation of costimulatory molecules) and create an immunoprivileged environment by secretion of certain mediators (e.g. Gal-1, IL-10, chemokines,TGF-β, TNF superfamily cytokines, PD-ligands).

Taken together, these results suggest that specific immunodeficiencies in mice are associated with increased incidence and/or accelerated onset of lymphoid tumors that exhibit reduced immunogenicity. The different immunogenic potentials of tumors arising in animals with different deficiencies suggest that the transition between "fully immunogenic, rejectable" to "non-immunogenic, transplantable" tumor involves an additional dynamic equilibrium stage during which the tumor is challenged by the immune system and loses its immunogenic potential (Fig. 2). Genetic instability and immune selection occurring during this phase finally result in the outgrowth of edited clones and the formation of clinically detectable tumors.

LYMPHOMA IMMUNE ESCAPE

As part of their response to selection pressure, lymphoma cells may exploit several different immunosuppressive strategies and immunological checkpoints to inhibit tumor-specific immune responses (Table 1 and Fig. 2). Tumor cells become resistant to proapoptotic signals from reactive cells or passively evade recognition or shape their microenvironment by producing immunoregulatory molecules that hijack or disarm the host immune response.

Role of HLA

An effective adaptive immune response requires interaction and cooperation between B and T cells. These interactions involve TCR-mediated recognition of an antigenic peptide presented on the MHC molecule and costimulatory signals. The immunological synapse formation is further enhanced by adhesion molecules which dock B and T cells, facilitating the recognition and exchange of costimulatory signals. Therefore, abnormalities in the expressions of the molecules involved in this process on lymphoma cells will result in immunological ignorance and derange the immune response to the tumor. Loss of either class I or class II HLA expression is associated with fewer infiltrating $CD8^+$ CTLs and inferior freedom from progression (FFP) and overall survival (OS) in patients with DLBCL [6, 71, 72]. Decreased expression of CD86 costimulatory molecule was also associated with lower tumoral infiltration by CTLs, suggesting that in the absence of costimulatory signal, T cells undergo apoptosis at the tumor site [84].

Given the complexity of antigen-processing and -presentation pathways, various molecular mechanisms responsible for complete or partial HLA loss have been reported, including abnormalities in transporter associated with antigen processing, β2m, hemizygous deletions, and loss of heterozygosity [6, 18]. Alternative splicing or proteolytic cleavage and shedding likely account for the loss of membrane-anchored HLA and increased levels of soluble forms of these molecules (sHLA-I) [1, 2, 100]. Given the proapoptotic function of sHLA-I to cytotoxic T and NK cells in the absence of costimulatory signal, it is likely that the shedding of these molecules from the tumor surface provides an immune escape mechanism [12, 82, 101]. Consistently, elevated sHLA-I molecules are associated with inferior survival in NHL patients. Importantly, this association was independent of β2m concentrations, suggesting mechanisms unrelated to tumor burden and cellular turnover [2].

Apart from complete or partial loss of surface HLA in lymphoma cells, certain inherited HLA repertoires are associated with inferior outcome in DLBCL and chronic lymphocytic leukemia (CLL) patients. The absence of the the HLA-DRB*02 and presence of the DRB*01 allele were related to adverse outcome of NHL and CLL, respectively [38, 49]. In an extended haplotype analysis, HLA A*01 and B*08 components of 8.1 HLA ancestral haplotype exhibited the strongest associations with shorter FFP and OS in DLBCL patients [65, 66].

Expression of the non-classical HLA molecule HLA-G has also been implicated in lymphoma immune escape. Non-classical HLA-I molecules include an oligomorphic family of molecules that predominantly function as inhibitors of the T and NK cells [36, 43, 44, 61]. HLA-G interaction with immunoglobulin-like transcript-family inhibitory receptors on T cells inhibits the proliferation of $CD4^+$ cells and induces anergy and differentiation into suppressive cells [50, 53]. Production of soluble isoforms in B-cell lymphomas is likely driven by the interaction with normal constituents of the microenvironment, resulting in frequently elevated plasma levels of these isoforms [77]. Soluble HLA-G purified from patients' plasma inhibited T-cell alloproliferation at the concentrations encountered *in vivo*, suggesting that sHLA-G may be a functional immune escape mechanism. In line with this, in patients with CLL, HLA-G expression is associated with an unfavorable outcome and immunodeficiency [67].

Tumor-derived factors

B-cell lymphomas express a variety of soluble or membrane-anchored factors that influence the immunopathology of host immune responses, shaping the microenvironment that fosters lymphoma's immune privilege. Local production of proapoptotic mediators by lymphoma cells eliminates potentially tumor-reactive effector cells, leading to underrepresentation of certain components of the immune response at the tumor site. At the same time, lymphomas produce chemokines, cytokines, and other substances that attract or induce the network of immunosuppressive cells, fostering tumor immune privilege.

One of the key components of the inhibitory network in B-cell lymphomas are regulatory T cells (Tregs) capable of suppressing anti-tumor $CD4^+$ and $CD8^+$ T-cell responses. This population of immunosuppressive $CD4^+CD25^{high}FOXP3^+$ T cells is frequently overrepresented in the reactive infiltrate of NHL and HL in humans [27, 32, 57, 97, 98]. Tregs isolated from tumor biopsies are capable of suppressing proliferation and cytokine or granule production of $CD4^+$ and $CD8^+$ T cells [32, 57, 97, 98]. Intratumoral Tregs express the chemokine receptor CCR4, suggesting that they can be recruited to the tumor site by the chemotactic factors CCL17 (thymus- and activation-regulated chemokine) and CCL22 secreted by malignant B cells or may differentiate from naïve T cells at the tumor site under the influence of transforming growth factor (TGF)-β, a Treg-inducing cytokine produced by tumor cells [34, 37, 68, 70]. An additional potential mechanism explaining Treg infiltration in HL has been identified recently. In a screening for T cell-inhibitory molecules in classical HL (cHL), Reed-Sternberg (RS) cells were shown to

