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An emerging role for immune regulatory subsets in chronic lymphocytic leukaemia

Morgan E. Wallace [a,b], Marice B. Alcantara [a,b], Yosuke Minoda [a,b], George Kannourakis [a,b], Stuart P. Berzins [a,b,c,*]

[a] Federation University, Ballarat, Victoria, Australia
[b] Fiona Elsey Cancer Research Institute, Ballarat, Victoria, Australia
[c] Department of Microbiology and Immunology, University of Melbourne, Parkville, Victoria, Australia

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ABSTRACT

The last few years has seen the burgeoning of a new category of therapeutics for cancer targeting immune regulatory pathways. Antibodies that block the PD-1/PD-L1 interaction are perhaps the most prominent of these new anti-cancer therapies, but several other inhibitory receptor ligand interactions have also shown promise as targets in clinical trials, including CTLA-4/CD80 and Lag-3/MHC class II. Related to this is a rapidly improving knowledge of 'regulatory' lymphocyte lineages, including NKT cells, MAIT cells, B regulatory cells and others. These cells have potent cytokine responses that can influence the functioning of other immune cells and many researchers believe that they could be effective targets for therapies designed to enhance immune responses to cancer. This review will outline our current understanding of FOXP3+ 'Tregs', NKT cells, MAIT cells and B regulatory cells immune regulatory cell populations in cancer, with a particular focus on chronic lymphocytic leukaemia (CLL). We will discuss evidence linking CLL with immune regulatory dysfunction and the potential for new therapies targeting regulatory cells.

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1. Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is a malignancy of mature B lymphocytes (B cells) characterized by clonal malignant B cells in peripheral blood exceeding 5 x 109/L (approximately 10 times the normal number of mature B cells found in adult PBMC) [1,2]. CLL patients frequently remain asymptomatic for long periods, maintaining stable but elevated numbers of malignant B cells for up to 20 years, but the progressive form of the disease can cause a massive expansion of malignant cells leading to organomegaly and death within 2–3 years [3–7]. Progression of CLL is variable and difficult to predict. Unmutated IgH V genes and increased expression of CD38 are associated with more rapid progression [8], but the causes of the transition from indolent to aggressive disease are not known.

Most current prognostic indicators focus on properties intrinsic to the malignant B cells themselves, however changes in the immune system that affect the growth of CLL cells could also influence disease progression. CLL patients exhibit significant dysregulation of normal immune function during progressive phases of the disease [9] so an improved understanding of changes and abnormalities in immune regulation may therefore provide a better understanding of CLL progression and help to identify potential new treatments. Longitudinal monitoring of regulatory (and other) immune cells in stable CLL patients could be an effective means of identifying immune changes associated with disease progression that could become useful biomarkers or targets of new immune-based treatments.

1.1. Immune defects associated with CLL

CLL patients accumulate large numbers of abnormal B cells but often have other immune defects [9]. For example, the absolute number of T cells is often increased and the peripheral T cell pool may have a decreased CD4:CD8 ratio [10]. Memory T cells are relatively overrepresented with a concurrent loss of naïve T cells [11] and CLL patients also reportedly accumulate CD8+ T cells with an exhausted or senescent phenotype and increased expression of PD-1 [10]. There are also reports of defective immune synapse formation and cytokine production following stimulation [12,13] although this seems at odds with studies suggesting that CD8 T cells from CLL patients are functionally competent in their recognition of antigen and cytokine (IFNγ) responses to CMV [14].

2. T cell defects in CLL

CLL B cells reportedly affect the responsiveness of both CD4 and CD8 T cells by causing changes in cytoskeletal dynamics (inhibiting F-actin polymerization), which causes defects in the formation of immune synapses required for full T cell activation [12]. These changes are mediated by direct cell contact involving molecules such as CD200, CD276 and CD279 (PD-1) [15]. The increased expression of PD-1 on CD4+ and CD8+ T cells has also been associated with decreased cytokine

* Corresponding author at: Federation University, Ballarat, Victoria 3010, Australia. Tel.: +61 3 5327 9828.
E-mail address: sberzins@federation.edu.au (S.P. Berzins).

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production, with IFNγ being more significantly reduced than IL-4, leading to Th2 skewing of CD4+ T cell responses [11].

CD4+ T cells are closely associated with CLL B cells in proliferative centres and appear to drive CLL B cell proliferation via cell contact and cytokines [16,17], however there are conflicting reports about the nature of these T cells. Early studies reported a preponderance of Th2 cells in CLL patients, with decreased numbers of Th1 cells [18]. Conversely, the upregulation of CD38 on CLL B cells associated with increased proliferation of malignant cells and more rapid disease progression [19] has recently been attributed to IFNγ from Th1 cells [20]. There is evidence that both IL-4 and IFNγ augment the proliferative capacity of CLL B cells [21,22].

There has also been a correlation noted between decreased numbers of Th17 cells and increased disease severity [23,24], and increased TH17 cell numbers are reported to correspond with better prognostic indicators [25]. This correlates well with a recent report that IL-17 producing cells are decreased in progressive vs indolent CLL patients and that this change is associated with an increase in CD39+ FOXP3+ T regulatory (Treg) cells [26], which inhibit Th17 differentiation. Interestingly, this study noted that Th1 and Th2 subsets were similarly represented in indolent and progressive patients. Collectively, however, these findings suggest that a shift in the balance between Th1, Th2 and Th17 regulatory immune subsets in CLL patients may be an important factor in driving disease progression.

