Chapter 4

Malignant Interaction between B Cells and T Helper Cells

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Abstract

Collaboration of T helper (T_h) cells with B cells is central for the generation of high-affinity antibodies with distinct effector function and thus for the establishment of effective immune responses. Physiological T cell help for B cells takes place in germinal centers (GC) in peripheral lymphoid organs, where follicular T helper (T_{fh}) cells interact with mature, antigen-stimulated B cells. Occasionally, B cells undergo malignant transformation, which may lead to the development of leukemia or lymphoma. Over the past decades, it has become increasingly clear that cancer cells depend on interactions with the tumor microenvironment for growth and survival. Since many B cell malignancies develop in GC—the place of physiological T_h cell-B cell interaction—T_h cells are a central part of the tumor microenvironment of B cell leukemia and lymphoma. Thus, while the interaction between T_h cells and normal B cells is crucial for the development of an effective immune response, this interaction also contributes to the development and pathogenesis of malignancies. The present chapter discusses the mechanisms underlying T_h cell-mediated support of malignant B cells contributing to the pathogenesis of leukemia and lymphoma. Research efforts aiming to elucidate such mechanisms are of high importance as therapeutic targeting of these malignant interactions may increase treatment efficiency and reduce disease relapse.

Keywords: T helper cells, B cells, leukemia, lymphoma, B cell malignancies, T_h cell-B cell interaction, tumor microenvironment

1. Introduction

The human immune system is made up of two branches: the innate immune system consisting of dendritic cells, macrophages, granulocytes and natural killer (NK) cells mounts a fast but nonspecific response against invading pathogens. The adaptive immune system, in contrast,

raises a delayed but highly specific response. In this response, T cells and B cells use their greatly diverse receptors—T cell receptors (TCRs) and B cell receptors (BCRs), respectively—to recognize antigenic epitopes of invading pathogens [1]. Antigenic stimulation of the receptors on the B cell's and T cell's surface induces intracellular signaling cascades that lead to the activation, proliferation and differentiation of the cell. The BCR is also synthesized in a soluble form and can be secreted by B cells as antibody, also known as immunoglobulin (Ig). Antibodies recognize pathogens and neutralize them by various mechanisms. In order to generate high-affinity antibodies with distinct effector functions, B cells need the help of T cells. Thus, the establishment of a specific and efficient immune response requires a close collaboration of T cells and B cells.

1.1. Physiological T_h cell-B cell interaction

T cells arise in the bone marrow (BM) and mature in the thymus. Two T cell populations can be distinguished: the $CD8^+$ T cytotoxic (T_c) cells and the $CD4^+$ T_h cells. T_c cells can kill infected cells through release of molecules like granzymes or perforin, while T_h cells have the task to activate other immune cells and to instruct them to raise an appropriate immune response.

Naïve T_h cells leave the thymus and migrate to the periphery, where they encounter antigenic peptides presented by antigen-presenting cells (APCs) such as macrophages, B cells and dendritic cells (DCs). APC secrete a distinct set of cytokines, the composition of which depends on the pathogen encountered. Upon stimulation, the activated T_h cells rapidly divide and differentiate into one of several different effector subsets that are characterized by the expression of distinct transcription factors, surface markers and cytokines. This differentiation is governed by the cytokines that are secreted by the APC and the surrounding cells at the time point of naïve T_h cell activation. Thereby, APC not only activates naïve T_h cells but also tailors their properties according to the pathogens to be defeated.

The first T_h cell subsets that have been described were T_h1 cells, characterized by expression interferon (IFN)-γ, and T_h2 cells, producing interleukin (IL)-4, IL-5 and IL-13 [2]. Later, further effector lineages such as T_h17, T_h9 or T_h22 have been described. In addition, several T_h cell subsets with regulatory or suppressive functions, so-called regulatory T (T_{reg}) cells, exist [3].

Follicular helper T (T_{fh}) cells are a unique population of T_h cells distinct from extrafollicular and peripheral T_h cells. T_{fh} cells are characterized by the expression of the inducible T cell costimulator (ICOS) receptor, the chemokine receptor CXCR5, the programmed cell death-1 (PD-1) inhibitory receptor and the transcription factor BCL6 that controls their development and function [4–6].