Table 1. Molecules and pathways involved in the immunopathogenesis of B-cell lymphomas

Molecule	Evidence	Proposed phase of immunoedition	References
BCR	Anti-idiotypic response in mouse models	elimination	54, 55, 63
Ifng$^{-/-}$	Spontaneous lymphomas (strain dependent)	elimination	87
Ifng$^{-/-}$*Gmcsf*$^{-/-}$	Increased lymphomagenesis associated with chronic inflammation	elimination	28
Pfp$^{-/-}$	Spontaneous "edited" lymphomas (augmented against a *p53*$^{-/-}$ and *Ifng*$^{-/-}$ background)	elimination	81
Pfp$^{-/-}$*Ifng*$^{-/-}$	Spontaneous "edited" lymphomas	elimination	87
Pfp$^{-/-}$*β2m*$^{-/-}$	Spontaneous "edited" lymphomas	elimination	86
HLA	Loss of HLA in aggressive tumors Increased sHLA in poor-outcome patients Increased HLA-G plasma levels in poor-outcome patients HLA polymorphisms associated with outcome	escape	2, 6, 38, 49, 67, 71, 72
TNF	Increased TNF and TNF-R levels in poor-outcome patients	escape	92–95
Fas/Fas ligand	Lymphoproliferative disorder in *Fas*$^{-/-}$ mice and humans Somatic hypermutations	elimination	14, 103
TRAIL	Late-onset mouse lymphoma Recurrent genetic abnormality in human lymphoma	elimination	75, 102
Gal-1	Th2/Treg-skewed microenvironment in cHL	escape	40
PD-1	T-cell exhaustion in cHL	escape	9, 73, 96
IL-10	Th2 polarization	escape	8, 47, 48, 83
CCL17, CCL22	Treg chemoattractants in cHL	escape	37, 68
TGF-β	Increased expression in cHL; T-cell suppression	escape	34

Abbreviations: BCR – B-cell receptor; IFN – interferon; β2m – β2-microglobulin; TNF– tumor necrosis factor; IL-10 – interleukin 10; TGF-β – transforming growth factor beta.

selectively overexpress the immunoregulatory lectin galectin-1 (Gal1) through an AP1-dependent enhancer [40]. In cocultures of activated T cells and HL cell lines, blockade of Gal1 expression in RS cells increased T-cell viability and restored the Th1/Th2 balance. In contrast, rGal1 treatment of activated T cells favored the secretion of Th2 cytokines and increased the relative abundance of $CD4^+CD25^{high}FOXP3^+$ Treg cells [40]. These data directly implicate RS cell Gal1 in the development and maintenance of an immunosuppressive Th2/Treg-skewed microenvironment in cHL.

In other B-cell malignancies, skewing and suppression of the host immune response is frequently mediated by local and/or systemic secretion of certain cytokines. IL-10 is a Th2 cytokine with pleiotropic effects in the immune system that include induction of peripherial T-cell anergy, induction of regulatory Tr-1 cells, and inhibition of dendritic-cell function [59]. In DLBCL, the immune response shift towards Th2-biased immunity is likely mediated by IL-10 secreted by malignant B cells. Increased serum levels of this critical Th2 cytokine were associated with poor prognosis and shorter survival of patients with DLBCL [8, 47, 48, 83].

A tumor's "counterattack" may also be mediated by the expression of certain tumor necrosis factor (TNF) family members, including TNF, lymphotoxin (LT)α, LTβ, and Fas ligand. TNF, LTα, LTβ, and their receptors are secreted by lymphoma cells and their elevated plasma levels are associated with larger tumor burden, disease dissemination, and B-symptoms [76, 92, 94, 95]. Prolonged local TNF production at the tumor site likely influences the reactive infiltrating cells, decreasing NK cell activity and participating in T-cell apoptosis induction (AICD – activation-induced T-cell death). These detrimental effects of excessive TNF production are more likely to occur in patients with genetic polymorphisms within the TNF promoter, associated with increased production of this cytokine [93]. Other lymphomas, including cHL and multiple myelomas, may utilize similar escape mechanisms involving FasL expression [70].

Another likely escape mechanism is mediated by programmed death (PD)-1 interaction with its ligands, including PD-L1 and PD-L2. PD-1 is a 55-kDa transmembrane receptor first identified in a murine hybridoma T-cell line undergoing AICD. PD-1 ligation in T cells induces phosphorylation of its ITIM motifs and recruitment of SHP-2, leading to inhibition of T-cell activation [79]. PD ligand's messenger RNA is overexpressed in primary mediastinal large B-cell lymphomas (PMBCLs) and cHL [73]. Genomic amplifications of PD ligand locus are present in over a half of PMBCLs and in HL cell lines, suggesting the likely mechanism of PD-L overexpression in these diseases [73]. PD-1 pathway engagement in these malignancies may lead to "T-cell exhaustion" and deficient cellular immunity. Blockade of the PD-1 signaling pathway in cHL-infiltrating T cells inhibited SHP-2 phosphorylation and restored the IFN-γ-producing function of T cells [96]. Functional consequences of this T-cell inhibitory interaction have also been documented in primary tumor biopsies from cHL patients analyzed by the genome-wide transcriptional approach, in which cHL-infiltrating T cells exhibited a specific profile of gene expression related to PD-1 engagement [9].

