Stress immunity in lymphomas: mesenchymal cells as a target of therapy

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1.ABSTRACT

The role of lymphocytes in eliminating lymphoma cells is based on the interaction between activating receptors on lymphocytes and target surface ligands on lymphoma cells. Stress-related immunity can be triggered both in Hodgkin's (HL) and non-Hodgkin lymphomas (NHL), through the activation of the NKG2D receptor on $CD8^+$T and gammadelta T lymphocytes, by NKG2D-ligands (NKG2D-L), as the MHC class-I related molecules MIC-A/B and the UL16-binding proteins 1-4 (ULBPs), expressed on lymphoma cells. Furthermore, NKG2D-L can be shed and interact with NKG2D on effector lymphocytes affecting the recognition of lymphoma cells. Proteolytic cleavage of MIC-A is known to depend on the thiol isomerase ERp5 and the disintegrins and metalloproteinases ADAM10 and ADAM17, which also cleave ULPBs. Mesenchymal stromal cells (MSC) are relevant in regulating effector T lymphocytes-mediated lymphoma surveillance. Indeed, MSC can be seen as targets of potential new therapeutic schemes acting on lymphoma microenvironment, to redirect the stress immune response and avoid escape strategies, by inducing stress molecules, inhibiting sheddase activity, shifting cytokine production to Th1 pattern and blocking Treg differentiation.

2.INTRODUCTION

Hodgkin's lymphoma (HL), diffuse large B cell lymphoma (DLBCL), among non-Hodgkin lymphomas (NHL), and primary mediastinal B cell lymphoma (PMBCL) that shares characteristics with HL, account for more than 60% of all lymphomas in the western world (1-4). Most patients can be cured with modern treatment strategies, although >40% die after relapse or progressive disease. Indeed, in the last years these lymphomas have become more resistant to conventional therapies, so that there are now major problems in managing patients, as non-responders are not easily treated with alternative therapeutic schemes; this makes of interest a focus on new diagnostic tools and therapies (1-4). Recent preclinical and clinical studies have demonstrated that the tumor microenvironment represents a promising therapeutic target not only in solid cancers but also in the case of lymphomas (1-4); we have previously reported data supporting this hypothesis both for HL and NHL (see below). Herein, we will describe what is known on the cross-talk between microenvironment and lymphoma cells, focusing on mesenchymal stromal cells, a new point of view of the immune response represented by the so called "stress-related immunity" and the possible site of therapeutic intervention.
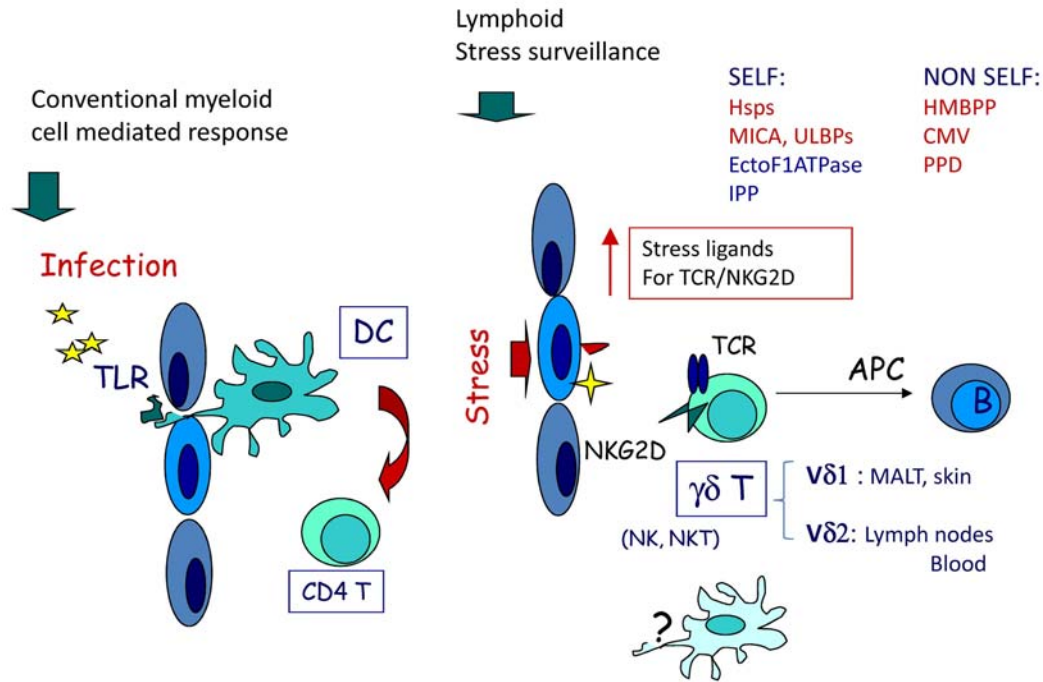
Figure 1. Gammadelta T cells and stress-related immunity. Left hand: conventional immune response: myeloid derived dendritic cells, activated by bacterial or viral products via toll-like receptor (TLR), present the antigen to CD4+ (helper) T lymphocytes that, in turn give rise to cellular responses mediated by CD8+ T cells or humoral response mediated by B lymphocytes. Right hand: stress molecules, as MIC-A or ULBP, expressed at the surface of epithelial or cancer cell during chronic inflammation, infection or tumor transformation directly stimulate unconventional T cells, including gammadelta T cells, through the NKG2D receptor and trigger both T and B cell responses. It is not clear the role of dendritic cells during the activation of gammadelta T cells in this context.