B cells develop and mature in the BM and then migrate to the secondary lymphoid organs, where the antigen-dependent phase of their development takes place. While this process can be independent of T cell help, conventional B cells predominantly undergo T cell-dependent (TD) responses. Upon BCR stimulation by an antigen presented by follicular dendritic cells (FDCs), B cells migrate to the boundary between the follicle and the outer T cell zone, where they interact with T_{fh} cells [7]. Cognate interaction of B cells and T_{fh} cells involves internalization and presentation of an antigen via the BCR, ligation of CD40 on the B cell by its ligand

CD40L on the T_{fh} cell, as well as the cytokines IL-4 and IL-21. B cells then develop either into short-lived plasma cells that secrete low-affinity antibodies or they differentiate into GC B cells that further give rise to long-lived memory B cells and plasma cells producing high-affinity antibodies. While memory B cells enter the circulation, plasma cells migrate and home to the BM.

The activating signals from T_{fh} cells induce upregulation of activation-induced cytidine deaminase (AID), a DNA-editing enzyme that initiates somatic hypermutation (SHM) and class-switch recombination (CSR) [8]. Introduction of point mutation by AID into the variable region of the *IG* genes during SHM leads to highly variable Ig proteins that build the base for high-affinity antibodies [9]. During CSR, the constant parts of IgM and IgD (C_{μ} and C_{δ}, respectively) are replaced by C_{γ}, C_{α} or C_{ε}, giving rise to IgG, IgA or IgE. Thereby, CSR creates antibodies with diverse effector functions while retaining the antigen specificity [10]. B cells then differentiate into highly proliferating GC B cells called centroblasts before developing into centrocytes. As centrocytes, they screen antigens on the surface of FDC using their newly mutated BCR. High-affinity interaction with antigen results in survival and thus selection of centrocytes with high-affinity BCR, leading to recycling of centrocytes into centroblasts and to the differentiation of centrocytes into memory B cells and plasma cells.

During B cell development, however, B cells or their precursors occasionally undergo malignant transformation, which may result in the development of leukemia or lymphoma (**Figure 1**). Such transformations are frequently initiated by genetic events leading to aberrantly expressed proteins. Nevertheless, these chromosomal abnormalities alone are usually not sufficient for

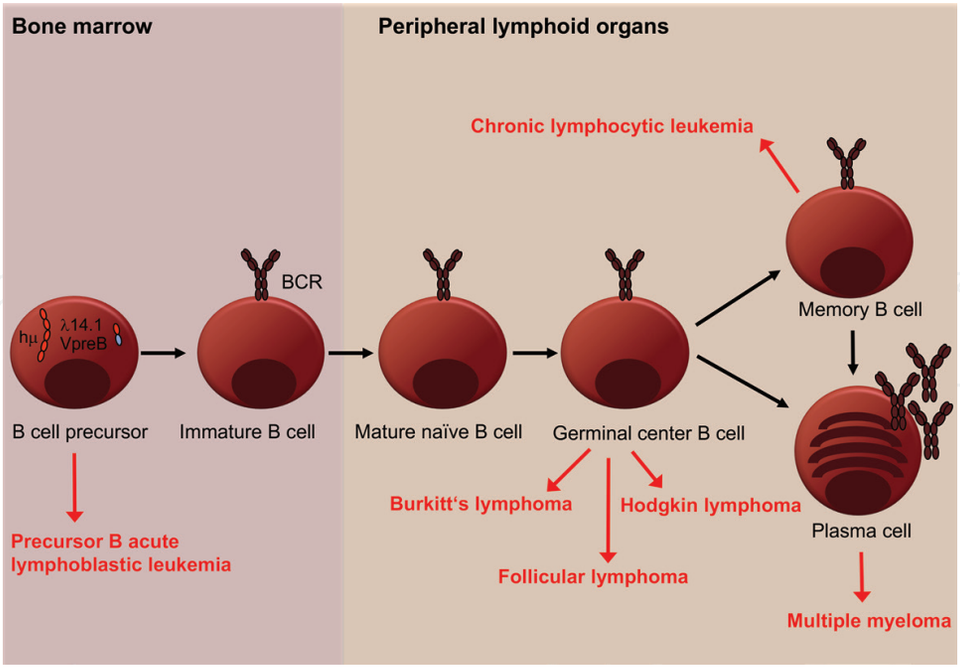

Figure 1. Schematic overview over the B cell development in the BM and GC with the most important developmental stages (black) and the B cell malignancies covered in this chapter (red). Red arrows indicate the presumed cell of origin of the malignant cells.