TRANSCRIPTIONAL AND HISTOLOGICAL FEATURES OF LYMPHOMA IMMUNE ESCAPE

These complex communication networks between malignant, stromal, and reactive cells lead to the formation of an inflammatory infiltrate with specific histological features. The variability in the composition of the infiltrate has led to several attempts to associate its specific components quantitatively with the efficacy of the immune response and patient survival. However, these attempts resulted in very conflicting results, related largely to inconsistent methodological criteria [4, 29, 31]. In addition, evaluation of a single component of the immune infiltrate in dissociation from the rest of its environment and its functional status may not be appropriate. These limitations can be circumvented using genome-wide transcriptional approaches in conjunction with immunohistochemical analyses. Using this approach, a DLBCL subtype with a brisk host immune/inflammatory response has been identified [60]. The DLBCLs in this category, termed host response (HR), exhibit increased expression of T/NK cell-receptor and activation-pathway components, complement cascade members, and macrophage/dendritic cell markers. Consistent with this signature, primary HR DLBCLs contain significantly higher numbers of morphologically distinct tumor-infiltrating lymphocytes and interdigitating dendritic cells [60]. The T-cell and dendritic-cell infiltrates in HR tumors resemble those of a histologically defined provisional World Health Organization subtype of DLBCL, namely T-cell/histiocyte-rich B-cell lymphoma (T/HRBCL). In spite of the brisk inflammatory infiltrates in HR (and T/HRBCL) tumors, patients with these DLBCLs do not have a more favorable outcome. In a screening for genes associated with prognosis, HR tumors were found to express a risk-related transcriptional modulator BAL1 and its binding partner BBAP (B-lymphoma- and BAL-associated protein) [39]. Expression of these genes was induced by host-derived IFN-γ, highlighting the dynamic interplay between the inflammatory infiltrate and malignant B cells in these tumors.

More recently, Dave et al. [13] identified distinct expression profiles associated with different outcomes in follicular lymphomas (FLs). The genes that best defined the prognostic signatures in FL were expressed primarily by T cells, macrophages, or dendritic cells, but not by the tumor cells themselves. Importantly, these signatures were not solely a surrogate for the number of infiltrating T cells, since many classical T-cell genes were not associated with either outcome, highlighting

the role of the functional status of infiltrate components in anti-lymphoma immune response. Consistent with this, in an immunohistochemical analysis of FL biopsies, two patterns of immune response were observed in which cellular localization and composition were directly associated with the clinical and biological features of the disease [5].

CONCLUDING REMARKS

Abundant experimental and clinical evidence supports the role of the immune system in the development and progression of B-cell lymphomas. The relationship between the host and the tumor is a complex and dynamic sequence of networked interactions that cannot be arbitrarily qualified as antagonistic or protagonistic. Therefore, the immune system is neither lymphoma's friend nor its foe. It is a uniquely dynamic component of the tumor's microenvironment that, depending on the individual tumor's features, phase of the disease, underlying conditions, and genetic predispositions, may promote or inhibit tumor growth. Understanding the role, dynamics, and the factors that participate in orchestrating the different components of the immune system at different phases may lead to more successful interventions in the host immune system to augment cancer elimination and avoid unexpected immunotherapy-induced editing of the tumor.

REFERENCES

1. Adamashvili I., Kelley R. E., Pressly T. and McDonald J. C. (2005): Soluble HLA: patterns of expression in normal subjects, autoimmune diseases, and transplant recipients. Rheumatol. Int., **25**, 491–500.
2. Albitar M., Vose J. M., Johnson M. M., Do K. A., Day A., Jilani I., Kantarjian H., Keating M., O'Brien S. M., Verstovsek S., Armitage J. O. and Giles F. J. (2007): Clinical relevance of soluble HLA-I and beta2-microglobulin levels in non-Hodgkin's lymphoma and Hodgkin's disease. Leuk. Res., **31**, 139–145.
