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# Hide or defend, the two strategies of lymphoma immune evasion: potential implications for immunotherapy

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## ABSTRACT

E vading immune eradication is a prerequisite for neoplastic progression and one of the hallmarks of cancer. Here, we review the different immune escape strategies of lymphoma and classify them into two main mechanisms. First, lymphoma cells may “hide” to become invisible to the immune system. This can be achieved by losing or down-regulating MHC and/or molecules involved in antigen presentation (including antigen processing machinery and adhesion molecules), thereby preventing their recognition by the immune system. Second, lymphoma cells may “defend” themselves to become resistant to immune eradication. This can be achieved in several ways: by becoming resistant to apoptosis, by expressing inhibitory ligands that deactivate immune cells and/or by inducing an immunosuppressive (humoral and cellular) microenvironment. These immune escape mechanisms may have therapeutic implications. Their identification may be used to guide “personalized immunotherapy” for lymphoma.

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## Introduction

Since the hypothesis of “cancer immunosurveillance” proposed by Burnet and Thomas about 60 years ago,<sup>1</sup> our knowledge about the interactions between cancer cells and the host immune system has dramatically increased. These interactions, referred to as “immunoediting”, are summarized in the three “Es” theory: Elimination, Equilibrium and Escape.<sup>2</sup> Because of: i) genetic instability and tumor heterogeneity; and ii) immune selection pressure, tumor cells become progressively capable of avoiding immune destruction during carcinogenesis. This property of cancer cells is now recognized as a hallmark of cancer.<sup>3</sup>

The generation of an antitumor immune response requires several steps, elegantly summarized in the “cancer immunity cycle”.<sup>4</sup> It consists of the release of tumor antigens (Ag), their capture by professional antigen-presenting cells (APC), and the priming of T cells. Then, effector T cells traffic to the tumor site, and recognize and kill cancer cells. To be effective, the priming of T cells needs two signals: i) the recognition of the MHC-Ag complex by the T-cell receptor (TCR) (signal 1); and ii) the co-stimulation by the CD80/CD86 molecules of CD28 (signal 2). Signal 1 without signal 2 leads to T-cell anergy.<sup>5</sup> Only professional APC express both class I (MHC-I) and class II (MHC-II) major histocompatibility complex, and co-stimulatory molecules. All nucleated cells present endogenous Ag to CD8 T cells through MHC-I. Professional APC present exogenous Ag to CD4 T cells through MHC-II, but also exogenous Ag to CD8 T cells through MHC-I, a process called cross-presentation.<sup>6</sup> B-cell lymphomas are unique among cancers because the tumor cells themselves are professional APC.<sup>7</sup> With the advent of new immunotherapies including checkpoint inhibitors, bispecific antibodies and CAR T cells, understanding lymphoma immunity and immune evasion may be crucial to determine the optimal treatment and/or combinations for a given patient.

Here, we review the different immune escape strategies of lymphoma and classify them into two main mechanisms. First, lymphoma cells may “hide” to become invisible to the immune system. Second, lymphoma cells may “defend” themselves to become resistant to immune eradication. Finally, we discuss how the understanding of

these immune escape mechanisms may be used to determine the optimal immunotherapy for patients with lymphoma.

## How lymphoma may hide from the immune system

In order to evade immune eradication, tumor cells may first become “invisible”. This can be achieved by the loss or downregulation of molecules involved in antigen presentation (MHC), co-stimulation (CD80, CD86), and/or adhesion (CD54),<sup>8</sup> thereby preventing their recognition by the immune system.

Two types of mechanisms may be responsible for the loss of these molecules: i) “hard lesions” which consist of irreversible genetic alterations of the gene of interest or genes implicated in their transcriptional regulation; and ii) “soft lesions” which are reversible epigenetic changes that repress gene expression<sup>9</sup> (Figure 1, “hide”).

### Prevention of antigen presentation

#### MHC-I loss/downregulation

Loss of MHC-I at the surface of lymphoma cells (total loss or miss-localization) occurs in 55-75% of diffuse large B-cell lymphoma (DLBCL)<sup>10,11</sup> and 63% of Hodgkin lymphomas (HL).<sup>11</sup> Most frequently, this results from mutations of the Beta2-microglobulin ( $\beta$ 2M) gene which occurs in 29% of DLBCL,<sup>10</sup> 50% of primary mediastinal B-cell lymphoma (PMBCL),<sup>12</sup> and at least 50% of classical HL (cHL).<sup>13</sup> In immune-privileged lymphomas, MHC-I loss was found in 18% of primary central nervous system lymphomas (PCNSL) but not in primary testicular lymphomas (PTL).<sup>11</sup> In HL, MHC loss is preferentially observed in EBV-negative rather than in EBV-positive HL (83% vs. 27%).<sup>11</sup> Patients whose Reed Stenberg cells (RS) are negative for MHC-I or  $\beta$ 2M have a shorter progression-free survival (PFS).<sup>14</sup> Interestingly, 9p24.1 amplification (leading to PD-L1 overexpression, as discussed below) adversely impacts survival only in HL patients in whom RS have lost MHC-I.<sup>15</sup> Loss of MHC-I is also observed in 30% of Burkitt lymphomas (BL) and 20% of follicular lymphoma (FL)<sup>16</sup> with rare  $\beta$ 2M mutations.<sup>17</sup> In FL, the frequency of  $\beta$ 2M mutations is higher after histological transformation<sup>18</sup> and is associated with a lower infiltration of the tumor by CD8 T cells.<sup>19</sup>

Other irreversible mechanisms leading to MHC-I loss include alterations in MHC-I gene.<sup>16,20</sup> Unlike non-hematologic cancers, epigenetic mechanisms do not seem to be frequently responsible for MHC-I loss/downregulation in lymphoma.<sup>7</sup>

Importantly, natural killer (NK) cells are activated in the absence of MHC-I and in the presence of CD58 (which stimulates NK cells through CD2). Interestingly, 67% of DLBCL lack CD58 surface expression, and 61% lack both CD58 and MHC-I expression, thereby preventing NK-cell activation.<sup>10</sup> Of note, genetic alterations of CD58 are also found in transformed FL but not in FL.<sup>18</sup> Genetic lesions disrupting the CD58 gene have been found only in 10-21% of DLBCLs, suggesting alternative mechanisms.<sup>10,21,22</sup>

#### MHC- II loss/downregulation

##### Transcriptional regulation

Expression of MHC-II is regulated, through epigenetic mechanisms. CREBBP regulates CIITA by catalyzing

H3K27 acetylation at its promoter/enhancer in normal GC B cells and lymphoma cell lines.<sup>23-25</sup> CREBBP may undergo loss-of-function mutation in the histone acetyl transferase domain. Thus, in FL and DLBCL, mutations of CREBBP prevent CIITA transcription, which in turn prevent MHC-II transcription.