cancer development, and the transformed cells are not able to survive and outgrow when isolated and cultured *in vitro*. Thus, while mutations may trigger malignant transformation, interactions with the tumor microenvironment seem to be essential for the development and pathogenesis of most B cell malignancies.

2. Main body

2.1. Malignant T_h cell-B cell interaction

The tumor microenvironment plays a key role in supporting survival and expansion of cancer cells in virtually all known malignancies [11–13]. Malignancies of B cell origin often arise from GC B cells. Consequently, the cells of the GC microenvironment represent key collaboration partners of cancer cells during pathogenesis, progression and relapse of leukemia and lymphoma. The supportive tumor microenvironment in GC is made up by nonhematopoetic as well as lymphoid cells such as mesenchymal stromal cells, fibroblasts, macrophages, FDC and T_{fh} cells, which build a complex network and mutually regulate their activation differentiation, migration and expansion. Thus, while cells of the microenvironment support the tumor cells, the tumor cells in turn support and shape the cells that surround them in a way that maximizes their own benefit.

Generally, malignantly transformed B cells seem to retain their ability to interact with T_h cells, and thus remain capable of profiting from T_h cell help. Hence, while the support of normal mature B cells by T_h cells plays a central role in the generation of an adaptive immune response, the support of malignant B cells by T_h cells may promote lymphoma or leukemia.

2.2. Malignant T_h cell-B cell interaction: follicular lymphoma

Follicular lymphoma (FL) is the most frequent indolent lymphoma. The initial response rates to therapy are relatively high but relapses are frequent. The malignant cells express the GC B cell markers BCL6 and CD10 and display a gene expression profile of centrocytes [14]. FL cells are characterized by an overexpression of the antiapoptotic protein BCL2 caused by a t(14;18) translocation. Nevertheless, this genetic aberration is not sufficient for lymphoma development, and isolated primary FL cells fail to survive and proliferate *in vitro*, suggesting that the tumor microenvironment plays a major role in FL development and progression. Both nonhematopoietic cells as well as T_h cells are crucially involved in FL cell growth and survival [15]. T_{fh} cells from FL-affected lymph nodes display a distinct gene expression profile that differs from normal tonsillar T_{fh} cells by an increased expression of *IL2, IL4* and the proinflammatory cytokines *IFN* and *TNF* [16]. Consistently, high levels of IL-4 are associated with FL cell activation [17]. Similarly, support of FL cells by T_h cells seems to be mediated by T_{fh} cell-derived CD40L and IL-4 [18]. The proinflammatory cytokines expressed by T_{fh} of FL patients, in contrast, seem to modulate the FL supportive environment rather than having a direct effect on FL cells. TNF, e.g., has been suggested to sustain differentiation and survival of the lymphoid stroma network in FL [19].

Besides cytokines, the membrane-bound molecule CD40L is important for T_h cell-mediated FL cell support, since FL cells showed an increased survival when stimulated by CD40 cross-linking *in vitro* [20] as well as upon cognate interaction with T_h cells [21], and it has been suggested that CD40L stimulation protects FL cells from TRAIL-mediated apoptosis in an NF-κB-dependent manner [22].

About 70% of FL patients display BM infiltration at diagnosis. Interestingly, the affected BM is characterized by an overrepresentation of T_h cells [23]. This further supports the importance of T_{fh} cells in FL disease pathogenesis.