3. Aljurf M. D., Owaidah T. W., Ezzat A., Ibrahim E. and Tbakhi A. (2003): Antigen- and/or immune-driven lymphoproliferative disorders. Ann. Oncol., **14**, 1595–1606.
4. Alvaro T., Lejeune M., Salvado M. T., Bosch R., Garcia J. F., Jaen J., Banham A. H., Roncador G., Montalban C. and Piris M. A. (2005): Outcome in Hodgkin's lymphoma can be predicted from the presence of accompanying cytotoxic and regulatory T cells. Clin. Cancer Res., **11**, 1467–1473.
5. Alvaro T., Lejeune M., Salvado M. T., Lopez C., Jaen J., Bosch R. and Pons L. E. (2006): Immunohistochemical patterns of reactive microenvironment are associated with clinicobiologic behavior in follicular lymphoma patients. J. Clin. Oncol., **24**, 5350–5357.
6. Amiot L., Onno M., Lamy T., Dauriac C., Le Prise P. Y., Fauchet R. and Drenou B. (1998): Loss of HLA molecules in B lymphomas is associated with an aggressive clinical course. Br. J. Haematol., **100**, 655–663.
7. Bende R. J., Aarts W. M., Riedl R. G., de Jong D., Pals S. T. and van Noesel C. J. (2005): Among B cell non-Hodgkin's lymphomas, MALT lymphomas express a unique antibody repertoire with frequent rheumatoid factor reactivity. J. Exp. Med., **201**, 1229–1241.
8. Blay J. Y., Voorzanger N., Favrot M., Burdin N., Rousset F. and Banchereau J. (1995): Presence of Epstein-Barr virus viral interleukin-10 in the serum of patients with non-human-immunodeficiency-virus-related diffuse large-cell non-Hodgkin's lymphomas. Blood, **86**, 4702–4704.
9. Chemnitz J. M., Eggle D., Driesen J., Classen S., Riley J. L., Debey-Pascher S., Beyer M., Popov A., Zander T. and Schultze J. L. (2007): RNA fingerprints provide direct evidence for the inhibitory role of TGFbeta and PD-1 on CD4+ T cells in Hodgkin lymphoma. Blood, **110**, 3226–3233.
10. Cheng T. Y., Lin J. T., Chen L. T., Shun C. T., Wang H. P., Lin M. T., Wang T. E., Cheng A. L. and Wu M. S. (2006): Association of T-cell regulatory gene polymorphisms with susceptibility to gastric mucosa-associated lymphoid tissue lymphoma. J. Clin. Oncol., **24**, 3483–3489.
11. Cohen P. L. and Eisenberg R. A. (1991): Lpr and gld: single gene models of systemic autoimmunity and lymphoproliferative disease. Annu. Rev. Immunol., **9**, 243–269.
12. Contini P., Ghio M., Merlo A., Poggi A., Indiveri F. and Puppo F. (2005): Apoptosis of antigen-specific T lymphocytes upon the engagement of CD8 by soluble HLA class I molecules is Fas ligand/Fas mediated: evidence for the involvement of p56lck, calcium calmodulin kinase II, and Calcium-independent protein kinase C signaling pathways and for NF-kappaB and NF-AT nuclear translocation. J. Immunol., **175**, 7244–7254.
13. Dave S. S., Wright G., Tan B., Rosenwald A., Gascoyne R. D., Chan W. C., Fisher R. I., Braziel R. M., Rimsza L. M., Grogan T. M., Miller T. P., LeBlanc M., Greiner T. C., Weisenburger D. D., Lynch J. C., Vose J., Armitage J. O., Smeland E. B., Kvaloy S., Holte H., Delabie J., Connors J. M., Lansdorp P. M., Ouyang Q., Lister T. A., Davies A. J., Norton A. J., Muller-Hermelink H. K., Ott G., Campo E., Montserrat E., Wilson W. H., Jaffe E. S., Simon R., Yang L., Powell J., Zhao H., Goldschmidt N., Chiorazzi M. and Staudt L. M. (2004): Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. N. Engl. J. Med., **351**, 2159–2169.
14. Davidson W. F., Giese T. and Fredrickson T. N. (1998): Spontaneous development of plasmacytoid tumors in mice with defective Fas-Fas ligand interactions. J. Exp. Med., **187**, 1825–1838.
15. De Re V., De Vita S., Gasparotto D., Marzotto A., Carbone A., Ferraccioli G. and Boiocchi M. (2002): Salivary gland B cell lymphoproliferative disorders in Sjogren's syndrome present a restricted use of antigen receptor gene segments similar to those used by hepatitis C virus-associated non-Hodgkin's lymphomas. Eur. J. Immunol., **32**, 903–910.
16. De Re V., De Vita S., Marzotto A., Rupolo M., Gloghini A., Pivetta B., Gasparotto D., Carbone A. and Boiocchi M. (2000): Sequence analysis of the immunoglobulin antigen receptor of hepatitis C virus-associated non-Hodgkin lymphomas suggests that the malignant cells are derived from the rheumatoid factor-producing cells that occur mainly in type II cryoglobulinemia. Blood, **96**, 3578–3584.
17. de Wolf-Peeters C., Pittaluga S., Dierlamm J., Wlodarska I. and Van Den Berghe H. (1997): Marginal zone B-cell lymphomas including mucosa-associated lymphoid tissue type lymphoma (MALT), monocytoid B-cell lymphoma and splenic marginal zone cell lymphoma and their rela-