3. THE CONCEPT OF STRESS-RELATED IMMUNITY: IMPLICATION FOR ANTICANCER SURVEILLANCE

In the last years the concept of "lymphoid stress surveillance" has emerged (5,6) (Figure 1). According to this concept, the immune system is equipped with two types of response: the former, the classic antigen-specific response, triggered by myeloid antigen presenting cells and followed by the expansion of specific T and B lymphocytes; the latter, mediated by so-called unconventional T lymphocytes, able to respond to stress-signals, independent of the activation of antigen presenting cells. Activation of non-specific myeloid cells, including neutrophils and macrophages, is rapid but broad (innate immunity); conversely, antigen- specific response is precise and focused (adaptive immunity), but time is needed to let it take place. The so called stress-surveillance response would fill the time gap between rapid activation of myeloid cell and delayed specific lymphocyte activation. In this type of immunity, infected or injured cells (either epithelial or parenchymal) express or up-regulate at the cell surface a set of molecules that are a signature of cell damage and referred to as stress-induced antigens. Besides the ureate and adenosine triphosphate (ATP) released from dying cells (7), many stress antigens may not be recognized by myeloid cells: these include a large set of major histocompatibility complex (MHC) class I-related

molecules, such as MIC-A/B, or the UL16 binding proteins (ULBPs), that are indeed recognized by natural killer (NK) cells, CD8+ memory T cells, and large numbers of "unconventional" T lymphocytes, of which gamma delta T cells are the prototype (5-11). Although not sufficient to clear the body from a specific pathogen or impede the development of cancer, lymphoid stress surveillance can quickly limit the dissemination of infected or malignant cells, maintain tissue integrity, and regulate the following adaptive responses.

3.1. MIC-A/B and ULBPs as stress-molecules and NKG2D ligands (L)

It is now clear that also during tumor transformation such events might occur, i.e. the exposure of "stress signals", such as MHC-related products, upon cell damage (5,6). These are able to bind the NK receptor group-2D (NKG2D), expressed by most T and NK cells, and are also referred to as NKG2D-ligands (NKG2D-L). In turn, NKG2D engagement delivers an activating signal to either NK or alphabeta or gammadelta T lymphocytes, leading to the release of lytic enzymes, such as perforin or granzymes, or anti-tumor cytokines as tumor necrosis factor (TNF)-alpha (8-12) (Figure 1). Among the stress molecules involved in this type of immune response, there are the MHC-class-I related molecules (MIC-A and MIC-B) that can be induced or up-regulated at the surface of epithelial

cells by physicochemical perturbations and inflammation, and the ULBP1-6, receptors for the UL16 protein produced by cytomegalovirus (CMV)-infected cells (8-12). All these molecules can be expressed at the surface of tumor cells, including lymphoma cells, or can be up-regulated both *in vitro* and *in vivo* at the surface of leukemic cells by the use of drugs, such as all-trans-retinoic acid (ATRA) or sodium valproate (VPA) (12-14). In turn, MIC-A/B and ULBPs can be cleaved by the thiol isomerase ERp5 or by the disintegrin and metalloproteinase ADAM10 and ADAM17 and released in the extracellular milieu (15,16). As soluble forms of the molecule, they bind to NKG2D but are unable to deliver the activating signal (see section 5.1).