HLA-DR expression is lost in 20% of DLBCL<sup>26</sup> and is associated with a reduced T-cell infiltrate within the tumor<sup>27</sup> and a poor outcome.<sup>27,28</sup> Moreover, 19% of DLBCL have MHC-II intra-cytoplasmic aberrant localization which is associated with a worse outcome. This mislocalization is preferentially seen in BCL-2 and c-MYC double expresser lymphomas. Of note, c-MYC down-regulates enzymes implicated in the antigen presentation machinery (cf 2.1.3).<sup>29</sup> The mechanisms of MHC-II downregulation remain incompletely understood but seem to occur at transcriptional level independently of genetic lesions on MHC-II gene.<sup>30</sup> Indeed, genes implicated in epigenetic regulation, including HMTs and HATs, are the most frequently altered genes in DLBCL (approx. 50% of GC-DLBCL and 30% of ABC-DLBCL).<sup>31</sup> Moreover, DLBCL frequently harbor inactivating mutations of CREBP (19% of all DLBCL, 31% of GC-DLBCL and 6% of ABC-DLBCL)<sup>12</sup> and CIITA (10% of DLBCL).<sup>12</sup> CIITA is a target of somatic hypermutation (SHM) caused by AID.<sup>12</sup> Finally, expression of CIITA and CREBP may be repressed through epigenetic silencing (i.e. independent of genetic alterations). Reduced expression of CIITA and CREBP is frequently found in DLBCL, leading to MHC-II downregulation and poor outcome.<sup>32-35</sup> In some cases, MHC-II may be restored by lifting the repression of CIITA with HDAC inhibitors.<sup>35</sup> MHC-II downregulation in DLBCL may also result from an overexpression of the transcription factor FOXP1 through a mechanism which, although not clearly elucidated, seems to be independent of CIITA.<sup>36</sup> FOXP1 expression is associated with the non-GC phenotype (48% of GC-DLBCL vs. 71% of non-GC-DLBCL)<sup>37</sup> and a poor prognosis.<sup>38</sup> The underlying mechanisms responsible for FOXP1 overexpression remain largely unknown. Genetic alterations on chromosome 3p leading to FOXP1 overexpression are found in a small subset of DLBCL.<sup>38</sup> FOXP1 translocations are found in 5% of DLBCL and are associated with extra-nodal localizations and high proliferative index.<sup>39</sup> Bea *et al.* also reported 15% of trisomy 3 and 31% of copy number gains of the chromosome 3p in ABC-DLBCL (*versus* 1% in GC-DLBCL), associated with MHC-II downregulation.<sup>40</sup>

In PMBCL, MHC-II downregulation also occurs at the transcriptional level and CIITA alterations is the most common mechanism:<sup>41</sup> CIITA breaks are found in 38-56% of PMBCL and correlate with poor outcome;<sup>12,42</sup> CREBP mutations are present in 11% of cases<sup>12</sup> and abnormalities on chromosome 3 can be found, although rarely.<sup>40</sup> However, loss of expression of MHC-II is found only in 12% of PMBCL.<sup>43</sup> This is associated with poor survival.<sup>43</sup>

In FL, there is no evidence for mutation in MHC-II genes<sup>17</sup> but CREBBP is mutated in 32-68% of cases<sup>17,34</sup> and CIITA in 35%<sup>44</sup> suggesting a downregulation at the transcriptional level. Furthermore, CREBBP mutation is an early event and a driver mutation in FL development.<sup>45</sup>

In HL, lack of MHC-II on RS occurs in 41% of cases and represents an independent prognosis factor.<sup>46</sup> In 37.2% of cases, RS show aberrant localization in their cytoplasm.<sup>46</sup> The mechanisms responsible for MHC-II loss in HL is not completely known but genomic CIITA break is found in 15% of HL<sup>42</sup> and FOXP1 is not implicated.<sup>47</sup>

*Genetic alterations*

Direct, genetic alterations leading to MHC-II loss are mostly seen in DLBCL of immune-privileged sites. PTL and PCNSL have lost HLA-DR in 61% and 46% of cases, respectively.<sup>48</sup> In contrast with other types of DLBCL, genetic lesions of MHC-II genes represent the main mechanism of HLA-DR loss.<sup>48,49</sup> MHC-II is mutated in 78% of PTL and 50% of PCNSL.<sup>49</sup> Transcription factors seem to be rarely implicated in HLA-II loss in PTL: CIITA and FOXP1 rearrangements are present in only 10% and 7% of cases, respectively.<sup>50</sup>