tion to the reactive marginal zone. Leuk. Lymphoma, **26**, 467–478.
18. Drenou B., Tilanus M., Semana G., Alizadeh M., Birebent B., Grosset J. M., Dias P., van Wichen D., Arts Y., De Santis D., Fauchet R. and Amiot L. (2004): Loss of heterozygosity, a frequent but a non-exclusive mechanism responsible for HLA dysregulation in non-Hodgkin's lymphomas. Br. J. Haematol., **127**, 40–49.
19. Du M., Diss T. C., Xu C., Peng H., Isaacson P. G. and Pan L. (1996): Ongoing mutation in MALT lymphoma immunoglobulin gene suggests that antigen stimulation plays a role in the clonal expansion. Leukemia, **10**, 1190–1197.
20. Dunn-Walters D. K., Boursier L., Spencer J. and Isaacson P. G. (1998): Analysis of immunoglobulin genes in splenic marginal zone lymphoma suggests ongoing mutation. Hum. Pathol., **29**, 585–593.
21. Dunn G. P., Bruce A. T., Sheehan K. C., Shankaran V., Uppaluri R., Bui J. D., Diamond M. S., Koebel C. M., Arthur C., White J. M. and Schreiber R. D. (2005): A critical function for type I interferons in cancer immunoediting. Nat. Immunol., **6**, 722–729.
22. Dunn G. P., Koebel C. M. and Schreiber R. D. (2006): Interferons, immunity and cancer immunoediting. Nat. Rev. Immunol., **6**, 836–848.
23. Dunn G. P., Old L. J. and Schreiber R. D. (2004): The immunobiology of cancer immunosurveillance and immunoediting. Immunity, **21**, 137–148.
24. Dunn G. P., Old L. J. and Schreiber R. D. (2004): The three Es of cancer immunoediting. Annu. Rev. Immunol., **22**, 329–360.
25. Eaton K. A., Ringler S. R. and Danon S. J. (1999): Murine splenocytes induce severe gastritis and delayed-type hypersensitivity and suppress bacterial colonization in Helicobacter pylori-infected SCID mice. Infect. Immun., **67**, 4594–4602.
26. Ekstrom-Smedby K. (2006): Epidemiology and etiology of non-Hodgkin lymphoma – a review. Acta Oncol., **45**, 258–271.
27. Elpek K. G., Lacelle C., Singh N. P., Yolcu E. S. and Shirwan H. (2007): CD4+CD25+ T regulatory cells dominate multiple immune evasion mechanisms in early but not late phases of tumor development in a B cell lymphoma model. J. Immunol., **178**, 6840–6848.
28. Enzler T., Gillessen S., Manis J. P., Ferguson D., Fleming J., Alt F. W., Mihm M. and Dranoff G. (2003): Deficiencies of GM-CSF and interferon gamma link inflammation and cancer. J. Exp. Med., **197**, 1213–1219.
29. Farinha P., Masoudi H., Skinnider B. F., Shumansky K., Spinelli J. J., Gill K., Klasa R., Voss N., Connors J. M. and Gascoyne R. D. (2005): Analysis of multiple biomarkers shows that lymphoma-associated macrophage (LAM) content is an independent predictor of survival in follicular lymphoma (FL). Blood, **106**, 2169–2174.
30. Grulich A. E., van Leeuwen M. T., Falster M. O. and Vajdic C. M. (2007): Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet, **370**, 59–67.
31. Hasselblom S., Sigurdadottir M., Hansson U., Nilsson-Ehle H., Ridell B. and Andersson P. O. (2007): The number of tumour-infiltrating TIA-1+ cytotoxic T cells but not FOXP3+ regulatory T cells predicts outcome in diffuse large B-cell lymphoma. Br. J. Haematol., **137**, 364–373.
32. Hilchey S. P., De A., Rimsza L. M., Bankert R. B. and Bernstein S. H. (2007): Follicular lymphoma intratumoral CD4+CD25+GITR+ regulatory T cells potently suppress CD3/CD28-costimulated autologous and allogeneic CD8+CD25– and CD4+CD25– T cells. J. Immunol., **178**, 4051–4061.
33. Hsiao F. C., Lin M., Tai A., Chen G. and Huber B. T. (2006): Cutting edge: Epstein-Barr virus transactivates the HERV-K18 superantigen by docking to the human complement receptor 2 (CD21) on primary B cells. J. Immunol., **177**, 2056–2060.
34. Hsu S. M., Lin J., Xie S. S., Hsu P. L. and Rich S. (1993): Abundant expression of transforming growth factor-beta 1 and -beta 2 by Hodgkin's Reed-Sternberg cells and by reactive T lymphocytes in Hodgkin's disease. Hum. Pathol., **24**, 249–255.
35. Hussell T., Isaacson P. G., Crabtree J. E. and Spencer J. (1993): The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to Helicobacter pylori. Lancet, **342**, 571–574.
36. Hviid T. V., Hylenius S., Rorbye C. and Nielsen L. G. (2003): HLA-G allelic variants are associated with differences in the HLA-G mRNA isoform profile and HLA-G mRNA levels. Immunogenetics, **55**, 63–79.
37. Ishida T., Ishii T., Inagaki A., Yano H., Komatsu H., Iida S., Inagaki H. and Ueda R. (2006): Specific recruitment of CC chemokine receptor 4-positive regulatory T cells in Hodgkin lymphoma fosters immune privilege. Cancer Res., **66**, 5716–5722.
38. Juszczynski P., Kalinka E., Bienvenu J., Woszczek G., Borowiec M., Robak T., Kowalski M., Lech-Maranda E., Baseggio L., Coiffier B., Salles G. and Warzocha K. (2002): Human leukocyte antigens class II and tumor necrosis factor genetic polymorphisms are independent predictors of non-Hodgkin lymphoma outcome. Blood, **100**, 3037–3040.
39. Juszczynski P., Kutok J. L., Li C., Mitra J., Aguiar R. C. and Shipp M. A. (2006): BAL1 and BBAP are regulated by a gamma interferon-responsive bidirectional promoter and are overexpressed in diffuse large B-cell lymphomas with a prominent inflammatory infiltrate. Mol. Cell. Biol., **26**, 5348–5359.
40. Juszczynski P., Ouyang J., Monti S., Rodig S. J., Takeyama K., Abramson J., Chen W., Kutok J. L., Rabinovich G. A. and Shipp M. A. (2007): The AP1-dependent secretion of galectin-1 by Reed Sternberg cells fosters immune privilege in classical Hodgkin lymphoma. Proc. Natl. Acad. Sci. USA, **104**, 13134–13139.
41. Katz I. R., Chapman-Alexander J., Jacobson E. B., Lerman S. P. and Thorbecke G. J. (1981): Growth of SJL/J-derived transplantable reticulum cell sarcoma as related to its ability to induce T-cell proliferation in the host. III. Studies on thymectomized and congenitally athymic SJL mice. Cell. Immunol., **65**, 84–92.
42. Kawasaki A., Shinkai Y., Yagita H. and Okumura K. (1992): Expression of perforin in murine natural killer cells and cytotoxic T lymphocytes *in vivo*. Eur. J. Immunol., **22**, 1215–1219.
43. Kirszenbaum M., Moreau P., Gluckman E., Dausset J. and Carosella E. (1994): An alternatively spliced form of HLA-G mRNA in human trophoblasts and evidence for the presence of HLA-G transcript in adult lymphocytes. Proc. Natl. Acad. Sci. USA, **91**, 4209–4213.
44. Kirszenbaum M., Moreau P., Teyssier M., Lafon C., Gluckman E., Dausset J. and Carosella E. (1995): Evidence for the presence of the alternatively spliced HLA-G mRNA forms in human mononuclear cells from peripheral blood and umbilical cord blood. Hum. Immunol., **43**, 237–241.