3.2. Unconventional T lymphocytes: two gammadelta T cell subsets

Besides other unconventional T lymphocytes, gammadelta T cells are good mediators of a stress-related response (5). T lymphocytes bearing the gammadelta T cell receptor (TCR) represent a relevant proportion of the mucosal-associated lymphoid tissue, known to play an important role in the first-line defense against viral, bacterial and fungal pathogens. Two main subsets of gammadelta T cells (Figure 1) are known: circulating Vdelta2 T lymphocytes are involved in the response to mycobacteria, Epstein Barr Virus (EBV) and some solid tumors, while Vdelta1 T cells, resident in mucosal-associated lymphoid tissues, contribute to the immunity against Listeria monocytogenes, CMV and certain hematological malignancies (5,12,13,17-19). Both gammadelta T cell subsets can interact with stress-induced MIC-A, MIC-B and ULBPs; the recognition is mainly mediated through the NKG2D surface receptor, also expressed by alphabeta T lymphocytes. In gammadelta T cells it seems to work in association with the TCR that also binds to these stress molecules: upon engagement of NKG2D, an activating signal is delivered in gammadelta T lymphocytes that are promptly able to exert their effector function, by proliferating, producing pro-inflammatory and antimicrobial cytokines, such as interferon-gamma (IFN)-gamma, or tumor necrosis factor (TNF)-alpha, or releasing lytic enzymes to destroy bacteria or infected cells, as a response to damage signals (5,6). A similar mechanism can be exploited by gammadelta T lymphocytes to face transformed cells that also overexpress NKG2D-L due to the stress-inducing tumor transformation (17-20). Another potent stimulus for gammadelta T cells of the Vdelta2 subset, acting through the TCR, is represented by low molecular weight phopshoantigens (P-Ag) (21-23). Consistent with the stress-surveillance model, P-Ag may be autologous, such as isoprenylpyrophosphate (IPP), which accumulates in many virus-infected or transformed cells, or microbial, such as hydroxymethyl but-2-enyl pyrophosphate (HMBPP), a metabolic intermediate specific to many prokaryotes and parasites (21-23). Of clinical interest, aminobisphosphonates (N-BPs), which are widely prescribed for osteoporosis and malignancy, indirectly activate Vgamma9Vdelta2$^+$ T cells by inhibiting farnesyl pyrophosphate synthase, which provokes IPP accumulation (24) (see section 6).

4. DEFINITION OF LYMPH NODE MICROENVIRONMENT AND ROLE OF MESENCHYMAL STROMAL CELLS (MSC)

Microenvironment is the tissue space where cells of either the same or different type can interact each other influencing the fate of eventually distantly located cells or even the entire organism (25). The tissue microenvironment is composed of blood and lymphoid vessel, cells involved in defining the tissue architecture producing the extraxcellular matrix proteins disposed as fibers including collagen, fibronectin, laminin and several others which are responsible for the integrity of the tissue itself. On this matrix and in the free space among the fibers, cells typical of that organ can interact each other and with the mesenchymal stromal cells (MSC). Within a lymph node several places can be shown with a peculiar microenvironment. For instance the dark and white zones of a lymphoid follicle represent a microenvironment where antigen presenting cells as follicular dendritic cells (FDC) can interact with B cells leading to activation and selection of antigen specific B cells responsible for the immune response against pathogens (1,2, 25). It is obvious that the integrity of this microenvironment is essential for an efficient immune response. It is conceivable that the microenvironment is different in follicular lymphomas (FL) compared to DLBCL. Indeed, in FL the architecture of the lymphoid follicle is maintained while in DLBCL is not (26). Consequently, this can lead to the presence of different soluble factors which in turn influence the growth of lymphoma cells and the immune response, if any, against them (26).

4.1. Cell types in the microenvironment

Within the lymph node (LN) microenvironment parenchymal cells like B and T cells at different stages of maturation, accessory cells and MSC. All these cells are present in appropriate ratio among each other and they play a role in maintaining the homeostasis (26, 27). During lymphoma cell growth the reciprocal interaction among these cells can be altered (26, 27). MSC can produce the extracellular matrix factor important for maintaining the integrity of the lymph node during the lymphoma B cell growth. This integrity can also have a role in sparing lymphoma B cells. In addition, MSC can produce soluble factors as interleukin (IL) 6, BAFF and IL15 which can support the growth and survival of lymphoma B cells. Of course, also accessory cells as FDC can support lymphoma B cells but at present is to be defined the respective role of FDC and MSC in regulating tumor B cell growth and expansion (26, 27).