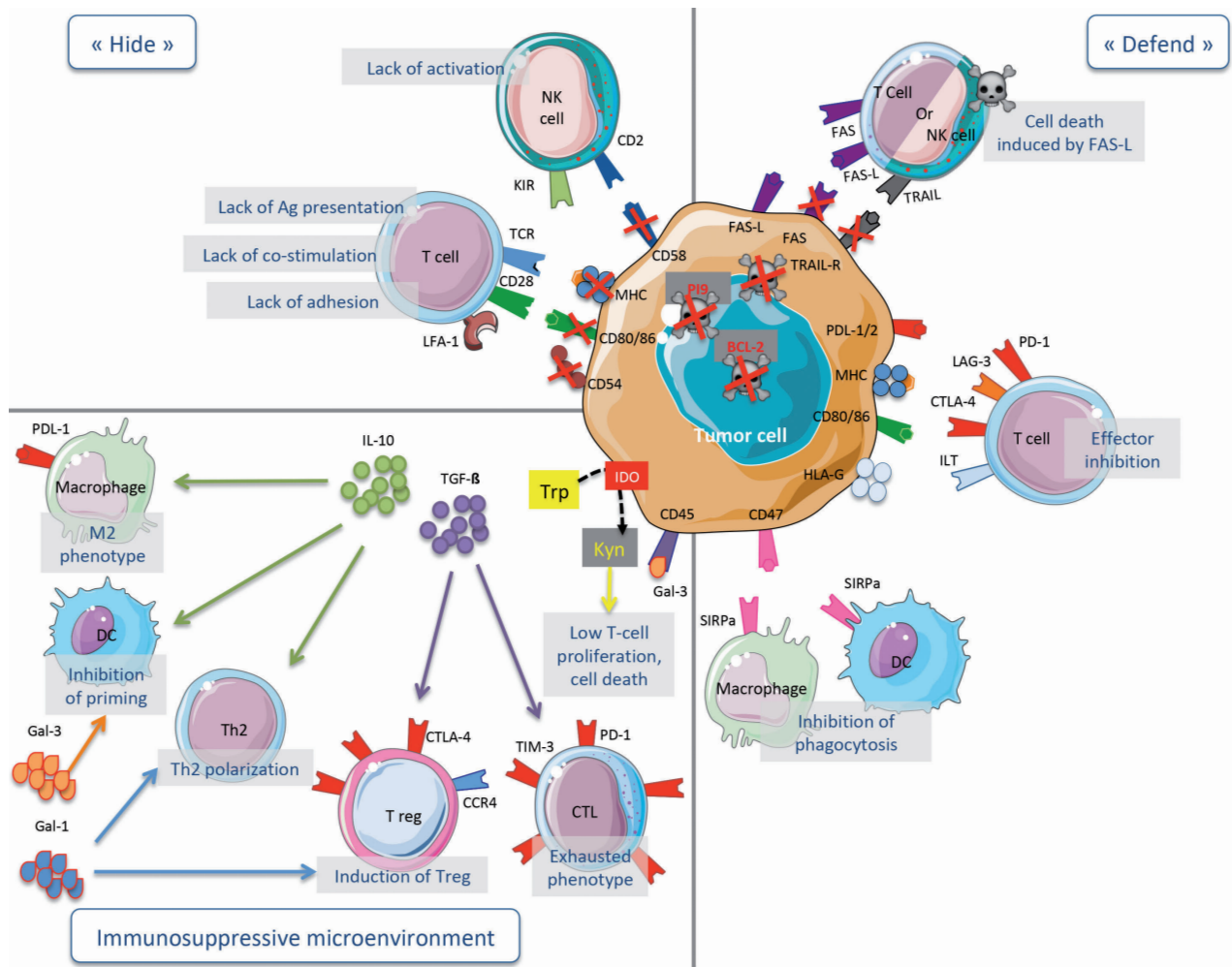
It is noteworthy that, when expressed, MHC-II may drive inhibitory signals. Indeed, lymphocyte-activation gene 3 (LAG-3), a member of immunoglobulin superfamily expressed on tumor infiltrating lymphocytes (TILs),<sup>51</sup> binds to MHC-II with greater affinity than CD4, leading

to the inhibition of TCR signaling, proliferation and cytokine secretion by antigen-specific T cells. Exhausted LAG-3 positive TILs are present in the immune infiltrate of FL, DLBCL and HL (mostly in EBV positive cases, mixed cellularity and rich lymphocyte subtypes).<sup>52,53</sup> Furthermore, circulating CD4 T cells from HL patients with active disease express LAG-3 at higher levels than healthy donors or patients in long-term remission.<sup>53</sup>

*Antigen processing machinery alterations*

GILT and HLA-DM are enzymes of the antigen processing machinery (APM), located in the endocytic compartment of APC and B cells. Both are down-regulated by cMYC, leading to a defective antigen presentation that can be restored *in vitro* by cMYC inhibitors.<sup>54</sup>

GILT generates epitopes to be loaded on MHC-II. In



**Figure 1. Lymphoma immune evasion mechanisms.** (Top left panel) "Hide". Tumor cells may become "invisible" to the immune system by down-regulating MHC, co-stimulatory (CD80 and CD86) and/or adhesion (CD54) molecules. Downregulation of CD58 allows tumor cells to escape killing by natural killer (NK) cells, which are activated by self-missing signal (loss of MHC-I). (Right panel) "Defend". Tumor cells are seen by the immune system but avoid destruction through resistance to apoptosis signals and/or expression of inhibitory receptors. Tumor cells may resist apoptosis by different means: loss of FAS and/or TRAIL receptors (extrinsic pathway), hyperexpression of anti-apoptotic molecules such as BCL-2 (intrinsic pathway) or PI9 (Granzyme pathway). T cells can be inhibited by inhibitory ligands which are expressed by lymphoma cells or cells from their microenvironment such as PD-L1 or PD-L2/PD-1, LAG-3/MHC-II, CTLA-4/CD80 or CD86 and HLA-G/ILT. CD47 sends a "don't eat me" signal to macrophages and DCs by interacting with its ligand SIRPa. Tumor cells may also express FAS-L to induce death of immune cells. Some molecules expressed by lymphoma cells may have dual roles: expression of MHC-II allows antigen presentation but also binds to the inhibitory receptor LAG-3; CD80 and CD86 stimulate T cells through CD28 but may also inhibit T cells through CTLA-4. (Bottom left panel) Immunosuppressive microenvironment. The tumor cells interact with their microenvironment to contribute to lymphoma immune evasion. IL-10 is a potent immunosuppressive cytokine that inhibits priming by dendritic cells (DC), promotes Th2 and Treg differentiation and M2 macrophages; TGF-β induces exhausted phenotype of CTL and Treg differentiation; IDO suppresses cytotoxic T lymphocyte (CTL) and NK immune response through degradation of tryptophan and production of kynurenine. Trp: tryptophan; Kyn: kynurenine; Gal: galectin; Ag: antigen.

DLBCL patients treated with CHOP or rituximab-CHOP, Phipps-Yonas *et al.* identified lower GILT expression as an adverse prognostic factor for OS.<sup>55</sup> Once formatted by GILT, peptides are loaded on MHC-II instead of CLIP fragment of invariant chain. This exchange is performed by HLA-DM. In absence of HLA-DM, antigens cannot be exposed and MHC-II present CLIP at the cell surface.<sup>11</sup> HLA-DM is lost in 49% of cHL, 14% of DLBCL, and 2.9% of PTL and PCNSL.<sup>11</sup>

### Prevention of co-stimulation: B7 molecule downregulation

CD80 and CD86 are members of the B7 co-stimulatory family and are expressed on professional APC, including B cells. They have a dual specificity: they can bind to the stimulatory receptor CD28 promoting T-cell activation and to the inhibitory receptor CTLA-4 (with a much higher affinity than CD28) leading to T-cell inhibition.<sup>56</sup>

In B-cell lymphomas, CD80 and CD86 may be expressed on tumor cells and/or on cells from their microenvironment.<sup>57</sup> CD80 is expressed in 97% of FL, 91% of marginal zone lymphomas (MZL), 90% of DLBCL, and 75% of mantle cell lymphomas (MCL).<sup>58</sup> Interestingly, T and non-T cells present in the microenvironment of these tumors also express CD80.<sup>58</sup> Loss of CD86 was found to be associated with decreased TIL infiltration in DLBCL.<sup>59</sup> However, the prognostic value of CD80 and CD86 expression in lymphoma remains unclear, maybe because of their dual activity.