2.3. Malignant T_h cell-B cell interaction: Burkitt's lymphoma

Burkitt's lymphoma (BL) is an aggressive B cell cancer, probably arising from GC B cells [24]. Three main subtypes of BL are currently identified epidemiologically, though histologically the tumors are indistinguishable. Endemic BL (eBL), the classical BL, is found in malaria-endemic regions, while sporadic BL (sBL) is relatively rare and most commonly found outside malaria-affected areas. HIV-associated BL is often described as separate subtype as well [25]. eBL is strongly associated with the Epstein-Barr Virus (EBV), even though the pathogenic mechanism is not clear [26, 27]. The role of T_h cells in BL development and progression is highly controversial. Several studies showed that EBV-specific T_h cells can kill BL cell lines or EBV-transformed B cells [28–35] or limit their proliferation [36]. Most of these studies, however, used a nonphysiologically high effector to target ratio and thus require careful interpretation. Other researchers, in contrast, have reported that EBV-specific T_h cells induced B cell proliferation [37], and in several mouse models EBV-specific T_h cells were even required for lymphomagenesis [38–40]. Finally, two studies found that virus and autoantigen-specific T_h cells can both kill and support EBV-transformed B cells [41, 42], suggesting that the role of T_h cells in BL and other EBV-associated malignancies is likely to be context dependent. Interestingly, the chance of BL development in HIV patients is associated with $CD4^+$ T cell count, as the incident of BL development decreases with reduced $CD4^+$ T cell numbers [43], supporting a BL-promoting role for T_h cells.

2.4. Malignant T_h cell-B cell interaction: Hodgkin lymphoma

In Hodgkin lymphoma (HL), the malignant B cells—called Reed-Sternberg (RS) cells—constitute only a minor fraction of the tumor. The remainder consists of eosinophils, fibroblasts, macrophages, plasma cells and T_c as well as T_h cells. Infiltration of certain T_h cell subsets has been correlated with reduced overall patient survival, even though the exact function of these infiltrating T_h cells is not fully clear [44, 45]. Several cytokines seem to have a stimulatory effect on RS cells, one of which is the T_h2 cytokine IL-13 [46]. Nevertheless, IL-13 can also be produced by RS cells themselves and act in an autocrine manner. Thus, a direct role of T_h cells remains to be demonstrated. The complexity of the tumor microenvironment in HL, where a wide range of cells mutually influence each other, makes it intricate to discern the roles of the individual components.

2.5. Malignant T_h cell-B cell interaction: chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a malignancy of mature clonal $CD5^+$ B cells, although the precise cell of origin is still debated [47]. CLL cells proliferate in pseudofollicles in secondary lymphoid organs and in the BM, where they receive support from cells of the stromal microenvironment [48]. CLL cells were found to interact with endothelial cells, stroma cells and monocyte-derived nurse-like cells, and to receive antiapoptotic signals via cytokines and chemokines. In addition, T_h cells infiltrate such CLL pseudofollicles [49]. The infiltrating T_h cells were shown to have an activated phenotype and to be actively recruited to these niches by CLL cells via chemokines [50]. Furthermore, they were able to activate CLL cells and to induce an upregulation of the surface molecule CD38, which is associated with poor prognosis [51].

We hypothesized that proliferation of CLL cells in patients was driven by a cognate interaction of T_h cells with CLL cells, comparable to the physiological interaction between T_h cells and GC B cells [52]. According to this hypothesis, CLL cells would present antigen to antigen-specific T_h cells and in turn receive stimuli for their survival. Such an antigen could either be endogenous or it could be derived from an external pathogen. A key premise for this mechanism of CLL expansion in patients is the ability of resting CLL cells to efficiently activate T_h cells. Thus, to study the antigen-presentation capacity of CLL cells, we used a human T_h cell clone that is specific for a peptide derived from the mouse Ig kappa (Igκ) light chain [53], and human leukocyte antigen (HLA)-matched CLL cells from CLL patients, which allowed us to study antigen-dependent cognate interaction of CLL cells and T_h cells (**Figure 2**). Using this model, we found that CLL cells were able to endocytose antigen through endocytic receptors such as the Fc receptors CD32 and CD23 and through their BCR. Furthermore, CLL cells were surprisingly potent stimulators of T_h cell proliferation. With the exception of one patient, the