4.2. Definition and characterization of lymph node (LN)MSC.

Mesenchymal stromal cells display a fibroblast-like morphology (28-30). They appear as small spindle cells when at confluence while when they are just seeded or after several culture passages can show a large and flat shape. LNMSC usually do not display an epithelial-like morphology as it can happen for MSC from bone marrow (BM) or from embryonic tissues (28-30). At present, it is difficult to define the phenotype of MSC and it is not clear
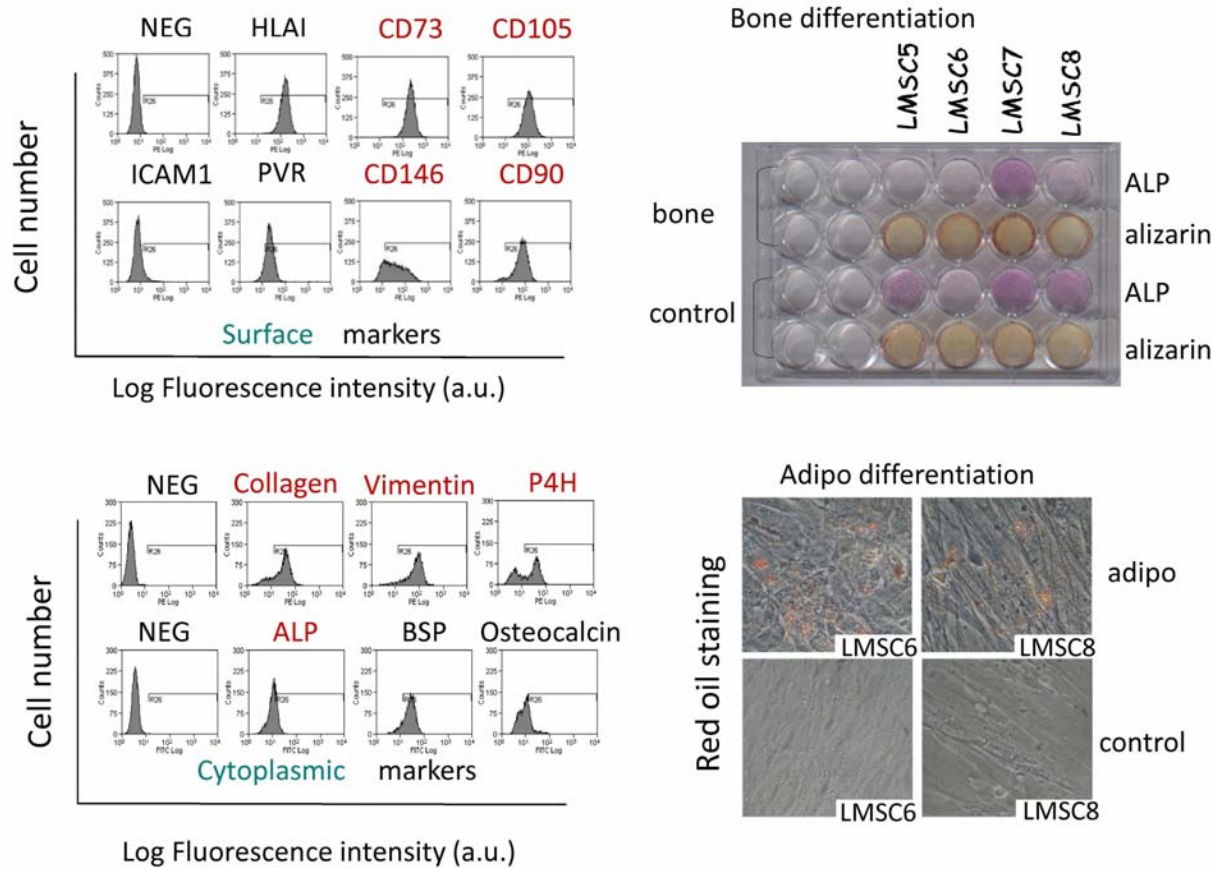
Figure 2. Phenotype and differentiation potential of lymph node mesenchymal stromal cells (LNMSC). Left hand: typical surface molecules expressed by lymph node mesenchymal stromal cells (LNMSC), as CD73, CD105, CD146 or CD90 (upper histograms) and collagen, prolyl-4-hydroxilase (P4H), alkaline phosphatase (ALP) and bone sialoprotein (BSP) (lower histograms). Right hand: bone (alizarin staining, upper panel) or adipocyte (red oil staining, lower panel) differentiation of LNMSC isolated from 4 different LN.