### Prevention of adhesion

Intercellular adhesion molecule 1 (ICAM-1 or CD54) plays a crucial role in cell-to-cell interaction, especially in the immune synapse and tumor cell adhesion and dissemination.<sup>8</sup> Lower expression of CD54 compromises the interaction between tumor and immune cells. In DLBCL, lymphocyte infiltration is decreased in tumors which have lost CD54.<sup>59</sup> However, in aggressive NHL, lower expression of CD54 correlates with more advanced stage of the disease, higher bone marrow infiltration and worse prognosis.<sup>60</sup>

Expression of CD54 is lost in 50%<sup>60</sup> of non-Hodgkin lymphomas (NHL), but only 7% in DLBCL.<sup>59</sup>

### How lymphoma may defend itself against the immune system

Lymphoma cells may “defend” themselves to become resistant to immune eradication. This can be achieved in several ways: by becoming resistant to apoptosis and/or by expressing inhibitory ligands that deactivate immune cells (Figure 1, “defend”).

### Resistance to apoptosis

Three apoptotic pathways may induce cell death: i) the perforin/granzyme pathway which results from the release of cytotoxic granules from NK cells or CTL activated through their TCR; ii) the extrinsic pathway, activated by T and NK cells through FAS or TRAIL death receptors; iii) the intrinsic pathway, involving BCL-2 family proteins and activated by intrinsic stress signals.<sup>61</sup>

By apoptotic gene profiling, Muris *et al.* identified two subsets of DLBCL with poor overall survival.<sup>62</sup> The activated apoptosis cascade group (mostly ABC-DLBCL) was

characterized by high expression level of many pro- and anti-apoptotic genes of the intrinsic pathway, suggesting that these lymphoma cells are “primed for death” and their survival depends on the high expression level of anti-apoptotic genes. The cellular cytotoxic response group was characterized by the expression of apoptosis-inducing effector molecules from CTL and NK cells (granzyme, TRAIL, FASL and other) and a high resistance to chemotherapy.<sup>63</sup> The large immune cell infiltration in this subset suggests a selection of resistant lymphoma cells under the pressure of a strong cellular immune response.

### Inhibition of granzyme

The protease inhibitor 9 (PI9) was found to inhibit granzyme B and therefore to protect against apoptosis.<sup>64</sup> PI9 is expressed in DLBCL, BL and HL (in RS), but it seems to be rarely found in low-grade lymphomas.<sup>57</sup> Of note, few studies have analyzed PI9 expression in B-cell lymphomas and there is no evidence of relationship between PI9 expression and CTL infiltration or clinical outcome.<sup>65</sup>

To our knowledge, there is no mechanism of perforin inhibition in lymphoma.

### Inactivation of death receptor extrinsic pathway: FAS/TRAIL-R

FAS (CD95) belongs to the TNF receptor family and ligation of FASL (CD95L) induces apoptosis through its intracellular death domain and caspase activation. This mechanism plays a crucial role in affinity selection during the GC reaction.<sup>66</sup> Immune cells also use this mechanism to kill cancer cells.<sup>67</sup>

In normal B cells, FAS is expressed on activated B cells from the GC and is absent in mantle zone or circulating B cells. CD95 is lost in 17% of FL<sup>68</sup> and 27% of MALT lymphomas.<sup>69</sup> In DLBCL, CD95 is lost in 51% of extra-nodal cases<sup>69</sup> but rarely in cutaneous cases.<sup>70</sup> CD95 expression on lymphoma cells is associated with improved survival and response to R-CHOP therapy in DLBCL.<sup>69-72</sup> In HL, CD95 is rarely lost.<sup>73</sup>

Mutations in the CD95 gene are more commonly found in post-GC lymphomas, including 20% of DLBCL, and 44% of extra-nodal lymphomas (all types).<sup>74,75</sup> Surprisingly, although derived from GC, no mutation of CD95 were found in BL.<sup>75</sup> CD95 mutations are rare in FL (6%) and in pre-GC lymphomas (<2%) such as MCL.<sup>74,75</sup> Only 5% of HL are associated with FAS mutation in RS.<sup>73</sup> Müschen *et al.* hypothesized that FAS mutations are mostly found in post-GC lymphomas because CD95 mutations are target errors in the SHM process during the GC reaction.<sup>74</sup> However, FAS mutations do not share features of AID-mediated activity and their underlying mechanism remains unclear. In some cases, lymphoma cells expressing CD95 are resistant to apoptosis, suggesting the existence of other mechanisms. For instance, HL resist to FAS-induced apoptosis by expressing c-FLIP which is located at the cell membrane where it binds to the death domain of CD95.<sup>73</sup> High levels of soluble CD95 are associated with poor outcome,<sup>76-78</sup> supposedly because it binds to CD95L and prevents apoptosis. As discussed below, Galectin 3 also protects tumor cells from FAS-induced death.

TRAIL is also a member of TNF receptor family, which triggers the extrinsic apoptotic pathway after ligation to death receptors (TRAIL receptors 1 and 2). The role of TRAIL in B-cell lymphomagenesis has been suggested by the association between TRAIL polymorphisms and higher risk of lymphoma<sup>79</sup> and the rapid development of spon-

taneous lymphoid malignancies in mice with TRAIL deficiency.<sup>80</sup> Loss of TRAIL receptor was found in 6.8% of NHL.<sup>81</sup> It is mainly caused by mutations of TRAIL death domain on chromosome 8p21.3 but may also occur at the transcriptional level by mutation of p53.<sup>82</sup> Mutations of TRAIL receptor are found in 26% of MCL (55% of leukemic MCL vs. 19% of nodal MCL) and have a more aggressive phenotype.<sup>83</sup>

#### *Inhibition of the stress-induced intrinsic pathway: BCL-2 overexpression*

BCL-2 family molecules are crucial regulators of the intrinsic pathway of mitochondrial apoptosis.<sup>84</sup> BCL-2 itself is an anti-apoptotic protein but other members of the BCL-2 family are pro-apoptotic.