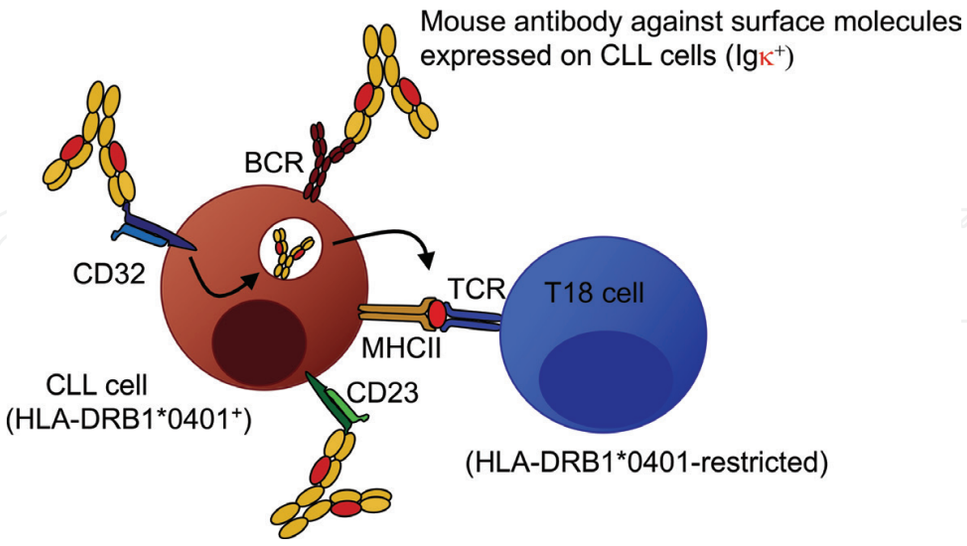

Figure 2. Model system to assess the antigen-presentation capacity of CLL cells: HLA-DRB1*0401+ CLL cells are cocultured with a human T_h cell clone (T18) that is specific for an epitope in mouse Igκ chain, when presented on HLA-DRB1*0401. Mouse Igκ+ antibodies against various surface molecules on the CLL cells such as CD23, CD32 or BCR are added. T18 cell proliferation is assessed as a read out for the capacity of CLL cells to endocytose and process these antibodies and to present Igκ peptides to the T18 cells together with provision of costimulatory signals.

function of CLL cells was comparable to that of normal B cells. Reciprocally, CLL cells were activated by antigen-activated T_h cells. They upregulated the activation markers CD38 and CD69, and molecules involved in the interaction with T_h cells such as HLA-DR, the costimulatory molecule CD86, the adhesion molecule CD54 and receptors for T_h cell help such as CD40 and CD25. Surface expression of CD27 and CD275 (ICOS-ligand) was reduced, in line with activation-induced shedding. In addition, CLL cells proliferated upon interaction with T_h cells, which was dependent on antigen and cell-cell contacts, as well as on CD40-CD40L interaction. Furthermore, the T_h cell-stimulated CLL cells had a gene expression profile similar to CLL cells within CLL proliferation centers, suggesting that *in vitro* interactions with T_h cells reflected interactions with the lymph node microenvironment in patients.

While the results obtained using this model system demonstrated that CLL cells had the ability to activate T_h cells and receive help for their survival and proliferation, it remained to be elucidated whether such interaction actually occurred in CLL patients. Indeed, we found that CLL patients harbored T_h cells that proliferated in response to both autologous CLL cells as well as autologous CLL cell lysate presented by peripheral blood mononuclear cells (PBMCs) from HLA-matched donors. Similar to the results obtained using the model system, CLL-specific T_h cells stimulated CLL cell activation and proliferation in an antigen- and CD40L-dependent manner. In *in vivo* xenograft experiments, the T_h cell-induced CLL proliferation was even more pronounced, suggesting that stromal factors may act synergistically during the T_h cell-CLL cell collaboration.

The remaining unresolved point was the identification of the antigenic source of the cognate interaction between T_h cells and CLL cells. The hypervariable regions of the CLL cells' BCR represent good candidate for endogenous antigens, since peptides derived from these regions are presented on major histocompatibility complex class II (MHCII), and are likely to be recognized as foreign by autologous T_h cells.

