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Immunologic Pathomechanism of Hodgkin's lymphoma

Q6 Adam Jona[a], Peter Szodoray[b], and Arpad Illés[a]

[a]Department of Hematology, Institute for Internal Medicine; University of Debrecen Medical and Health Science Center, Debrecen, Hungary; [b]Institute of Immunology, Rikshospitalet, University of Oslo, Oslo, Norway

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Hodgkin's lymphoma is a lymphoid malignancy of the immune system. The pathognomonic Hodgkin and Reed-Sternberg cells (HRS) are derived mainly from monoclonal, preapoptotic B cells, and they carry rearranged, somatically mutated immunoglobulin heavy chains. In an appropriate microenvironment, HRS cells escape from apoptosis by several mechanisms, including single mutations, aberrant signaling pathways. Eventually, weakened immune surveillance leads to uncontrolled, disproportional B cell proliferation. This review summarizes the latest findings on the pathogenesis of Hodgkin lymphoma, with a special emphasis on immunologic processes, and depicts current and future immunotherapeutic regimens, which improve treatment outcomes and reduce late toxicities.

In 1832, Sir Thomas Hodgkin first described cases of a previously unknown lymphoid lesion [1], which was named Hodgkin disease. Later, Dorothy Reed [2] and Carl Sternberg [3] discovered the characteristic multinucleated cells that are the hallmark of the disease. After the identification of the malignant, clonal expansion of B cells in the pathogenesis, the disease was named Hodgkin lymphoma (HL) [4]. The initially lethal disease became treatable with good survival rates after the introduction of irradiation and chemotherapy (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine [ABVD]) in the 1970s [5], which became the standard of care in 2003 based on the results by the Intergroup trial [6].

The World Health Organization classification distinguishes nodular lymphocyte predominant HL (NLPHL) and classical HL, which is further subdivided to lymphocyte rich, mixed cellularity, nodular sclerosis and lymphocyte depletion subgroups (cLD). Seldom, the histologic subgroup cannot be determined, and an intermediate form exists between HL and diffuse large B cell lymphoma. Tumor cells are lymphocytic and histiocytic in NLPHL, whereas Hodgkin (mononuclear) and Reed-Sternberg cells (multinuclear; HRS) can be identified in classical HL. These cell types represent approximately 1% of the tissue cells, and they are surrounded by large amounts of nonmalignant, reactive cell mass.

Current treatment regimens have excellent outcome with high survival rates, but there are still a number of relapsing and primary refractory patients. Treatment-related late toxicities can occur, as well (e.g., secondary malignancies and cardiovascular diseases). In HL, the demand for future therapeutic regimes is to reduce treatment related toxicities, while maintaining high cure rates. Ongoing molecular research identifies possible novel therapeutic targets; however, the pathogenesis of HL is still largely unclear. This review summarizes the most important current information about the biology and pathogenesis of HL.

Origin of HRS cells

The B cell nature of the pathognomonic HRS cells has been identified only in the past decade. HRS cells carry rearranged and somatically mutated immunoglobulin variable heavy chains, showing the features of a B cell that has been exposed to antigens [4]. In some cases, nonfunctional crippled mutations have been described in cells that normally would undergo apoptosis [7]. Moreover, these cells originate from a single clone, which is the hallmark of tumor cells [8]. Thus, HRS cells most likely derive from preapoptotic germinal center B cells, which are resistant to apoptosis (Fig. 1A). Nevertheless, a minority of HL cases shows T cell characteristics, and these cells are derived from T cells. A global loss of B cell phenotype of the cells is also known [9].

Offprint requests to: Adam Jona, M.D., Department of Hematology, Institute for Internal Medicine, University of Debrecen, Medical and Health Science Center, Nagyerdei krt. 98., H-4032 Debrecen, Hungary; E-mail: jona.adam1@gmail.com