Given the changes observed in conventional T cells subsets, there has also been interest in the potential role of regulatory cell populations. Increased numbers of the recently defined T follicular helper subset (Tfh cells) in CLL reportedly promote increased IL-4 and IL-21 production [27]. Tfh cells normally support B cell differentiation into plasma cells in germinal centres, but may support proliferation and survival of CLL B cells in proliferative centres [27].

One problem that probably requires longitudinal analysis is that it is difficult to know whether these immune defects precede disease progression or are caused by the malignant B cells. In proliferative centres, CLL B cells interact with stromal cells and nurse like cells to secrete chemokines (e.g., CCL3/4) and cytokines that recruit monocytes and CD4+ T cells, resulting in a microenvironment conducive to survival and proliferation of tumour cells [28]. The kinetics of Th2, Tfh and T regulatory cell entry and expansion in these proliferative centres relative to other cells types is poorly understood, although it is clear that CD4+ T cells and PD1+ lymphocytes are in close contact with CLL B cells [11,16].

These studies suggest that developing a deeper understanding of the interactions between all of these different stimulatory and suppressive or regulatory T cell subsets will be critical for identifying important checkpoints for CLL progression.

3. Regulatory immune cell subsets

T cell lineages with regulatory functions include FOXP3+ Tregs, NKT cells and mucosal associated invariant T (MAIT) cells. These are classed as regulatory lineages because of their ability to modulate immune responses primarily through cytoekine release. NKT cells in particular have well established roles in preventing autoimmunity and facilitating anti-tumour immunity. Here we consider the evidence that one or more of these regulatory subsets may be important in CLL and whether they have potential as targets of novel immune based therapies.

3.1. FOXP3 + T regulatory cells

FOXP3+ regulatory T cells (Tregs) are CD4+ T cells that express the Forkheadbox P3 (FoxP3) transcription factor required for their development and function [29]. Tregs are capable of suppressing immune responses through direct cell–cell interactions and through the release of cytokines such as IL-10 and Tgf-β [30]. Increased frequencies of Tregs have been documented in many types of cancer and the presence of high numbers of Tregs within solid tumours is associated with a poor prognosis [29].

The role of Tregs in CLL remains to be fully elucidated. More studies are needed to assess changes in the frequency of these cells at different stages of disease and their functional competency. A number of studies have reported an increased number of Tregs in CLL patients [31–33] associated with suppression of anti tumour responses [31] and disease progression [33], although one also noted that CLL patients with a poor prognosis had slightly lower Treg cell frequencies [31]. Inconsistencies in approaches used to identify FOXP3+ Tregs and the lack of age matched controls have sometimes complicated interpretations of data from patients with CLL, where the median age of patients at diagnosis is approximately 70 yrs. [34,32]. In addition to Tregs, innate-like T cells such as natural killer T (NKT) cells and mucosal associated invariant T (MAIT) cells also have the potential to influence immune responses and are yet to be studied in detail in CLL patients.

3.2. NKT cells

NKT cells are one of several innate like T cell lineages that express surface antigens such as CD56 and CD161 that are more commonly associated with natural killer cells [35]. Type 1 NKT cells (also called 'invariant' or 'iNKT cells') are restricted by the MHC-like antigen presenting molecule CD1d, and express a semi-invariant T cell receptor that recognizes lipid antigens. They respond to stimulation by rapidly releasing cytokines that can influence the function of both innate and adaptive immune cells. Type 1 NKT cells are the most well studied NKT cell lineage and [36] from this point onwards, 'NKT cells' will refer only to these cells. In humans, NKT cells normally represent less than ~0.1% of PBMCs but deficiencies are associated with autoimmune diseases, cancer and allergies [36]. Mature NKT cells can be classified into three phenotypically distinct subsets CD4+CD8−, CD4−CD8+ or CD4−CD8− (double negative; DN) [37], although the CD4−CD8+ and DN subsets are normally grouped together as a CD4− subset in functional assays. CD4+ NKT cells release Th1 (including IFNγ and TNF) and Th2 (IL-4, IL-10) cytokines, whereas CD4–CD8– NKT cells are biased towards a Th1 profile and are often promoted as supporting anti-tumour activity. Defects in NKT cell cytokine production are also associated with cancer and autoimmunity, although the importance of NKT cells and associated defects remains controversial [36].

NKT cell defects are associated with several haematological cancers, including myelodysplastic syndromes (MDS) and multiple myeloma (MM) [38,39]. The status of NKT cells in CLL is unclear. Jadidi-Niaragh et al. reported decreased NKT cell numbers in progressive CLL patients compared to those with indolent disease [40]. However another study found no defects in overall NKT cell number or function in untreated CLL patients at various stages of disease [41]. These discrepancies may in part result from differences in the parameters used to identify NKT cells in each case. The latter study also reported a trend towards an increased ratio of CD4+ to CD4− NKT cells in CLL. This is highly reminiscent of findings in both MDS and MM where no overall defect in NKT cells frequency or function was identified, but where the distribution of subsets was abnormal [38,39]. This is potentially significant not only because the defect has been observed across three separate haemopoietic cancers, but because NKT cell researchers are increasing highlighting the importance of separately analysing NKT cell subsets, rather than as a homogenous population [36,42].

NKT cells are a prime candidate for further investigations in CLL because they have a proven role in other cancers and NKT cell defects have already been identified. Mouse studies have demonstrated that administration of specific lipid antigens can selectively activate NKT cells, resulting in NKT cell proliferation, extended cytokine release and tumour rejection. A strong NKT cell agonist, alpha galactosylceramide, has been used in early phase clinical trials to treat head and neck cancers

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