BCL-2 is one of most commonly mutated genes in NHL, notably in DLBCL (37% of cases, particularly in GC subtype) and FL (54% of cases),<sup>85-87</sup> whereas it is a rare event in peripheral T-cell lymphomas, MCL and PMBL.<sup>86</sup>

The t(14;18), present in almost all FL<sup>45</sup> and 34% of GC-DLBCL<sup>88</sup> (vs. 17% of non-GC DLBCL), juxtaposes the BCL-2 gene and the enhancer of the heavy chain immunoglobulin. Thus, it induces a constitutive overexpression of BCL-2 and exposes BCL-2 oncogene to somatic hyper-mutations in the GC.<sup>84</sup> Other mechanisms may explain genetic variations of the BCL-2 gene in t(14;18) negative DLBCL.<sup>84</sup>

In DLBCL, BCL-2 expression (but not mutation nor translocation) was historically associated with a worse prognosis but this negative impact seems to be overcome by the addition of rituximab to CHOP chemotherapy.<sup>86,89,90</sup> Nevertheless, BCL-2 protein expression remains the strongest independent prognostic factor in primary cutaneous DLBCL.<sup>91</sup> In FL, Correia *et al.* found that the presence of BCL-2 mutation at diagnosis was an independent risk factor of transformation and death, but patients were mostly treated without rituximab.<sup>92</sup> This observation was not confirmed in another study in which FL patients were treated with a rituximab-containing regimen.<sup>87</sup>

### **Inhibition / killing of immune cells**

#### *PD-L1/L2 expression*

PD-L1 and PD-L2 are members of the CD28 family and inhibit T cells through ligation to PD-1 receptor.<sup>56</sup> Most FL contain a rich immune infiltrate of PD1<sup>+</sup> cells, mostly in the inter-follicular areas, but tumor cells do not express PD-L1 (PD-L2 is weakly expressed in some rare tumor cells).<sup>52</sup> In contrast, DLBCL often express PD-L1 and PD-L2 on tumor cells and in their microenvironment.<sup>52</sup> PD-L1 and PD-L2 are more frequently expressed on tumor cells of ABC-DLBCL (36% and 60%, respectively) than GC-DLBCL (4% and 26%, respectively).<sup>93</sup> PD-L1 is also frequently expressed on tumor cells of PMBL (71% of cases)<sup>94</sup> and HL (97% of cases).<sup>14</sup> In immune-privileged lymphomas, level of PD-L1 protein expression is unknown in PTL and reported in a small study of PCNS lymphomas.<sup>95</sup> The mechanisms responsible for PD-L1 and/or PD-L2 overexpression include: i) genetic alteration in 9p24; and ii) Epstein-Barr virus (EBV) infection. In the first case, the 9p24 amplicon contains the PD-L1 and PD-L2 genes that are directly amplified and over-expressed. It also contains the JAK2 gene that, indirectly, induces the transcription of

the PD-L1 and PD-L2 genes. 9p24 alterations are found in all cases of HL,<sup>14</sup> in most cases of PMBL (9p24 amplification in 63% of cases and translocation in 20% of cases),<sup>96,97</sup> in 54% of PTL, and 52% of PCNSL (mainly due to copy number gain, whereas translocations are rare),<sup>98</sup> and in 19% of DLBCL (mainly due to copy number gains) particularly in the non-GC subset.<sup>99</sup> Structural variations disrupting the 3' region of the PD-L1 gene are also implicated in 8% of DLBCL.<sup>100</sup> Notably, immunoglobulin locus and CIITA are common partners of PD-L1 translocation.<sup>42,98,99</sup> Finally, EBV infection (which is present in approx. 40% of HL tumors) also induces PD-L1 expression *via* the viral protein LMP1.<sup>101</sup>

PD-L1 expression in the tumor is an adverse prognostic factor for HL,<sup>14</sup> PMBL,<sup>94</sup> and DLBCL.<sup>93</sup> Soluble PD-L1, although not correlated with PD-L1 expression by the tumor, is also associated with a poor prognosis in DLBCL.<sup>102,103</sup> In these studies, high level of PD-L1 was associated with the clinical and histological aggressiveness of the disease.<sup>14,52,93,102</sup>

#### *HLA-G expression*

HLA-G is a non-classical MHC-I molecule transcribed in membrane-bound or soluble (sHLA-G) isoforms. HLA-G binds to the inhibitory receptors ILT2 (on lymphoid cells, including B cells, and myeloid cells) and ILT4 (on myeloid cells). HLA-G also binds to CD8 co-receptor and induces FAS-mediated apoptosis of T and NK cells.<sup>104</sup>

HLA-G is expressed in 24% of DLBCL<sup>105</sup> and 67% of cHL (on RS) at a higher level than healthy controls.<sup>73,106</sup> In HL, HLA-G expression is associated with the loss of MHC-I on RS and the absence of EBV.<sup>107</sup>

sHLA-G is increased in lymphoproliferative disorders and contributes to immune escape.<sup>108,109</sup> Indeed, sHLA-G purified from plasma of patients with lymphoproliferative disorders inhibits T-cell proliferation *in vitro*.<sup>108</sup> However, there is no correlation between the level of sHLA-G and clinical or pathological characteristics of the disease<sup>108</sup> or its prognosis.<sup>110</sup>

Thus, HLA-G may have ambivalent effects in lymphoma: on one hand, sHLA-G may inhibit the proliferation of tumor B cells through ILT2 receptor whereas, on the other hand, HLA-G expressed in the tumor may promote immune escape by inhibiting NK and CTL.<sup>104</sup>

#### *CD47 expression*

CD47, the expression of which is ubiquitous, interacts with the inhibitory receptor SIRP $\alpha$  expressed by myeloid cells and macrophages. CD47-SIRP $\alpha$  interaction delivers a "don't eat me" signal to the phagocytic cells which prevents phagocytosis.<sup>111</sup> Thus, CD47 may lead to immune evasion in two ways: i) by inhibiting phagocytosis;<sup>112,113</sup> and ii) by inhibiting cross-presentation by dendritic cells (DC).<sup>114</sup>

In NHL, CD47 is expressed at a higher level on tumor B cells compared to normal B cells.<sup>112</sup> Additionally, CD47 expression is increased on lymphoma cells circulating in the blood compared to lymphoma cells in lymph nodes supporting the role of CD47 in lymphoma dissemination.<sup>113</sup> Finally, high expression of CD47 is associated with poor prognosis in DLBCL and MCL.<sup>112</sup>

#### *FASL expression*

Tumor cells may also "counter-attack" immune effector cells by expressing FASL in order to kill them.<sup>115</sup> FASL was found to be strongly expressed in aggressive B-cell lym-

phomas,<sup>116</sup> secondary cutaneous DLBCL, primary cutaneous leg-type DLBCL,<sup>70</sup> and HL,<sup>117</sup> but seems to be weak in non-aggressive lymphomas (such as small lymphocytic lymphoma, lymphoplasmacytic lymphoma, and grade 1 FL) and MCL.<sup>116</sup> In DLBCL, FASL expression is an adverse prognostic marker.<sup>69-72</sup>

**Immunosuppressive microenvironment**

Lymphoma cells may evade immune eradication by inducing an immunosuppressive (humoral and cellular) microenvironment. Interactions between the lymphoma cells and their microenvironment have been reviewed in detail by Scott and Gascoyne.<sup>118</sup> Here, we highlight the main immunosuppressive components present in the lymphoma microenvironment (Figure 1, "immunosuppressive microenvironment").