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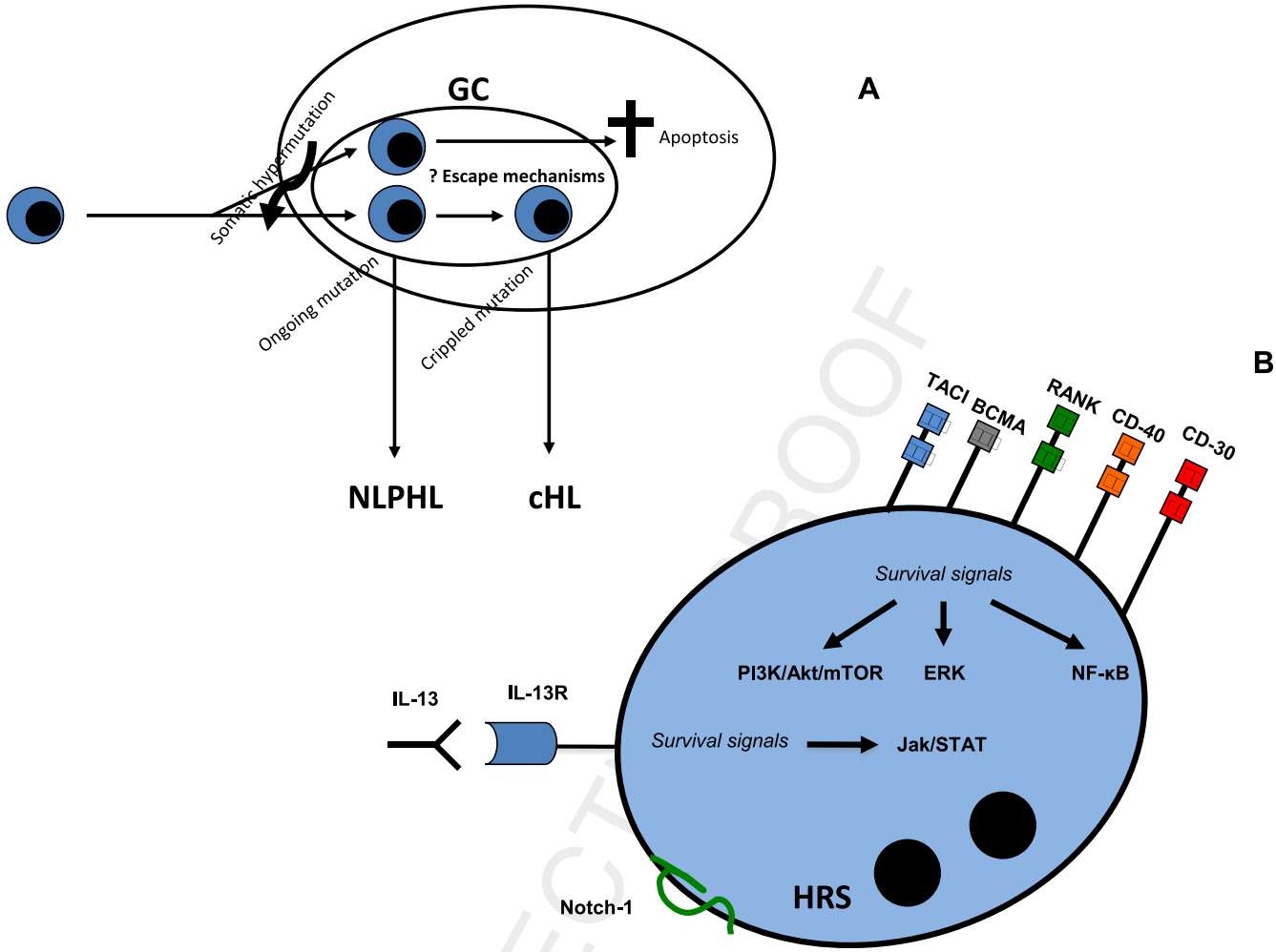

Figure 1. **(A)** Hodgkin lymphoma is of B cell origin. HRS cells carry rearranged, somatically mutated immunoglobulin heavy chains. HRS cells carry crippled mutations, whereas lymphocytic and histiocytic cells carry ongoing mutations. Pathognomonic HRS cells and lymphocytic and histiocytic cells would normally undergo apoptosis; however, several mechanisms help them to avoid it. **(B)** A summary of dysregulated signaling pathways, which inhibit or regulate apoptosis inside the Hodgkin and Reed-Sternberg cells. BCMA = B cell maturation antigen; cHL = classical Hodgkin lymphoma; ERK = extracellular signal-regulated kinase; GC = germinal center; HRS = Hodgkin and Reed-Sternberg cell; IL-13 = interleukin 13; IL-13R = interleukin 13 receptor; Jak/STAT = Janus kinase-signal transducers and activators of transcription; mTOR = mammalian target of rapamycin; NF-κB = nuclear factor κ-light-chain-enhancer of activated B cells; NLPHL = nodular lymphocyte predominant Hodgkin lymphoma; PI3K = phosphatidylinositol 3-kinase; RANK = receptor activator of NF-κB; TACI = transmembrane activator and calcium modulator and cyclophilin ligand interactor.

Lymphocytic and histiocytic cells can also originate from the germinal center, because they express several B cell markers and grow in a follicular pattern [10]. In contrast to HRS cells, lymphocytic and histiocytic cells carry ongoing mutations and express markers of a B cell.

The constitutive upregulation of the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathway has been known since 1996, [11] which is crucial for cell survival. This upregulation leads to the expression of cellular FLICE-like inhibitory protein (cFLIP) [12] and X-linked inhibitor of apoptosis (XIAP) [13] that inhibit the apoptotic pathways.

HRS cells at least partly would normally undergo apoptosis within the germinal center reaction by inducing the CD95/FAS-R pathway. However, these cells look resistant to CD95-mediated cell death, [14] most likely because of the constitutive expression of cFLIP, which is a key regulator of death receptor resistance.

Genetic aberrations

Several studies showed recurrent genetic alterations, reflecting the unstable condition of the HRS cells. These alterations are considered rather secondary because of the instability, because these changes are not sufficient to propagate HL [15]. Most mutations are numeric aberrations, which can be observed in almost all HRS cells. Cytogenetic studies depicted nonrandom breakpoints in the HRS cells (e.g., 3q27, 6q15, 7q22, 11q23, 14q32) [16]. Whole-genome studies showed recurrent amplifications on 2p13

[17], which leads to the constitutive activation of NF-κB and signal transducer and activator of transcription (STAT) and resistance to apoptosis. Comparative genome hybridization showed amplifications of the 4p16, 4q23-q24, and 9p23-p24 regions; the latter affects Janus kinase 2 (Jak2) [18]. Fluorescent in situ hybridization also revealed amplifications of the murine double minute 2 gene on 12q14, which inhibits apoptosis [19].