45. Kuppers R., Klein U., Hansmann M. L. and Rajewsky K. (1999): Cellular origin of human B-cell lymphomas. N. Engl. J. Med., **341**, 1520–1529.
46. Lasky J. L. and Thorbecke G. J. (1989): Characterization and growth factor requirements of SJL lymphomas. II. Interleukin 5 dependence of the *in vitro* cell line, cRCS-X, and influence of other cytokines. Eur. J. Immunol., **19**, 365–371.
47. Lech-Maranda E., Baseggio L., Bienvenu J., Charlot C., Berger F., Rigal D., Warzocha K., Coiffier B. and Salles G. (2004): Interleukin-10 gene promoter polymorphisms influence the clinical outcome of diffuse large B-cell lymphoma. Blood, **103**, 3529–3534.
48. Lech-Maranda E., Bienvenu J., Michallet A. S., Houot R., Robak T., Coiffier B. and Salles G. (2006): Elevated IL-10 plasma levels correlate with poor prognosis in diffuse large B-cell lymphoma. Eur. Cytokine Netw., **17**, 60–66.
49. Lech-Maranda E., Juszczynski P., Szmigielska-Kaplon A., Jamroziak K., Balcerczak E. and Robak T. (2007): Human leukocyte antigens HLA DRB1 influence clinical outcome of chronic lymphocytic leukemia? Haematologica, **92**, 710–711.
50. LeMaoult J., Krawice-Radanne I., Dausset J. and Carosella E. D. (2004): HLA-G1-expressing antigen-presenting cells induce immunosuppressive CD4+ T cells. Proc. Natl. Acad. Sci. USA, **101**, 7064–7069.
51. Lerman S. P., Carswell E. A., Chapman J. and Thorbecke G. J. (1976): Properties of reticulum cell sarcomas in SJL/J mice. III. Promotion of tumor growth in irradiated mice by normal lymphoid cells. Cell. Immunol., **23**, 53–67.
52. Li Z., Woo C. J., Iglesias-Ussel M. D., Ronai D. and Scharff M. D. (2004): The generation of antibody diversity through somatic hypermutation and class switch recombination. Genes Dev., **18**, 1–11.
53. Lila N., Rouas-Freiss N., Dausset J., Carpentier A. and Carosella E. D. (2001): Soluble HLA-G protein secreted by allo-specific CD4+ T cells suppresses the allo-proliferative response: a CD4+ T cell regulatory mechanism. Proc. Natl. Acad. Sci. USA, **98**, 12150–12155.
54. Lundin K. U., Hofgaard P. O., Omholt H., Munthe L. A., Corthay A. and Bogen B. (2003): Therapeutic effect of idiotype-specific CD4+ T cells against B-cell lymphoma in the absence of anti-idiotypic antibodies. Blood, **102**, 605–612.
55. Lundin K. U., Screpanti V., Omholt H., Hofgaard P. O., Yagita H., Grandien A. and Bogen B. (2004): CD4+ T cells kill Id+ B-lymphoma cells: FasLigand-Fas interaction is dominant *in vitro* but is redundant *in vivo*. Cancer Immunol. Immunother., **53**, 1135–1145.
56. Marasca R., Vaccari P., Luppi M., Zucchini P., Castelli I., Barozzi P., Cuoghi A. and Torelli G. (2001): Immunoglobulin gene mutations and frequent use of VH1--69 and VH4-34 segments in hepatitis C virus-positive and hepatitis C virus-negative nodal marginal zone B-cell lymphoma. Am. J. Pathol., **159**, 253–261.
57. Marshall N. A., Christie L. E., Munro L. R., Culligan D. J., Johnston P. W., Barker R. N. and Vickers M. A. (2004): Immunosuppressive regulatory T cells are abundant in the reactive lymphocytes of Hodgkin lymphoma. Blood, **103**, 1755–1762.
58. Mitra-Kaushik S., Harding J., Hess J., Schreiber R. and Ratner L. (2004): Enhanced tumorigenesis in HTLV-1 tax-transgenic mice deficient in interferon-gamma. Blood, **104**, 3305–3311.
59. Mocellin S., Marincola F., Rossi C. R., Nitti D. and Lise M. (2004): The multifaceted relationship between IL-10 and adaptive immunity: putting together the pieces of a puzzle. Cytokine Growth Factor Rev., **15**, 61–76.
60. Monti S., Savage K. J., Kutok J. L., Feuerhake F., Kurtin P., Mihm M., Wu B., Pasqualucci L., Neuberg D., Aguiar R. C., Dal Cin P., Ladd C., Pinkus G. S., Salles G., Harris N. L., Dalla-Favera R., Habermann T. M., Aster J. C., Golub T. R. and Shipp M. A. (2005): Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. Blood, **105**, 1851–1861.
61. Moreau P., Carosella E., Teyssier M., Prost S., Gluckman E., Dausset J. and Kirszenbaum M. (1995): Soluble HLA-G molecule. An alternatively spliced HLA-G mRNA form candidate to encode it in peripheral blood mononuclear cells and human trophoblasts. Hum. Immunol., **43**, 231–236.
62. Morse H. C. 3rd, Kearney J. F., Isaacson P. G., Carroll M., Fredrickson T. N. and Jaffe E. S. (2001): Cells of the marginal zone-origins, function and neoplasia. Leuk. Res., **25**, 169–178.
63. Munthe L. A., Corthay A., Os A., Zangani M. and Bogen B. (2005): Systemic autoimmune disease caused by autoreactive B cells that receive chronic help from Ig V region--specific T cells. J. Immunol., **175**, 2391–2400.
64. Muschen M., Rajewsky K., Kronke M. and Kuppers R. (2002): The origin of CD95-gene mutations in B-cell lymphoma. Trends Immunol., **23**, 75–80.
65. Nowak J., Kalinka-Warzocha E., Juszczynski P., Bilinski P., Mika-Witkowska R., Zajko M., Bienvenu J., Coiffier B., Salles G. and Warzocha K. (2007): Association of human leukocyte antigen ancestral haplotype 8.1 with adverse outcome of non-Hodgkin's lymphoma. Genes Chromosomes Cancer, **46**, 500–507.
66. Nowak J., Kalinka-Warzocha E., Juszczynski P., Mika-Witkowska R., Zajko M., Graczyk-Pol E., Coiffier B., Salles G. and Warzocha K. (2008): Haplotype-specific pattern of association of human major histocompatibility complex with non-Hodgkin's lymphoma outcome. Tissue Antigens, **71**, 16–26.
67. Nuckel H., Rebmann V., Durig J., Duhrsen U. and Grosse-Wilde H. (2005): HLA-G expression is associated with an unfavorable outcome and immunodeficiency in chronic lymphocytic leukemia. Blood, **105**, 1694–1698.
68. Ohshima K., Tutiya T., Yamaguchi T., Suzuki K., Suzumiya J., Kawasaki C., Haraoka S. and Kikuchi M. (2002): Infiltration of Th1 and Th2 lymphocytes around Hodgkin and Reed-Sternberg (H&RS) cells in Hodgkin disease: Relation with expression of CXC and CC chemokines on H&RS cells. Int. J. Cancer, **98**, 567–572.
69. Pappo J., Torrey D., Castriotta L., Savinainen A., Kabok Z. and Ibraghimov A. (1999): Helicobacter pylori infection in immunized mice lacking major histocompatibility complex class I and class II functions. Infect. Immun., **67**, 337–341.
70. Poppema S., Potters M., Visser L. and van den Berg A. M. (1998): Immune escape mechanisms in Hodgkin's disease. Ann. Oncol., **9** (suppl. 5), S21–24.
71. Rimsza L. M., Roberts R. A., Campo E., Grogan T. M., Bea S., Salaverria I., Zettl A., Rosenwald A., Ott G., Muller-Hermelink H. K., Delabie J., Fisher R. I., Unger J. M., Leblanc M., Staudt L. M., Jaffe E. S., Gascoyne R. D., Chan W. C., Weisenburger D. D., Greiner T., Braziel R. M. and Miller T. P. (2006): Loss of major histocompatibility class II expression in non-immune-privileged site dif-