whether MSC isolated from different tissues (BM, thymus, parenchymal tissues) show different surface markers (28-30). In general, the expression of a series of surface and cytoplasmic markers can aid in defining MSC. Indeed, MSC express at the cell surface CD105 and CD90 antigens as well as CD146 (also named melanoma cell adhesion molecule) while collagen and prolyl-4-hydroxilase (P4H) the enzyme involved in hydroxylation of collagen, are present into the cytoplasm. The lack of CD1a, CD14, CD80, CD83, CD86 receptors at the MSC cell surface indicate that these cells are not from monocyte-dendritic origin. Again, the absence of several markers typical of hematopoietic cells as CD34, CD33 or endothelial cells as CD31 and vascular cell adhesion molecule (VCAM)1 further characterize the LNMSC. It is of note that LNMSC can also express some markers typical of embryonic stem cells as Sox-2 (unpublished data). As shown in figure 2, LNMSC can constitutively express at the cell surface molecules as poliovirus receptor (PVR) which are ligands of DNAM1 activating receptor expressed on different subsets of effector T and NK lymphocytes (31). Also, LNMSC can express counter-ligands of NKG2D and the

enzymes involved in the shedding of these ligands (see below).

One of the typical characteristics of MSC is their plasticity that is the capacity of MSC to differentiate in mesodermal cells as adipocytes, osteocytes and condrocytes. LNMSC can indeed differentiate into adipose or bone forming cells (Figure 2) provided they are cultured in appropriate medium. In our hands, LNMSC did not differentiate into condrocytes (unpublished results) however, the differentiation towards condrocytes is usually less easy than that to adipocytes or osteocytes. Likewise MSC from other sources (28-30) LNMSC can effectively inhibit T cell proliferation to several stimuli as polyclonal mitogen, anti-CD3 monoclonal antibodies (mAbs) or bacterial toxin as staphylococcus enterotoxin B (unpublished data). This inhibition is maximal when co-cultures with lymphocytes are performed using a monolayer of LNMSC and lymphocytes are in contact with LNMSC. It is relevant to state that the inhibition is not present or it is less evident when low number of MSC not forming a monolayer are co-cultured with lymphocytes.

This would suggest that different regulating effects can be found in the lymph node microenvironment depending on the presence of low or high amounts of LNMSC. It is to be determined whether LNMSC can give rise to regulatory T cells as it happens for MSC isolated from BM (32). In addition, LNMSC can produce factors involved in survival and proliferation of B cells as IL15 and IL6 (unpublished results). Pharmacological down-regulation of LNMSC-mediated immune-suppression of T cell response and inhibition of LNMSC–mediated help to B cells, as shown for BMMSC (33), can be an useful tool to favour immune cell response to B cell lymphoma growth.

5. NKG2D-L STRESS-INDUCED RESPONSE IN THE LYMPHOMA MICROENVIRONMENT

In several lymphomas the microenvironment seems to be crucial for the survival and proliferation of tumor cells (1-4). In follicular lymphomas, neoplastic cells reside and accumulate in follicular structures in close association with both lymphocytes and dendritic cells, as occurs in the germinal center (GC) of healthy LN. In contrast, neoplastic B cells are rarely encountered in the interfollicular areas, so the lymphoma cells seem to require the GC-like microenvironment to grow and expand (3). In classical HL, the tumor (Reed-Sternberg, RS) cells account for less than 1% of all cells in the tumor tissue, most of which is composed of lymphocytes, eosinophils and macrophages, suggesting an unsuccessful inflammatory response against the tumor. Both in NHL and HL, isolated lymphoma cells can grow in culture much better when seeded onto a layer of stromal cells; likewise, stromal and nurse-like cells are responsible for increased survival of chronic lymphocytic leukemias (CLL). On the other hand, in all these lymphoproliferative diseases, expression of stress-related molecules, including the NKG2D-L, has been described (12,13,17,19,34), although not always leading to an effective anti-lymphoma response, possibly due to the cytokine milieu predominant in the microenvironment (18,34-37) (see also section 5.2).

5.1. Significance of NKG2D/NKG2D-L interaction in lymphoid malignancies

We have described that gammadelta T lymphocytes belonging to the Vdelta1 subset are expanded in patients with CLL and NHL (13,19), where they proliferate in response to tumor cells, provided they express NKG2D-L. These gammadelta T cells can exert cytotoxicity against the autologous tumor cells and produce anti-neoplastic or pro-differentiating cytokines, such as TNF-alpha and IL4 (13,14,19,38). Also, circulating Vdelta1 T lymphocytes proliferate and produce IFN-gamma in response to autologous cells, once they express MIC-A or ULBPs upon exposure to ATRA or VPA. Of note, IL4 can be found in the sera of NHL patients with good prognosis, while plasma levels of sNKG2D-L correlate with disease progression in multiple myeloma, CLL, NHL and acute myeloid leukemias (12,13,34,39). In particular, both sMIC-A and sULBP2 have been shown as prognostic marker for multiple myeloma and for the identification of early-stage CLL patients with risk of