Epstein-Barr virus (EBV) is considered as having a pivotal pathogenic role in HL. Patients who developed infectious mononucleosis in adulthood had a threefold greater risk of developing HL compared with those who did not [20]. EBV is found in approximately 40% of cases, more often in the mixed cellularity and lymphocyte depletion subtype [21]. EBV^+ HRS cells express EBV nuclear antigen 1 (EBNA1) and latent membrane proteins 1 and 2A (LMP1, LMP2A). EBNA1 is responsible for the replication of the viral genome [22]; furthermore, it helps in attracting regulatory T cells (Tregs) through the chemokine ligand 20 (CCL20) production, thus inhibiting EBV specific immune responses, resulting in tumor progression. In EBV-negative cases, human leukocyte antigen (HLA) class I downregulation helps to avoid effective immune responses, whereas in EBV-positive cases, HLA I polymorphism functions through avoiding $CD8^+$ cytotoxicity [23]. HLA-G expression allows HRS cells to escape from natural killer (NK) cells. Inhibition of T cells is mediated through programmed cell death protein 1 (PD-1), which is expressed on the surface of T cells that link to the PD-1 ligand on the surface of HRS cells [24]. LMP1 contributes to the activation to NF-κB by mimicking an activated CD40 receptor, whereas LMP2A imitates a B cell receptor, thus inhibiting apoptosis [25].

EBV infection influences the composition of microenvironment through molecules, which affect infiltrating T cells. Interleukin (IL) 10 is expressed in 66% of EBV-positive cases, but in only 16% of EBV-negative cases [26]. Regulated on Activation Normal T Cell–Expressed and Secreted (RANTES) expression is significantly higher in EBV-positive cases [27].

The link between HL and autoimmune disorders is well known. There is evidence that, in certain autoimmune diseases, there is an increased risk of developing lymphoid malignancies. The background of this phenomenon includes common genetic predisposition, viral infection (e.g., EBV virus), use of immunosuppressive agents, persistent antigen stimuli, chronic inflammation, uncontrolled B cell proliferation, and defected apoptosis [28].

Dysregulated signaling pathways

Several signaling pathways have been reported to inhibit or regulate apoptosis, hence lymphomagenesis. The NF-κB transcription factor family consists of five members: Rel, RelA (p65), RelB, p50, and p52. These members form homodimers or heterodimers [29]. LMP1 in EBV-positive cases, activation of cell-surface receptors CD30 and CD40, receptor activator of NF-κB (RANK) and Notch contribute to the constitutive upregulation of the pathway. The dysregulated NF-κB pathway eventually leads to the activation of cFLIP, XIAP, and B cell lymphoma–extra large; it eventually contributes to apoptosis inhibition [15].

These activating factors by themselves are not sufficient for activating NF-κB, and several recently additional genetic lesions have been described. Gene amplification of c-Rel has been observed in approximately 50% of all HL cases [17,30]. Nuclear factor of κ light polypeptide gene enhancer in B cells inhibitor, α (i.e., NFKBIA) holds inactivating mutations in IκBα [31], and mutations affecting IκBε have been described previously [32]. Tumor necrosis factor (TNF) α induced protein 3 (TNFAIP3), which is a tumor suppressor, is frequently inactivated. Its protein product A20 negatively regulates NF-κB activity through ubiquitination and deubiquitination [33,34]. Surprisingly, an inverse correlation was found between the EBV status of the HRS cells and TNFAIP3 mutation, indicating that these are alternative mechanisms of NF-κB activations and further supporting the pathogenic role of EBV.

Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway is the main mediator of the cytokine signaling. Members of the STAT family are transcription factors. STAT3, STAT5A, STAT5B, and STAT6 have been reported to be active in the HRS cells [35–38]. STATs are activated by cytokine receptors via JAK kinases and by receptor tyrosine kinases [39]. STAT3 and STAT6 are most often activated [37]. STAT3 downregulation leads to apoptosis induction, indicating its potential role in HL pathogenesis [40]. NF-κB activates both STAT5A and STAT5B [41]. STAT6 activation seems to be the result of the autocrine activation of IL-13 receptor (IL-13R) and IL-13 [42,43]. Amplification of Jak2 and mutation in the suppressor of cytokine signaling 1 (SOCS1) have been reported to activate STAT6 [44]. The autocrine activation of IL-21 receptor and its ligand IL-21 leads to the activation of both STAT3 and STAT5 [45].

Activator protein-1 (AP-1), which is another transcription factor complex, is characterized by the marked overexpression of c-Jun and JunB [46]. An autoregulatory process activates c-Jun, whereas JunB is NF-κB dependent. AP-1 cooperates with NF-κB via induction of cyclin D2, c-MET, and the chemokine receptor 7, thus contributing to lymphomagenesis. The transcription of CD30 is activated by AP-1, thus establishing a positive feedback loop and contributing to processes driven by NF-κB [47].