fuse large B-cell lymphoma is highly coordinated and not due to chromosomal deletions. Blood, **107**, 1101–1107.
72. Rimsza L. M., Roberts R. A., Miller T. P., Unger J. M., LeBlanc M., Braziel R. M., Weisenberger D. D., Chan W. C., Muller-Hermelink H. K., Jaffe E. S., Gascoyne R. D., Campo E., Fuchs D. A., Spier C. M., Fisher R. I., Delabie J., Rosenwald A., Staudt L. M. and Grogan T. M. (2004): Loss of MHC class II gene and protein expression in diffuse large B-cell lymphoma is related to decreased tumor immunosurveillance and poor patient survival regardless of other prognostic factors: a follow-up study from the Leukemia and Lymphoma Molecular Profiling Project. Blood, **103**, 4251–4258.
73. Rosenwald A., Wright G., Leroy K., Yu X., Gaulard P., Gascoyne R. D., Chan W. C., Zhao T., Haioun C., Greiner T. C., Weisenburger D. D., Lynch J. C., Vose J., Armitage J. O., Smeland E. B., Kvaloy S., Holte H., Delabie J., Campo E., Montserrat E., Lopez-Guillermo A., Ott G., Muller-Hermelink H. K., Connors J. M., Braziel R., Grogan T. M., Fisher R. I., Miller T. P., LeBlanc M., Chiorazzi M., Zhao H., Yang L., Powell J., Wilson W. H., Jaffe E. S., Simon R., Klausner R. D. and Staudt L. M. (2003): Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J. Exp. Med., **198**, 851–862.
74. Royer B., Cazals-Hatem D., Sibilia J., Agbalika F., Cayuela J. M., Soussi T., Maloisel F., Clauvel J. P., Brouet J. C. and Mariette X. (1997): Lymphomas in patients with Sjogren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. Blood, **90**, 766–775.
75. Rubio-Moscardo F., Blesa D., Mestre C., Siebert R., Balasas T., Benito A., Rosenwald A., Climent J., Martinez J. I., Schilhabel M., Karran E. L., Gesk S., Esteller M., deLeeuw R., Staudt L. M., Fernandez-Luna J. L., Pinkel D., Dyer M. J. and Martinez-Climent J. A. (2005): Characterization of 8p21.3 chromosomal deletions in B--cell lymphoma: TRAIL-R1 and TRAIL-R2 as candidate dosage-dependent tumor suppressor genes. Blood, **106**, 3214–3222.
76. Salles G., Bienvenu J., Bastion Y., Barbier Y., Doche C., Warzocha K., Gutowski M. C., Rieux C. and Coiffier B. (1996): Elevated circulating levels of TNFalpha and its p55 soluble receptor are associated with an adverse prognosis in lymphoma patients. Br. J. Haematol., **93**, 352–359.
77. Sebti Y., Le Maux A., Gros F., De Guibert S., Pangault C., Rouas-Freiss N., Bernard M. and Amiot L. (2007): Expression of functional soluble human leucocyte antigen--G molecules in lymphoproliferative disorders. Br. J. Haematol., **138**, 202–212.
78. Shankaran V., Ikeda H., Bruce A. T., White J. M., Swanson P. E., Old L. J. and Schreiber R. D. (2001): IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature, **410**, 1107–1111.
79. Sharpe A. H., Wherry E. J., Ahmed R. and Freeman G. J. (2007): The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat. Immunol., **8**, 239–245.
80. Smyth M. J., Ortaldo J. R., Shinkai Y., Yagita H., Nakata M., Okumura K. and Young H. A. (1990): Interleukin 2 induction of pore-forming protein gene expression in human peripheral blood CD8+ T cells. J. Exp. Med., **171**, 1269–1281.
81. Smyth M. J., Thia K. Y., Street S. E., MacGregor D., Godfrey D. I. and Trapani J. A. (2000): Perforin-mediated cytotoxicity is critical for surveillance of spontaneous lymphoma. J. Exp. Med., **192**, 755–760.
82. Spaggiari G. M., Contini P., Carosio R., Arvigo M., Ghio M., Oddone D., Dondero A., Zocchi M. R., Puppo F., Indiveri F. and Poggi A. (2002): Soluble HLA class I molecules induce natural killer cell apoptosis through the engagement of CD8: evidence for a negative regulation exerted by members of the inhibitory receptor superfamily. Blood, **99**, 1706–1714.
83. Stasi R., Zinzani P. L., Galieni P., Lauta V. M., Damasio E., Dispensa E., Dammacco F., Papa G. and Tura S. (1994): Prognostic value of serum IL-10 and soluble IL-2 receptor levels in aggressive non-Hodgkin's lymphoma. Br. J. Haematol., **88**, 770–777.
84. Stopeck A. T., Gessner A., Miller T. P., Hersh E. M., Johnson C. S., Cui H., Frutiger Y. and Grogan T. M. (2000): Loss of B7.2 (CD86) and intracellular adhesion molecule 1 (CD54) expression is associated with decreased tumor-infiltrating T lymphocytes in diffuse B-cell large-cell lymphoma. Clin. Cancer Res., **6**, 3904–3909.
85. Straus S. E., Jaffe E. S., Puck J. M., Dale J. K., Elkon K. B., Rosen-Wolff A., Peters A. M., Sneller M. C., Hallahan C. W., Wang J., Fischer R. E., Jackson C. M., Lin A. Y., Baumler C., Siegert E., Marx A., Vaishnaw A. K., Grodzicky T., Fleisher T. A. and Lenardo M. J. (2001): The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. Blood, **98**, 194–200.
86. Street S. E., Hayakawa Y., Zhan Y., Lew A. M., MacGregor D., Jamieson A. M., Diefenbach A., Yagita H., Godfrey D. I. and Smyth M. J. (2004): Innate immune surveillance of spontaneous B cell lymphomas by natural killer cells and gammadelta T cells. J. Exp. Med., **199**, 879–884.
87. Street S. E., Trapani J. A., MacGregor D. and Smyth M. J. (2002): Suppression of lymphoma and epithelial malignancies effected by interferon gamma. J. Exp. Med., **196**, 129–134.
88. Sutkowski N., Conrad B., Thorley-Lawson D. A. and Huber B. T. (2001): Epstein-Barr virus transactivates the human endogenous retrovirus HERV-K18 that encodes a superantigen. Immunity, **15**, 579–589.
89. Tierens A., Delabie J., Michiels L., Vandenberghe P. and De Wolf-Peeters C. (1999): Marginal-zone B cells in the human lymph node and spleen show somatic hypermutations and display clonal expansion. Blood, **93**, 226–234.
90. Tsiagbe V. K., Asakawa J., Miranda A., Sutherland R. M., Paterson Y. and Thorbecke G. J. (1993): Syngeneic response to SJL follicular center B cell lymphoma (reticular cell sarcoma) cells is primarily in V beta 16+ CD4+ T cells. J. Immunol., **150**, 5519–5528.
91. Tsiagbe V. K., Yoshimoto T., Asakawa J., Cho S. Y., Meruelo D. and Thorbecke G. J. (1993): Linkage of superantigen-like stimulation of syngeneic T cells in a mouse model of follicular center B cell lymphoma to transcription of endogenous mammary tumor virus. EMBO J., **12**, 2313–2320.
92. Warzocha K., Bienvenu J., Ribeiro P., Moullet I., Dumontet C., Neidhardt-Berard E. M., Coiffier B. and Salles G. (1998): Plasma levels of tumour necrosis factor and its soluble receptors correlate with clinical features and outcome of Hodgkin's disease patients. Br. J. Cancer, **77**, 2357–2362.