disease progression (39,40). More recently, we described that in classical Hodgkin lymphomas the LN stroma displayed *in situ* very low levels of MIC-A/B or ULBPs together with high levels of expression of ERp5 and ADAM10, both related to the shedding of soluble NKG2D-L (34,41-44). These enzymes (see also section 6) were detected both in LNMSC and in RS cells; also, MIC-A and ULBP3 were present in culture supernatants of LNMSC or RS cells. NKG2D-L-negative RS cells could not be killed by CD8^{+}alphabeta or gammadelta T cells; tumor cell killing could be partially restored by treating RS cells with VPA that enhanced NKG2D-L surface expression (14,34). On the other hand, both in the LN and in the LNMSC cultures, overpression and production of TGF beta, that is able to down-regulate the surface expression of NKG2D, was found; at variance, IL15 that enhances NKG2D expression, was down regulated in HL stroma (34,35). Thus, at the tumor site, at least in the case of HL, tumor microenvirnment is prone to impede a stress-induced response, either through the shedding of NKG2D-L or by the down-regulation of NKG2D receptor.

5.2. Cellular (Th1), humoral (Th2) and regulatory (Treg) responses in the lymph node

In NHL, it has been hypothesized that hyperproduction of IL6, capable of inducing B lymphocyte proliferation, and decreased production of IL4, that displays a differentiating activity on B lymphocytes, contributes significantly to lymphoma progression and is associated to a defective or altered Th1 (cellular responses) or Th2 (humoral immunity) profile (4,33,45). The development of Th1 or Th2 responses is regulated also by IL12 that enhances cellular responses and IL10, a Th2 cytokine that is largely produced by regulatory T cells (Treg) and exerts the opposite effect (46,47). Alterations in IL10 secretion might contribute to an impaired Th differentiation with a predominance of Treg that have been shown to produce also TGFbeta1, that in turn down-regulate IL12 production and Th1 development on one side, and NKG2D receptor expression on the other (46,47). IL12, besides contributing to the maintenance of a Th1 type (cellular) response, induces activation of gammadelta T cells, that are potentially able to kill tumor cells. We described alterations in the number, distribution and function of gammadelta T cells, together with the type of cytokine produced (IFN-gamma or TNF-alpha vs IL4 vs IL10, that is Th1 vs Th2 vs Treg profile) in CLL and NHL patients (13,19). Some of these changes paralleled changes in clinical manifestations, such as disease progression. In HL the microenvironment seems to be committed to develop a regulatory, rather than a helper response, as both IL10 and Treg cells have been shown at the tumor site (34,36). Recently, it has been reported that resident gammadelta T lymphocytes can produce IL17 (48); these cells have been shown to exert a regulatory, rather than an effector function, and express the cytokines (IL10) and markers (FoxP3) of Treg (47). As already underlined, stress surveillance can contribute to limit the dissemination of lymphoma cells, whereas Tregs may exert their function too early and lead to an impairment of anti-lymphoma immune responses.
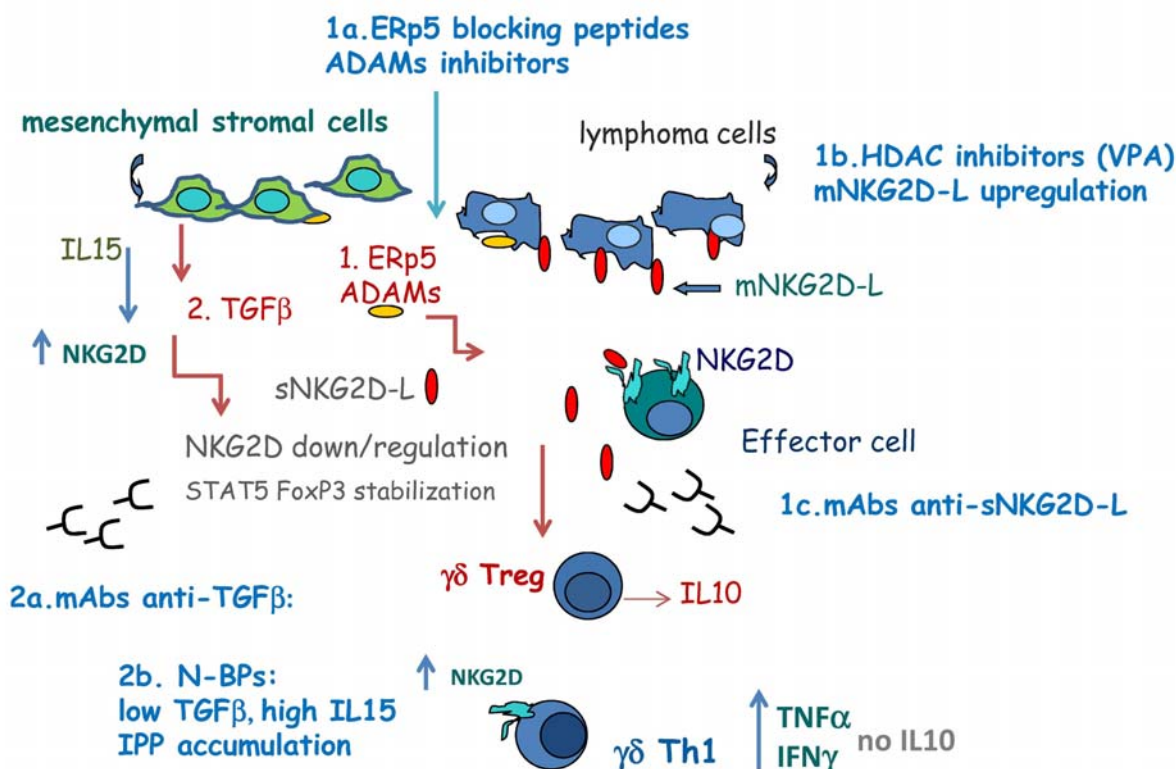
Figure 3. Lymphoma microenvironment and stress surveillance. Scheme of the possible therapeutic interventions to shift the lymphoma microenvironment to a stress-related immune response. 1. Influencing on sNKG2D-L-mediated effects: (1a) ERp5 and ADAMs inhibitors can inhibit or reduce the shedding of NKG2D-L as soluble (s) molecules; (1b) histone deacetilase (HDAC) inhibitors, as valproic acid (VPA), can induce the membrane (m) upregulation of stress related molecules, as NKG2D-L; (1c) mAbs to sNKG2D-L can block the interaction of these soluble molecules with NKG2D; 2. Acting on regulating cytokine produced by the microenvironment through: (2a) mAbs to TGFbeta to block its immunesuppressive effects neutralizing the down-regulation of NKG2D and prevent the activation of matrix metalloproteinase (MMPs); (2b) N-BPs administration to reduce TGFbeta production by LNMSC, stimulating generation of effector memory (EM, Th1) gammadelta T cells instead of Treg cells. Also, N-BPs can stimulate LNMSC to increment IL15 expression inducing NKG2D at the lymphocyte surface and accumulation of isopentenyl-pyrophosphates (IPP) to trigger gammadelta effector Th1 cells.