Notch1, a transmembrane receptor, was found only on HRS cells, not on normal B cells or other B cell lymphomas. It is likely that it has an important role in the loss of the B cell phenotype, because its activation inhibits B cell development toward lymphoid lineages. Notch dimerization leads to strong proliferation and apoptosis resistance [48]. Recently, Notch signaling was also showed to be an

upstream regulator of NF-κB [49], providing a cross-link between these two pathways.

The phosphatidylinositol 3-kinase (PI3K)-Akt pathway is active in HRS cells; it inhibits apoptosis and promotes cell cycle progression [50]. Inhibition of this pathway in combination with chemotherapy could improve disease outcome. The extracellular signal-regulated kinase pathway is activated through CD30, CD40, RANK, and receptor tyrosine kinases [51], and it regulates apoptosis, proliferation, and differentiation (Fig. 1B).

Microenvironment

The aberrant cytokine–chemokine network and the receptors are crucial to attract cells that form and maintain a specific microenvironment to help proliferating HRS cells. Effective immune responses cannot occur in this network (Fig. 2).

Tumor tissue consists of 98%–99% of nonmalignant, reactive cell mass, consisting of B cells, T cells, mast cells, macrophages, eosinophils, neutrophils, plasma cells, epithelioid cells, fibroblasts, and collagen [52].

RANTES (chemokine ligand 5 [CCL5]), IL-5, IL-9, mucosa-associated epithelial chemokine (CCL28), granulocyte-monocyte colony stimulating factor, and CCL11 are responsible for attracting eosinophils (tissue eosinophilia) [53]. Eosinophils and mast cells help HRS cells to survive through CD30L/CD30 interaction.

RANTES and IL-9 are responsible for attracting mast cells, whereas IL-8 attracts neutrophils. CCL28 and IL-6 attracts plasma cells, whereas thymus and activation-regulated chemokine (TARC; CCL17), macrophage-derived chemokine (MDC; CCL22), RANTES (CCL5), and CCL20 are the leading compounds, which accumulate T helper 2 (Th2) cells and Tregs [54].

HRS cells secrete a variety of chemokines and cytokines (e.g., IL-4 through stimulating MDC synthesis), which shifts from antitumor T helper 1 (Th1) cells to pro-tumor T helper 2 (Th2) cells, thus changing the immunosurveillance and allowing HRS cells to survive [55]. IL-4 is produced by HRS and Th2 cells, resulting in an amplification circuit [56].

Fibroblasts are responsible for forming a significant amount of scar tissue. They are attracted by IL-13, TNF-α,