To test this hypothesis, we used monoclonal antibodies derived from CLL cell hybridoma as source of antigen and HLA-matched donor PBMC as antigen-presenting cells, and assessed proliferation of autologous T_h cells. Indeed, a significant fraction of T_h cells proliferated upon stimulation with CLL-BCR-derived antigen, demonstrating that effector T_h cells specific for endogenous CLL antigens are present in CLL patients and that they can support CLL cell activation and expansion.

Interestingly, the patient-derived CLL-specific T_h cells had a T_h1-like phenotype, characterized by IFN-γ secretion as well as expression of the IFN-γ-associated transcription factor T-bet and the surface markers CXCR3 and CCR5. In contrast, they lacked typical T_{fh} markers such as CXCR5, ICOS, PD-1, or IL-21 and BCL-6. These findings are in agreement with the observation that IFN-γ levels in CLL patients as well as IFN-γR expression on CLL cells correlated with disease severity [54–56]. Even though the exact mechanisms remain to be elucidated, IFN-γ seems to confer resistance to apoptosis and to increase CLL migration. We further demonstrated that IFN-γ secretion was a major mechanism by which CLL-specific T_h cells increased CD38 expression on CLL cells [57]. CD38 levels on CLL cells are an indicator of poor prognosis, even though a mechanistic involvement of CD38 in CLL pathogenesis is still debated [58]. Within a patient, proliferating CLL cells are more frequently found in the population that

has a higher CD38 expression, and CD38 has been linked to CLL cell migration and survival. In our studies, we found that expression of the IFN-γ-inducible transcription factor T-bet in peripheral blood CLL cells is significantly correlated with CD38 expression [57]. Furthermore, T_h cell-derived IFN-γ upregulated CD38 in a mechanism that involved binding of the transcription factor T-bet to two consensus sites in 5′-regulatory regions of intron 1 of the *CD38* gene. Thus, it seems that T_h cell promote the development of a more aggressive CLL subset through secretion of IFN-γ.

CLL cells seem to express polyreactive and/or autoreactive BCR that provide a certain level of constant signaling [59, 60]. However, sustained BCR signaling can induce anergy and apoptosis. Our studies are in agreement with the view that CLL cells are autoreactive B cells that are rescued from anergy by combined BCR and CD40L activation [50–52, 57, 61, 62]. BCR signaling components such as the kinase Syk are promising drug targets in CLL [63–65]. Thus, we studied how BCR pathway inhibitors may impact the T_h cell help of CLL cells [66]. Interestingly, we found that stimulation by CD40L activated the BCR pathway in CLL cells, including Syk and the downstream components Akt, BLNK, Btk/Itk and pErk1/2. This activation—indicated by blastogenesis and proliferation—was significantly higher in CLL cells compared to normal B cells and could be blocked by Syk inhibition in CLL cells but not in normal B cells.

2.6. Malignant T_h cell-B cell interaction: multiple myeloma

Multiple myeloma (MM) is a malignancy characterized by the expansion of plasma cell-derived myeloma cells in the BM. The BM of MM patients and patients with monoclonal gammopathy of undetermined significance (MGUS) display increased numbers of T cells [67], but their role in MM disease development is not fully understood. Primary human MM cells express MHCII molecules as well as the costimulatory molecules CD80 and CD86 and have been shown to be good antigen-presenting cells for T_h cells [68, 69]. In addition to the fact that they express high levels of CD40, this suggests that they can participate in cognate interactions with T_h cells and benefit from their support. Indeed, CD40 stimulation induced MM cell migration, which is associated with MM disease progression [70]. CD40 stimulation also triggered secretion of IL-6 by myeloma cells, which may mediate MM cell proliferation in an autocrine and/or paracrine mechanism [71]. In addition to CD40L-mediated stimulation, myeloma-specific T_h cells can also support MM cells by secreting cytokines [72]. T_h17 cytokines such as IL-17 enhanced proliferation of MM cell lines *in vitro* and *in vivo*, and supported colony formation of primary human MM cells.