**Cytokines**

*IL-10 secretion*

IL-10 is an immunosuppressive cytokine which inhibits myeloid effector cells and priming functions of DC, promotes Th2 immune responses, induces Treg, and stimulates growth and differentiation of B cells.<sup>119</sup> Thus, IL-10 may promote lymphoma in two ways: i) by stimulating the growth of tumor B cells; ii) by inducing an immunosuppressive environment. IL-10 serum level is higher in lymphoma patients than in healthy subjects and is associated with poor prognosis.<sup>120,121</sup> Moreover, high levels of IL-10 before treatment is associated with treatment failure and a worse outcome.<sup>120-122</sup>

*TGF-β secretion*

TGF-β inhibits CTL function and promotes an immuno-

**Table 1.** Overview of lymphoma immune escape mechanisms. The respective contribution of each immune escape mechanism according to lymphoma subtype.

Type of immune escape	B-cell lymphomas										T-cell lymphomas					Ref		
	HL	BL	GC-DLBCL	ABC-DLBCL	PMBL	PTL	PCNSL	MCL	FL	MZL	MALT	PTCL-NOS	AITL	ALCL	CTCL MF*/SS#		ATLL	ENKTL
Hide																		
MHC-I loss	63%	30%	55-75%		+	0%	18%		20%									10,11,16
B2M mutation	50%	Rare	29%		50%				Rare									10,12,13
CD58 loss			67%															10
MHC-II loss	41%		20%		12%	61%	46%		+									26,43,46,48
APM loss: GILT* / HLA-DM**	49%**		+* / 14%**			2.9%**												11,55
CD80 loss			10%					25%	3%	9%								58
CD86 loss			10%															59
CD54 loss			7%															59,60
Defend																		
Resistance to apoptosis																		
Inhibition of granzyme (PI9 expression)	18%	25%	37-43%									27%		21%			80%	63,65
<i>FAS inactivation:</i>																		
FAS loss	Rare		51%					17%		27%				+#				69,73-75,151-153
FAS DD mutation	5%	0%	20%				<2%	6%						14%*		50%		
Epigenetic downreg.	+				+									90%	45%#			
cFLIP expression																		
TRAIL loss						6.8%												81
<i>BCL-2 overexpression:</i>																		
BCL-2 mutation			37%		Rare			Rare	54%									45,86-88
t(14;18)			34%	17%					96%									
Inhibition of immune cells																		
PDL1 expression	97%		36%	4%	71%		+					60%	70-93%	10%	27%	10%	56-80%	14,93-95,98,154
PDL2 expression			60%	26%														73,105,106
HLA-G expression	67%		24%															171-173
HVEM loss	23%		22%						18-									112
CD47 expression			+					+										70,116,117,152,155,156
FASL expression	+		+					0%	0%					12%	80%*			
Immunosuppressive microenvironment																		
IL-10 secretion	+		+															120-122
TGF-β secretion			+															125
IDO expression	30%		+													+		131-133
Galectin-1 overexpression																		135
Galectin-3 overexpression		0%	66%						0%									137
Treg	+		+						+									139,140,142
MDSC	+		+						+									144,145
TAM	+		+					+	+									146-148

HL: Hodgkin lymphoma; BL: Burkitt lymphoma; DLBCL: diffuse large B-cell lymphoma; PMBL: primary mediastinal B-cell lymphoma; PTL: primary testicular lymphoma; PCNS: primary central nervous system lymphoma; MCL: mantle cell lymphoma; FL: follicular lymphoma; MZL: marginal zone lymphoma; MALT: mucosal associated lymphoid tissue; PTCL-NOS: primary T-cell lymphoma not otherwise specified; AITL: angio-immunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; CTCL: cutaneous T-cell lymphoma; MF: mycosis fungoid; SS: Sezary syndrome; ATLL: acute T-cell lymphoma/leukemia; ENKTL: extranodal NK/T lymphoma; MDSC: myeloid-derived suppressor cell; TAM: tumor associated macrophage; APM: antigen processing machinery. \*Refers to GILT. \*\*Refers to HLA-DM. #Refers to mycosis fungoid. #Refers to Sezary syndrome.

suppressive environment in several ways: i) it induces an exhausted phenotype in CTL (mostly on memory T cells) with a high PD-1 and TIM-3 expression;<sup>123</sup> ii) it leads to FOXP3 expression, mostly in naïve T CD4<sup>+</sup> cells<sup>123</sup> and induces the differentiation of Treg; and iii) represses the expression of CD95, perforin, granzyme and cytokines.<sup>124</sup> Because TGF- $\beta$  suppresses lymphoma growth by inhibiting proliferation and apoptosis, lymphoma cells may first acquire resistance or aberrant response to TGF- $\beta$ .<sup>124</sup> This may be achieved by several mechanisms including down-regulation of TGF- $\beta$  receptor on lymphoma cells<sup>125</sup> through epigenetic mechanisms,<sup>126</sup> abnormal signal transduction<sup>127</sup> and expression of CD109, a negative regulator of TGF- $\beta$  signaling.<sup>128</sup> Thus, there is no clear prognostic impact of TGF- $\beta$  in lymphoma.

#### IDO expression

IDO is an enzyme, expressed by lymphoma cells and cells from the microenvironment, which suppresses CTL and NK immune responses and induces Treg through

degradation of tryptophan. The most important metabolite of tryptophan is kynurenine which inhibits antigen specific proliferation and induces T-cell death.<sup>129</sup>

IDO protein is expressed in stromal cells of HL<sup>130</sup> and approximately 30% of NHL express IDO, and intratumoral levels are significantly higher than in reactive lymph nodes.<sup>131-133</sup> In DLBCL<sup>131-133</sup> and HL,<sup>130,134</sup> IDO activity is associated with a more aggressive disease and a worse outcome. Upregulation of IDO is associated with Treg infiltration in both DLBCL and HL.<sup>130,133</sup>

#### Galectins expression

Galectins (Gal) are key regulators of inflammation. These molecules act in the extra-cellular milieu by interacting with glycosylated receptors and, at the intra-cellular level, by modulating signalization and splicing.<sup>135</sup> Among the 15 different galectins identified, types 1 and 3 have been implicated in lymphoma immune escape. Gal-1 is known to suppress Th1 responses and promote secretion of Th2 cytokines and expansion of Treg. Gal-1 is over-