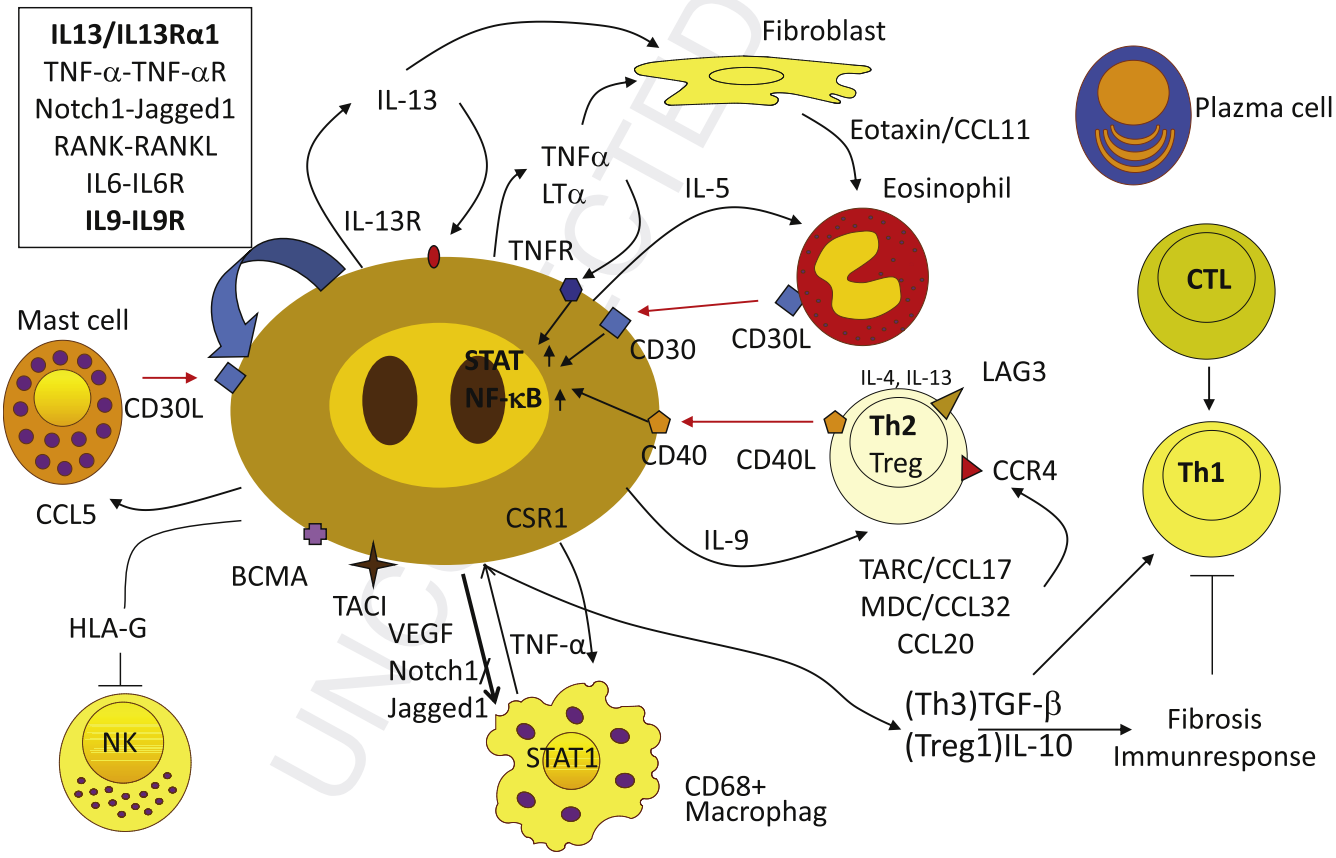

Figure 2. Interactions in the microenvironment of HRS cells. BCMA = B cell maturation antigen; CCL5 = chemokine ligand 5; CCR4 = chemokine receptor type 4; CD30L = CD30 ligand; CSR1 = cellular stress response 1; CTL = cytotoxic T lymphocyte; HLA-G = human leukocyte antigen G; IL = interleukin; LAG3 = lymphocyte-activation gene 3; MDC = macrophage-derived chemokine; LT = lymphotoxin; NF-κB = nuclear factor κ-light-chain-enhancer of activated B cells; NK = natural killer; R = receptor; RANK = receptor activator of NF-κB; RANKL = receptor activator of NF-κB ligand; STAT = signal transducers and activators of transcription; TACI = transmembrane activator and calcium modulator and cyclophilin ligand interactor; TARC = thymus and activation-regulated chemokine; TGF = tumor growth factor; Th2 = T helper 2 cell; TNF = tumor necrosis factor; Treg = regulatory T cell; VEGF = vascular endothelial growth factor.

transforming growth factor (TGF) β, CD40, and fibroblast growth factor. Activated fibroblasts produce eotaxin and RANTES, thus contributing to the attraction of eosinophils and Tregs. Furthermore, it has been reported that fibroblasts influence doxorubicin resistance by producing IL-7 in vitro [57].

Tumor-infiltrating $CD68^+$ macrophages are activated by TNF-α, which is produced by HRS cells. Macrophages affect HRS cells through Notch1/Jagged1 mediators. Angiogenesis is controlled through vascular endothelial growth factor along with endothelial and smooth muscle cells. The unfavorable prognostic role of $CD68^+$ macrophages has been reported previously [58–60]. Tumor-infiltrating $CD68^+$ macrophages can help to distinguish patients with a high risk for early relapse and those who are overtreated despite of their good prognosis.

HRS cells and their microenvironment generate elevated levels of IL-6, IL-7, IL-8, IL-10, soluble CD30, B cell–activating factor of the TNF family (BAFF), and thymus- and activation-regulated chemokine, which are decreased by continuous treatment and diminishing tumor burden. These mediators can be used as potential prognostic factors during treatment [61–63]. Because the HL microenvironment consists of 20%–50% of reactive, polyclonal B cells, elevated serum-free light chain levels can be detected in approximately 30% of the patients and can be predictive of treatment outcome [64].

Autocrin and paracrin factors contributing to HRS cell proliferation and survival

A number of receptors belonging to the TNF receptor superfamily help to promote survival signals. $CD40L^+$ T cells rosetting $CD40^+$ HRS cells seem to be crucial for neoplastic tumor cell growth [65]. Eosinophils and mast cells stimulate HRS cells through CD30-CD30L interaction, which leads to a constitutive NF-κB pathway activation [66].

IL-13 is an autocrine growth factor, and its receptor is expressed on the surface of HRS cells. The IL-13R activation eventually leads to STAT6 upregulation [42,43].

As a result of NF-κB activation, HRS cells secrete BAFF and a proliferation-inducing ligand (APRIL). Myeloid cells in the environment secrete BAFF and APRIL as well, thus providing paracrine signals to the tumor. HRS cells express transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) and B cell maturation antigen (BCMA), which is eventually engaged with BAFF and APRIL, thus helping the attenuation of HL expansion [67].

Tumor infiltrating T cells

HRS cells are surrounded mostly by T cells. These $CD4^+$ T cells are either Tregs or T helper (Th) cells [68]. TARC (CCL17), IL-13, CD80, CD86, and CD40-CD40L interactions all contribute to the formation of tumor infiltrating T cells. HRS cells also produce some immunosuppressive factors (IL-10, TGF-β, galectin-1, and prostaglandin E2) [69–71], whereas CD95/FAS ligand expressed by HRS cells stimulate the apoptosis of activated Th1 and $CD8^+$ T cells. Tregs also produce IL-10, which indirectly contributes to the protection against cytotoxic T and NK cells [63]. A reasonable fraction of Tregs can be characterized by the $CD4^+CD25^+FoxP3^+$ phenotype; they contribute to ineffective immune responses against HRS cells [72]. Another cell subset is characterized by the $CD4^+CD26^-$ phenotype, which identifies Tregs in an anergic condition. These cells do not express CCR3 that would link to RANTES and eotaxin from the microenvironment. $CD4^+CD26^-$ T cells are related to a specific set of T cells, producing IL-17 (Th17) [73]. PD-1 signaling has been reported to be upregulated in HL; HRS cells overexpress PD-1 ligand, which systemically arrests the exhausted T cell function by stimulating apoptosis of cytotoxic T cells and increases the number of immunosuppressive Tregs, resulting in tumor progression. Moreover, it has been shown that a high number of infiltrating PD-1–positive cells predicted a negative prognosis [24]. Immune escape of the tumor cells includes inhibiting of Th1, $CD8^+$, and NK cells and promoting Tregs and Th2 cells.