Very recently, we demonstrated that polyclonally activated allogeneic as well as autologous T_h cells stimulated blastogenesis and proliferation of MM cells in a CD40L-dependent manner [73]. MM cells increased their cell size, became more granular, reduced their cell surface Ig expression and upregulated the expression of HLA-DR. Proliferation of MM cells was even more pronounced when the T_h cell growth factors IL-2 and IL-15 were added. The T_h cells from MM patients expressed the chemokine receptors CXCR3 and CCR6 and the transcription factor T-bet as well as low levels of ROR-γt, thus displayed a $T_h1/17$ phenotype. Compared to T_h cells from healthy controls, the MM patient-derived T_h cells produced lower amounts of IL-4,

IL-10, IL-13, and IFN-γ and TNF-α, but higher levels of IL-1β, IL-2, IL-6 and IL-17. Together, our recent study and the previous reports by others suggest that CD40L stimulations is a key mechanism in T_h cell-mediated MM cell support, but cytokines such as IL-6 and IL-17 are important components as well.

2.7. Malignant T_h cell-B cell interaction: precursor B cell acute lymphoblastic leukemia

The B cell malignancies described in this chapter so far all originate from mature B cells. In contrast, precursor B acute lymphoblastic leukemia (BCP-ALL) derives from B cells of precursor stages during B cell development in the BM. As in most malignancies, the tumor microenvironment plays a key role in BCP-ALL development and progression [12]. Mesenchymal stromal cells, BM endothelial cells, osteoblasts as well as adipocytes have been described to support survival and proliferation of BCP-ALL cells and to confer drug resistance in mechanisms involving both soluble factors and cell membrane-bound molecules.

Memory T_h cells generated in the periphery during an immune response migrate to the BM in order to provide long-term memory [74–77]. These BM T_h cells seem to play a crucial role in normal hematopoiesis [78], but the knowledge about the physiological interactions between BM T_h cells and normal precursor B cells is very limited. Both normal precursor B cells and BCP-ALL cells express CD40 [79], MHCII, molecules for adhesion and costimulation [80], receptors for cytokines such as IL-2 and IL-6 [81–85] and receptors for BAFF [86, 87]. Thus, they possess all molecules required for cognate interaction with T_h cells and therefore seem to be capable of receiving support through the conventional T_h cell-B cells interaction pathways. BCP-ALL cells are indeed able to respond to CD40L stimulation with proliferation [88] and with upregulation of the surface molecule CD70 [89]. Furthermore, they upregulate the receptor for IL-3 [90], a cytokine that induces BCP-ALL cell proliferation. Stimulation with CD40L also induces the secretion of chemoattractants [91] and upregulates components of the antigen-processing machinery [92], suggesting that BCP-ALL cells are able to attract T_h cells and activate them, thereby inducing a positive feedback loop. T_h cell-derived *cytokines* can act on BCP-ALL cells as well, albeit with diverse effects. IL-2, IL-17 and IL-21, e.g., have been found to stimulate proliferation [83, 93], while IL-4 and IL-13 inhibited BCP-ALL cell growth [88, 94–96], and IL-4 as well as TGF-β-induced apoptosis [97, 98]. Cell-cell contact of BCP-ALL cells and activated allogenic T_h cells induced activation and maturation of BCP-ALL cells [99]. Further support of an involvement of T_h cell in BCP-ALL development comes from the observation that BCP-ALL is associated with certain MHCII haplotypes, suggesting that antigen-presentation to T_h cells is involved in the pathogenic mechanisms contributing to BCP-ALL development [100, 101]. In summary, there is evidence that BCP-ALL possess the capacity to exploit microenvironmental T_h cells, but whether such leukemia supportive T_h cell-BCP-ALL cell interactions actually taking place in patients remains to be determined.

2.8. Concluding remarks

The tumor microenvironment plays a key role in supporting malignant cells. In B cell leukemia and lymphoma, the malignant B cells seem to have retained their ability to receive help from their physiological interaction partners, the T_h cells. Consistently, current research supports a

contribution of T_h cells to the development and progression of various types of B cell malignancies. Effective anticancer therapies should include targeting the cells of the tumor microenvironment. Thus, research efforts leading to the identification and characterization of malignant collaboration between T_h cells and malignant B cells may provide novel strategies for therapies aiming to target the tumor microenvironment.

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