**Table 2.** Strategies to reverse immune escape mechanisms in lymphoma.

Hide			
<b>MHC loss/downregulation</b>			
<i>Hard (i.e. irreversible) lesions</i>	Anti CD19 CAR T cells	Bypass MHC-dependent antigen presentation/recognition	158,159
	Anti CD19/CD3 Bi-specific T-cell engager		
<i>Soft (i.e. reversible) lesions</i>	Epigenetic drugs, chemotherapy, radiotherapy, immunotherapy (CpG, CD40, etc...)	Induce re-expression of MHC molecules	7,160
	Radiotherapy, epigenetic drugs, immunotherapy (CpG, CD40, etc...)	Induce re-expression of co-stimulatory molecules	7,160
<b>CD80, CD86 molecules downregulation</b>			
<b>Adhesion molecules downregulation</b>	Radiotherapy, epigenetic drugs, immunotherapy (CpG, CD40, etc...)	Induce re-expression of adhesion molecules	7,160
Defend			
Resistance to apoptosis			
<b>FAS/TAI loss</b>	Epigenetic drugs <sup>#</sup>	Restore FAS expression if loss is caused by epigenetic modifications	174
	Radiotherapy, chemotherapy*	Increase FAS and TRAIL expression	160
<b>BCL-2 expression</b>	BCL-2 inhibitors	Re-sensitize tumor cells to death induced through the intrinsic pathway	163
<b>Gal 3 expression</b>	Gal 3 inhibitors <sup>#</sup>	Inhibition of Gal 3	175
	GCS-100 <sup>#</sup>	Remove Gal 3 from CD45 and re-sensitize tumor cells to death	137
Inhibition of immune cells			
<b>PD-L1/L2</b>	Anti-PD1/PD-L1 mAb	Release inhibitory signals from T cells at the effector phase	158,176
<b>CD47 expression</b>	Anti-CD47 mAb <sup>#</sup>	Release inhibitory ("don't eat me") signal and restores phagocytosis of lymphoma cells by macrophages and DC	112-114
Immunosuppressive microenvironment			
<b>IL-10 secretion</b>	Anti-IL-10 mAb* <sup>#</sup>	Restore priming function of DC	177,178
<b>IDO secretion</b>	IDO inhibitors*	Inhibit IDO and restore T-cell function	149
	Fludarabine +/- Cyclophosphamide	Down-regulate IDO and restore T-cell function	169,170
<b>Treg infiltration</b>	Anti-CTLA4, Anti-CCR4 mAb*	Deplete Treg	141,167,179
	Low-dose cyclophosphamide *	Down-regulate FOXP3	160
<b>Macrophage infiltration</b>	Anti-CSF-1 receptor mAb*	Deplete macrophages	165
	Taxanes*	Inhibit M2 macrophages	160

Treg: regulatory T cells; mAb: monoclonal antibody; DC: dendritic cell. \*No result available in lymphoma patients. <sup>#</sup>Pre-clinical data.

expressed in EBV-associated lymphoma cells and is associated with an increased secretion of Th2 cytokines and infiltration by Tregs.<sup>135</sup>

Gal-3 can positively or negatively regulate T-cell survival, cytokine profiles and DC function. Gal-3 protects tumor cells from death induced by FAS,<sup>136</sup> possibly through interaction with CD45.<sup>137</sup> Gal-3 is over-expressed in 66% of DLBCL<sup>136</sup> (but not in BL nor in FL).

## Cells

### Regulatory T cells

Tregs, which are characterized by the expression of CD4, FOXP3 and CTLA-4, are responsible for the prevention of autoimmunity.<sup>138</sup> Tregs suppress immune cells through direct contact-dependent mechanisms, including induction of effector cell death, and indirect mechanisms by secreting inhibitory cytokines (IL-10, TGF- $\beta$ ) or interfering with effector T-cell metabolism.<sup>138</sup>

Tregs are more numerous in lymphoma tumors than in reactive lymph nodes<sup>139</sup> and in the blood of lymphoma patients compared to healthy controls or cured patients.<sup>139,140</sup> Tregs are recruited by CCR4 ligands (notably in cutaneous DLBCL, HL and EBV-associated lymphomas<sup>141</sup>) or converted from a conventional into a regulatory phenotype within the tumor microenvironment by modulation of tryptophan catabolism. Interestingly, Liu *et al.* demonstrated that Tregs found within the tumor microenvironment of FL are highly clonal.<sup>142</sup> In this study, the diversity of Treg TCR repertoire inversely correlated with the TCR repertoire of CD8 T cells, suggesting an antigen-specific suppression of CTL by Tregs. High level of circulating Tregs at diagnosis is an adverse prognostic factor in DLBCL and correlates with elevated LDH, advanced stage of the disease,<sup>139</sup> and poor survival.<sup>138,143</sup>

### Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSC) were recently described and remain poorly characterized. While their immunosuppressive properties are well established, only few mechanisms have been explored in lymphoma.<sup>144</sup> Immunosuppressive functions of MDSC include: i) secretion of immunomodulatory factors and Treg expansion; ii) modulation of amino-acid metabolism and decrease of T- or NK-cell proliferation; iii) oxidative stress; iv) inhibition of T- or NK-cell viability and homing into the lymph nodes; and v) induction of T-cell apoptosis. In B-cell lymphoma, MDSC are involved in T-cell defect through PDL-1 expression, IL-10 secretion, Treg expansion, and modulation of amino-acid metabolism.<sup>144</sup> MDSC are increased in various B-cell lymphomas (including HL, DLBCL, FL) and correlate with poor prognosis.<sup>144,145</sup>

### Macrophages

Macrophages are divided into M1 (pro-inflammatory, CD163<sup>-</sup>) and M2 (anti-inflammatory, CD163<sup>+</sup>) subsets. M2 macrophages are recruited into the tumor or differentiated *in situ* (notably by IL-10) and promote tumor progression.<sup>146</sup>

In HL, a meta-analysis of 22 studies showed that a high density of CD68<sup>+</sup>/CD163<sup>+</sup> macrophages was associated with poor survival.<sup>147</sup> In DLBCL<sup>146</sup> and MCL,<sup>148</sup> CD163<sup>+</sup> macrophages correlates with poor clinical outcome. In FL, a high density of CD68<sup>+</sup> macrophages was associated with a poor prognosis in the pre-rituximab era while it was associated with a good prognosis in the post-ritux-

imab era.<sup>146</sup> This may be due to the antitumor activity of macrophages through phagocytosis of rituximab-coated tumor B cells.<sup>149</sup> This observation was further supported by the GELA-GOELAMS study showing that macrophages were associated with adverse outcome only in patients treated without rituximab while there was no difference in survival in patients treated with rituximab.<sup>150</sup> Finally, macrophages may also promote immune evasion by expression of PDL-1.<sup>146</sup>

## Immune escape mechanisms in T-cell lymphomas

Mechanisms of immune evasion in T-cell lymphomas are less well characterized. Best described mechanisms result from resistance to apoptosis and from PD-L1 expression.