Considering these findings, we conclude that chemokines and cytokines secreted by HRS cells promote cell proliferation and contribute to the establishment of the appropriate microenvironment for HL (Fig. 3).

Prospective therapeutic solutions and possibilities of targeted therapy

The identification and targeting of particular pathways and receptors can lead to better treatment outcomes and to lower treatment-related toxicities. Figure 4 summarizes immune-treatment modalities of HL.

18-Fluoro-deoxyglucose positron emission tomography PET is currently one of the most reliable diagnostic procedures to identify early response to treatment and survival [74]. A low number of pathognomic HRS cells expresses low and alternating number of glucose-transporters and hexokinases involved in glucose metabolism [75]. A relation between FDG uptake and transporter expression of the tumor cells could not be found. FDG uptake is influenced much more by the microenvironment; therefore, current therapeutic decisions are based more on the metabolic activity of the background in PET positive cases than on the tumor cells [76]. This evidence provides a rationale for developing novel therapies that target the tumor-infiltrating background.

HRS cells do not express CD52, but the anti-CD52 antibody alemtuzumab can eliminate $CD52^+$ infiltrating T cells [77]. No specific trials have been conducted, although indirect evidence using reduced intensity conditioning allogenic stem cell transplantation shows promising results. The elimination of tumor-infiltrating T cells might improve