6. RELEASE OF sNKG2D-L AND BLOCKING OF NKG2D: SHEDDASE INHIBITORS TO RESCUE THE STRESS-INDUCED IMMUNE REACTION

On the basis of the stress-related immunity hypothesis, in order to avoid the onset of a lymphoma, the lymph node microenvironment should be able to induce a cellular response against the stress-related antigens expressed by neoplastic cells, and limit the release of these antigens as soluble molecules. Such molecules can be induced upon tumor transformation on cancer cells, but also at the surface of stromal cells in the microenvironment as a consequence of chronic inflammation (5,6) (Figure 3). In turn, physiopathological and pharmacological upregulation of NKG2D-L might be counteracted by the enzymatic activity of different sheddases, including ERp5 and ADAM10/17, leading to the release of these ligands and inhibition of cancer cell recognition (Figure 3) (12-16, 41-44). Of note, a correlation between the levels of sNKG2D-L and the stage of disease has been reported in CLL (13,40); moreover, in solid cancers, tumor progression seems to be inversely related to sheddase activity (49,50).

Proteolytic cleavage of MIC-A has been shown to depend on the thiol isomerase ERp5, that binds its alpha3 domain, and the disintegrin and metalloproteinases ADAM10 or ADAM17, which are also able to cleave ULPBs (41-43). Overexpression of these enzymes, called sheddases, have been reported in multiple myeloma, and other tumors, including HL and some NHL (34,39,44). Blocking of ERp5 would be possible with antagonistic peptides mimicking the alpha domain of MIC-A, thus impeding the interaction of the enzyme with its substrate (49-51), whereas for ADAM10 and ADAM17 there are inhibitors with a certain degree of selectivity recently described (52-54).