PI9 granzyme inhibitor is expressed in 21% of anaplastic large cell lymphoma (ALCL), 27% of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), 80% of NK-/T-cell nasal type lymphoma (ENKTL), and 89% of enteropathy-type NHL.<sup>65</sup> A defect in the extrinsic apoptosis (i.e. FAS) pathway is observed in many T-cell lymphomas which may be caused by three distinct mechanisms: i) FAS mutations, which are present in 50% of ENKTL<sup>151</sup> and in some cases of MF (<20% of cases);<sup>152</sup> ii) decreased expression of FAS through epigenetic mechanisms such as promoter methylation (45% of Sezary Syndrome) or splicing (43% of MF, 50% of CD30-CTCL);<sup>152</sup> iii) expression of c-FLIP inhibitory protein, which is seen in 90% of ALCL<sup>153</sup> (although the underlying mechanism is not completely elucidated).

Both PD1 and PD-L1 may be expressed in T-cell lymphomas, both on tumor cells and in their microenvironment. PD-L1 is expressed on tumor cells in less than 10% of ALCL and adult T-cell lymphoma / leukemia (ATLL), 27% of cutaneous T-cell lymphoma (CTCL), approximately 60% of PTCL-NOS, 56-80% of ENKTL and 70-93% of angio-immunoblastic T-cell lymphoma (AITL).<sup>154</sup> In both ALK negative and positive ALCL, and in CTCL, PD-L1 overexpression occurs through the STAT3 pathway.<sup>154</sup> Like in B-cell lymphomas, structural variations disrupting the 3' region of the PD-L1 gene (27% of ATLL) and EBV infection (particularly in ENKTL) are also responsible for PDL-1 expression.

FAS-L is expressed in 12% of ALCL,<sup>155</sup> 81% of mycosis fungoid (MF),<sup>155</sup> and a majority of CTCL<sup>156</sup> which may lead to the elimination of CTL (through FAS-induced death) and to a worse outcome.<sup>155,156</sup>

Finally, IDO may also contribute to immune escape in ATLL and is associated with a worse outcome.<sup>157</sup>

## Implications for immunotherapy

### Restoring antigen recognition

When tumor cells hide from the immune system by preventing Ag presentation, strategies to circumvent this escape mechanism depend on the type of lesions (Table 1).

If antigen presentation deficiency results from genetic irreversible lesions, then immunotherapies that are MHC-independent may bypass the lack of antigen presentation. This can be achieved with bi-specific T-cell engager antibodies (BiTE) or CAR T cells which target surface antigens



without the need for MHC.<sup>158,159</sup>

If antigen presentation deficiency results from epigenetic reversible lesions, then one may use therapies which can induce re-expression of MHC, co-stimulatory or adhesion molecules, such as epigenetic drugs, chemotherapy, radiotherapy or certain immunotherapies (*e.g.* CD40 agonists, CpG, IFN).<sup>7,160</sup> Notably, the addition of histone deacetylase inhibitor (HDACI) to R-CHOP restored MHC-II expression<sup>161</sup> and erased the negative prognostic value associated with MHC-II loss in DLBCL.<sup>162</sup>

### Restoring cell death

BCL-2 inhibitors, such as venetoclax, may sensitize tumor cells to death induced through the intrinsic pathway. They have a strong efficacy in CLL and, to a lesser extent, in some NHL (MCL, FL, DLBCL).<sup>163</sup> Surprisingly, despite the pathophysiological importance of BCL-2 translocation in FL, venetoclax demonstrated only poor efficacy in this disease.

In pre-clinical models, Gal-3 inhibitor can disturb CD45/Gal-3 interaction and restore apoptosis.<sup>157</sup>

### Blocking inhibitory signals

Immune checkpoint (ICP) blockade releases inhibition of effector cells but requires an intact antigen presentation and a pre-existing anti-tumor immune response. Blockade of CTLA4, PD1 and PD-L1 have demonstrated efficacy in solid tumors and hematologic malignancies.<sup>158</sup> Surprisingly, anti-PD1 mAbs were found to be particularly efficient in HL despite the fact that MHC expression was lost in most cases, suggesting an alternative mechanism of action.

Phagocytosis may be blocked by CD47 signaling. Blocking antibodies against CD47 or SIRP $\alpha$  can disrupt CD47-SIRP $\alpha$  interaction and restore phagocytosis. Blocking CD47 signaling may also potentiate the efficacy of anti-CD20 mAb by increasing antibody-dependent cellular phagocytosis (ADCP).<sup>112-114</sup>

### Modulating the tumor microenvironment

Immunosuppressive macrophages may be depleted by chemotherapy<sup>164</sup> or anti-CSF-1 receptor mAb.<sup>165</sup> Treg

depletion may be achieved with anti-CTLA4 mAbs (such as ipilimumab)<sup>166,167</sup> or mAbs against CCR-4 (such as mogamulizumab) which is preferentially expressed by Th2 and Tregs.<sup>141,168</sup> Treg infiltration may also be decreased by low doses of cyclophosphamide through downregulation of FOXP3.<sup>160</sup> IDO enzyme may be down-regulated using IDO inhibitors or fludarabine.<sup>169,170</sup>

### Conclusion

The recent success of ICP blocking antibodies in cancer patients confirmed the hypothesis of “cancer immunosurveillance” and demonstrated the potency of immunotherapy for the treatment of cancer. The goal of immunotherapy is to re-educate the immune system and to reverse the immune escape mechanisms to destroy the tumor cells.

B-cell lymphoma is unique because tumor cells are professional APC and therefore can present their own antigens to the immune system. Immune escape in lymphoma may occur at the priming or at the effector phase. It may result from defects in antigen presentation (which may prevent the priming of T cells or the recognition of tumor cells at the effector phase), from resistance to immune killing, or from immunosuppressive mechanisms (either directly by the tumor cells or indirectly by their microenvironment).

The advent of new classes of immunotherapies (including checkpoint inhibitors, bispecific antibodies and CAR T cells) offers novel opportunities to mobilize the immune system against lymphoma.<sup>159</sup> However, we need to determine which of these immunotherapies will be optimal for a given patient. Furthermore, some immune escape mechanisms may dampen the efficacy of these immunotherapies and may require combination with other therapies to sensitize tumor cells to immune eradication. The characterization of immune escape mechanisms may be used to guide “personalized immunotherapy”, *i.e.* determine the optimal immunotherapy and/or combination in a given lymphoma patient.

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