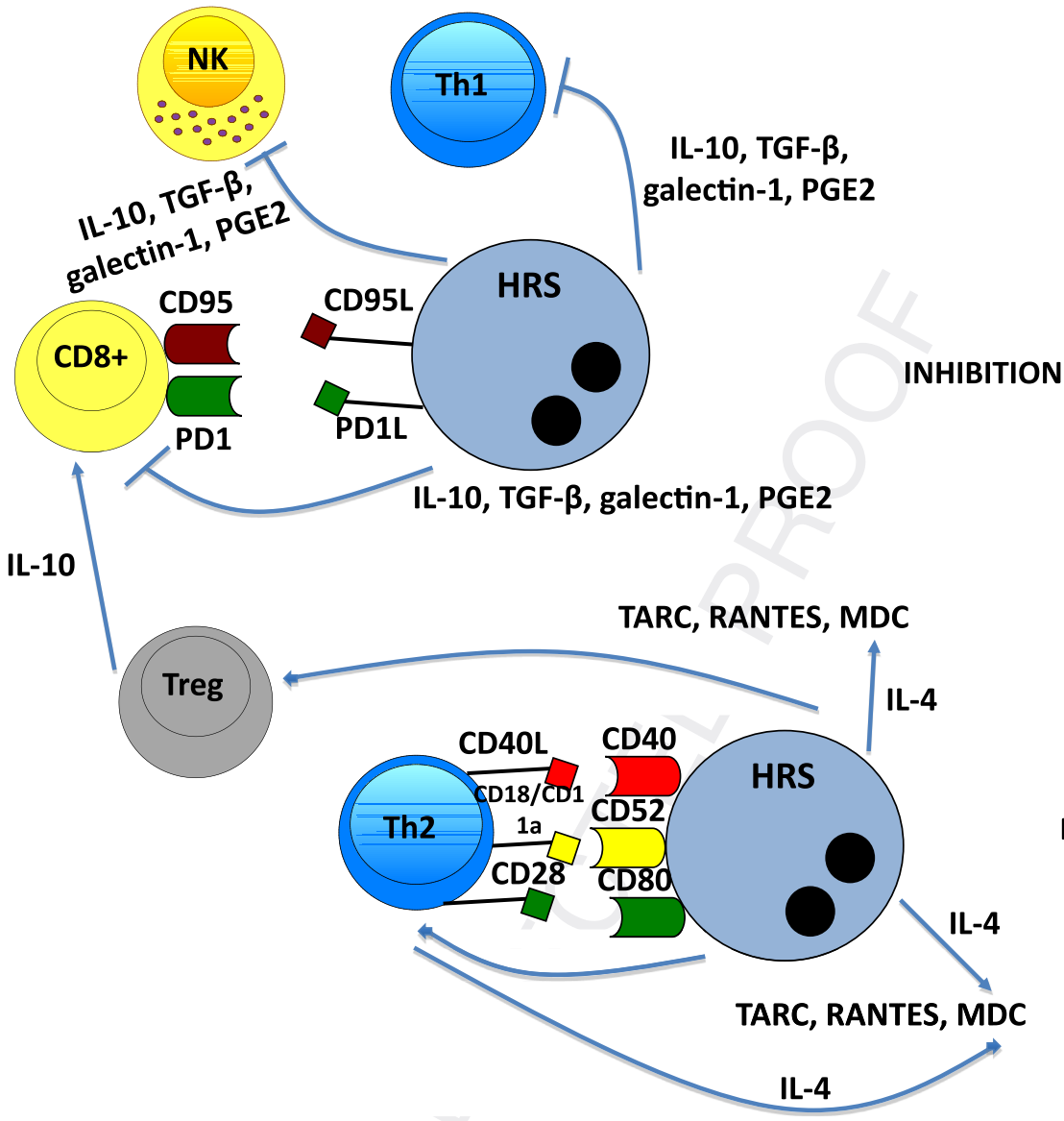

Figure 3. Interactions between HRS cells and surrounding cells; they contribute to immune escape through the inhibition of Th1, $CD8^+$, and NK cells and the promotion of Tregs and Th2 cells. HRS = Hodgkin and Reed-Sternberg cell; IL = interleukin; MDC = macrophage-derived chemokine; NK = natural killer cell; PD1 = programmed cell death protein 1; PD1L = programmed cell death protein 1 ligand; PGE2 = prostaglandin E2; RANTES = Regulated on Activation Normal T cell Expressed and Secreted; TARC = thymus and activation-regulated chemokine; TGF = tumor growth factor; Th1 = T helper 1 cell; Treg = regulatory T cell.

survival, and donor lymphocytes are beneficial to eradicate residual malignancy [78,79].

Rituximab, an anti-CD20 antibody, is already used in the treatment on non-Hodgkin lymphoma. Although HRS cells rarely express CD20 on their surface (20%–30%), there are several rationales for using rituximab to treat HL. The elimination of reactive B cells from the microenvironment would deprive malignant cells, and it would increase host immune response against HRS cells. Furthermore, HRS stem cells express CD20 [80]. Rituximab can sensitize patients to conventional chemotherapy. Based on these facts, a phase 2 study has been recently reported treating patients with advanced-stage HL with R-ABVD (rituximab, Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine). This study has had promising results [81]. Furthermore, a large comparative study (R-ABVD vs. ABVD) is currently enrolling patients.

Targeting CD30 has been recently reached its goal in HL. Brentuximab vedotin, an anti-CD30 antibody combined with an antitubulin agent (monomethyl auristatin E) was approved by the U.S. Food and Drug Administration (FDA) in 2011 and the European Medicines Agency in 2012 to treat $CD30^+$ lymphomas, HL, and anaplastic large-cell lymphoma [82]. Brentuximab links to the CD30