93. Warzocha K., Ribeiro P., Bienvenu J., Roy P., Charlot C., Rigal D., Coiffier B. and Salles G. (1998): Genetic polymorphisms in the tumor necrosis factor locus influence non-Hodgkin's lymphoma outcome. Blood, **91**, 3574–3581.
94. Warzocha K., Salles G., Bienvenu J., Barbier Y., Bastion Y., Doche C., Rieux C. and Coiffier B. (1997): Prognostic significance of TNF alpha and its p55 soluble receptor in malignant lymphomas. Leukemia, **11** (suppl. 3), 441–443.
95. Warzocha K., Salles G., Bienvenu J., Bastion Y., Dumontet C., Renard N., Neidhardt-Berard E. M. and Coiffier B. (1997): Tumor necrosis factor ligand-receptor system can predict treatment outcome in lymphoma patients. J. Clin. Oncol., **15**, 499–508.
96. Yamamoto R., Nishikori M., Kitawaki T., Sakai T., Hishizawa M., Tashima M., Kondo T., Ohmori K., Kurata M., Hayashi T. and Uchiyama T. (2008): PD-1-PD-1 ligand interaction contributes to immunosuppressive microenvironment of Hodgkin lymphoma. Blood, **111**, 3220–3224.
97. Yang Z. Z., Novak A. J., Stenson M. J. Witzig T. E. and Ansell S. M. (2006): Intratumoral CD4+CD25+ regulatory T-cell-mediated suppression of infiltrating CD4+ T cells in B-cell non-Hodgkin lymphoma. Blood, **107**, 3639–3646.
98. Yang Z. Z., Novak A. J., Ziesmer S. C., Witzig T. E. and Ansell S. M. (2006): Attenuation of CD8(+) T-cell function by CD4(+)CD25(+) regulatory T cells in B-cell non-Hodgkin's lymphoma. Cancer Res., **66**, 10145–10152.
99. Zangani M. M., Froyland M., Qiu G. Y., Meza-Zepeda L. A., Kutok J. L., Thompson K. M., Munthe L. A. and Bogen B. (2007): Lymphomas can develop from B cells chronically helped by idiotype-specific T cells. J. Exp. Med., **204**, 1181–1191.
100. Zavazava N. (1998): Soluble HLA class I molecules: biological significance and clinical implications. Mol. Med. Today, **4**, 116–121.
101. Zavazava N. and Kronke M. (1996): Soluble HLA class I molecules induce apoptosis in alloreactive cytotoxic T lymphocytes. Nat. Med., **2**, 1005–1010.
102. Zerafa N., Westwood J. A., Cretney E., Mitchell S., Waring P., Iezzi M., and Smyth M. J. (2005): Cutting edge: TRAIL deficiency accelerates hematological malignancies. J. Immunol., **175**, 5586–5590.
103. Zhang J. Q., Okumura C., McCarty T., Shin M. S., Mukhopadhyay P., Hori M., Torrey T. A., Naghashfar Z., Zhou J. X., Lee C. H., Roopenian D. C., Morse H. C. 3rd and Davidson W. F. (2004): Evidence for selective transformation of autoreactive immature plasma cells in mice deficient in Fasl. J. Exp. Med., **200**, 1467–1478.