7. POTENTIAL ROLE OF AMINOBIPHOSPHONATES (N-BPs) ON MSC IN THE BALANCE BETWEEN Th1 AND Treg DIFFERENTIATION

Vdelta2 T lymphocytes can recognize unprocessed non-peptide molecules, namely P-Ag derived from the mevalonate (Figure 3) or the 1-deoxy-D-xylolose-5-phosphate pathway in mammalian or bacterial cells,

respectively (21-23). Aminobisphosphonates (N-BPs), commonly used to treat bone diseases and hypercalcemia in myeloma patients, have been shown to activate Vdelta2T cells by blocking protein prenylation along the cholesterol synthesis pathway and accumulating phosphorylated metabolites (20, 24, 55-57). In addition, stimulation by PAg, accumulated in dendritic and also in cancer cells upon exposure to N-BPs, drives Vdelta2 T cell maturation from naive to effector-memory (EM) cells (56). Our recent unpublished data show that pre-treatment of LNMSC with the N-BPs pamidronate or zoledronate can rescue the ability of gammadelta T cells to recognize lymphoma cells via NKG2D, inhibiting TGFbeta and stimulating IL15 production. Furthermore, zoledronate-treated LNMSC drive gammadelta T lymphocyte differentiation into effector memory (EM) T cells, producing Th1-type cytokines, rather than IL10 that might contribute, together with TGFbeta, to the expansion of regulatory T cells (Treg).

8. SUMMARY AND PERSPECTIVES

Based on all these considerations, and following the "stress-related" immunity viewpoint, the aim of a potential new therapeutic scheme acting on lymphoma microenvironment, would be to redirect the stress immune response and avoid escape strategies. In detail: induce stress molecules, inhibit sheddase activity, modulate stromal cells to shift cytokine production toward a Th1, rather than a Treg network (Fig.3). First, expression of membrane-bound NKG2D-L by tumor cells might be up-regulated by drugs as ATRA or VPA (13,14,58,59) or, as recently reported, by proteasome inhibitors (60), all already approved for the treatment of hematological malignancies. Second, both ERp5 and ADAM10/17 may represent targets for selective inhibitors of their enzymatic activity (9-54); recent data in preclinical studies with ADAM17 inhibitors in solid cancers would support this idea (619. Third, enhancement of NKG2D-mediated antitumor immune response by RNA interference targeting TGFbeta has been reported to inhibit tumorigenicity *in vivo* in an animal model (62). In addition, N-BPs may contribute to shift the cytokine mileu at the tumor site from a Treg to a Th1 pattern (63-65), thus sustaining NKG2D expression and function on effector lymphocytes.

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Abbreviations: ADAM: a disintegrin and metalloproteinase, ALP: alkaline phosphatise, ATRA: all-trans-retinoic acid, ATP: adenosine triphosphate, BAFF: B-cell activating factor from the tumor necrosis factor family, BM: bone marrow, BSP: bone sialoprotein, CLL: chronic lymphocytic leukemia, CMV: cytomegalovirus, DLBCL: diffuse large B cell lymphoma, EBV: Epstein Barr virus, EM: effector memory, ERp: endoplasmic reticulum protein, FDC: follicular dendritic cells, GC: germinal center, HDAC: hystone deacetilase, HL: Hodgkin's lymphoma, IFN: interferon, IL: interleukin, IPP: isopentenyl pyrophosphate, LN: lymph node, LNMSC lymph node mesenchymal stromal cells, mAbs: monoclonal antibodies, MHC: major histocompatbility complex, MIC: MHC class-I related molecules, MMP: matrix metalloproteinase, MSC: mesenchymal stromal cells, NK: natural killer, NKG2D: NK receptor group-2D, NKG2D-ligands (NKG2D-L), natural killer (NK), NHL: non-Hodgkin lymphoma, N-BPs: aminobisphosphonates, P-Ag: phosphoantigens, PMBCL: primary mediastinal B cell lymphoma, PVR: poliovirus receptor; P4H: prolyl-4-hydroxilase, RS: Reed-Stemberg, TCR: T cell receptor, TGF: transforming growth factor, Th: T helper, TLR: Toll like receptor, TNF: tumor necrosis factor, Treg: regulatory T cells, ULBP: UL16-binding protein, VCAM: vascular cell adhesion molecule, VPA: sodium valproate

Key Words: MSC, NKG2D, ADAM, ERp5, MIC-A/B, ULBP, sheddases, regulatory T cells, Review

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