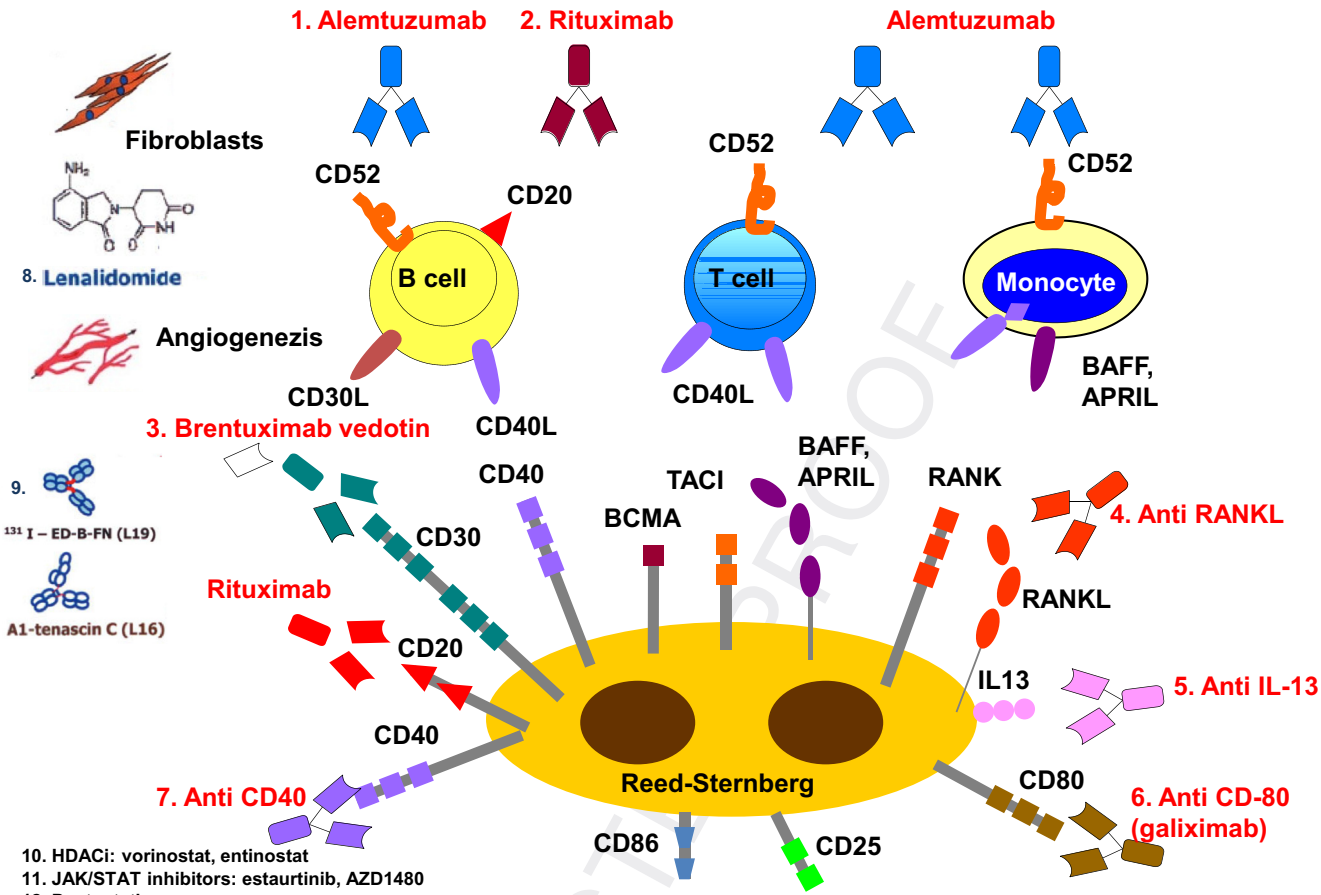

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Figure 4. Possible novel therapeutic solutions in Hodgkin's lymphoma. APRIL = a proliferation-inducing ligand; BAFF = B cell–activating factor of the TNF family; BCMA = B cell maturation antigen; CD30 = CD30 ligand; HDACi = histone deacetylase inhibitor; I^{131}-ED-B-FN = I^{131}-extradomain B of fibronectin; JAK/STAT = Janus kinase-signal transducers and activators of transcription; RANK = receptor activator of NF-κB; RANKL = receptor activator of NF-κB ligand; TACI = transmembrane activator and calcium modulator and cyclophilin ligand interactor.

antigen, which is expressed on the surface of the HRS cell, and it subsequently internalizes in a lysosome. Next, monomethyl auristatin E is released from the antibody conjugate and links to tubulin in the proliferating cell, thus inducing cell cycle arrest in the G2/M phase and eventually apoptosis [83]. Brentuximab can be beneficial in patients with relapsed or refractory HL after autologous stem cell transplantation [84], in patients with prolonged cycles of treatment, or as maintenance therapy in the same patient group [85]. In addition, the therapy can be used before allogenic stem cell transplantation (SCT) [86], before reduced intensity allogeneic SCT [87], in combination with ABVD or AVD in a frontline setting [88], and in transplant-naive patients who refused or were ineligible for transplant [89].

Epigenetic modulation (e.g., acetylation and deacetylation of histones) plays an important role in gene regulation, particularly in those involved in cell proliferation, survival, angiogenesis, and immunity [90–93]. Therefore, histone deacetylase inhibitors became attractive targets to treat HL. It has been demonstrated that in vitro vorinostat, in addition to its direct antitumor activity, alters cytokine balance and shifts toward a favorable Th1 composition through inhibiting STAT6 and decreasing TARC expression [94]. Vorinostat and romidepsin have been approved by the FDA in the treatment of relapsed cutaneous T cell lymphoma. Panobinostat seems to be the most promising compound among patients with relapsed or refractory HL after autologous stem cell transplantation [95].

The mechanism of action of the immune modulator lenalidomide is not fully understood; it could include direct cytotoxic effects, inhibition of angiogenesis, and alteration of the microenvironment of the HRS cells [96]. Inhibitors of the JAK/STAT pathway have been investigated mostly in vitro—specifically, AZD1480 [97] and lestaurtinib [98]. Targeted therapy against surface receptors of the HRS cells includes anti-RANK ligand antibody and anti-CD80 antibody (galiximab) [99]. Noncellular targets of the microenvironment include extra domain B of fibronectin (ED-B-FN), because it is expressed stronger on newly formed vessels in lymphoma-involved lymph nodes (I^{131}-ED-B-FN) [100]. L16-A1-tenascin C, which is specific for the extracellular A1 domain of tenascin C, could

be useful for targeting fibroblasts and other extracellular tissue components [101]. The adenosine deaminase pentostatin, commonly used in leukemia treatment, can be useful in HL because of its selective antiinflammatory features. It induces proinflammatory cytokine production, but it does not affect Tregs; therefore, its cytotoxic effect is not significant. Pentostatin also specifically targets $CD4^+CD26^-$ T cells in the microenvironment, leading to a decrease in numbers [102,103]. Gemcitabine is commonly used to treat relapsed HL; it inhibits immunosuppressing cells, thus modifying the immunologic properties of the microenvironment [104].

Novel findings on HRS cells and their microenvironment may provide further information about the pathogenesis of HL. The investigation of these factors and their interactions could provide new, targeted therapeutic solutions, both as single agents and in combination with conventional chemotherapy. We believe that it is possible to improve the survival of patients and provide better therapeutic outcome; therefore, refractory patients can achieve durable response and cure.

Take-home messages

- Survival of HRS cells includes several mechanisms that eventually lead to the development of HL.
- The most important aberrant signaling pathways are the constitutively upregulated NF-κB pathway, the JAK/STAT pathway, and the PI3K-Akt pathway.
- A wide range of cytokines and chemokines form a specific microenvironment in which effective immune response against HRS cells cannot occur.
- The most promising agent, the antibody-drug conjugate brentuximab vedotin, is approved for treating relapsed and refractory HL, and it is currently under investigation in combination with other treatment modalities

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