Hodgkin lymphoma

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Hodgkin lymphoma (HL), a B cell–derived cancer, is one of the most common lymphomas. In HL, the tumor cells — Hodgkin and Reed-Sternberg (HRS) cells — are usually very rare in the tissue. Although HRS cells are derived from mature B cells, they have largely lost their B cell phenotype and show a very unusual co-expression of markers of various hematopoietic cell types. HRS cells show deregulated activation of multiple signaling pathways and transcription factors. The activation of these pathways and factors is partly mediated through interactions of HRS cells with various other types of cells in the microenvironment, but also through genetic lesions. The transforming events involved in the pathogenesis of HL are only partly understood, but mutations affecting the NF-κB and JAK/STAT pathways are frequent. The dependency of HRS cells on microenvironmental interactions and deregulated signaling pathways may offer novel strategies for targeted therapies.

Introduction

Hodgkin lymphoma (HL) is one of the most frequent lymphomas in the Western world, with an annual incidence of about 3 cases per 100,000 persons. This lymphoid malignancy involves peripheral lymph nodes and can also affect organs such as liver, lung, and bone marrow. About 40% of patients suffer from constitutional symptoms ("B-symptoms"). Based on differences in the histological picture and the phenotype of the tumor cells, HL is subclassified into nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte-depleted, and nodular lymphocyte-predominant HL (NLPHL) (1). The first four subtypes are collectively called classical HL. The tumor cells of HL are very rare and usually account for only about 0.1%–2% of cells in the tissue (Figure 1). In classical HL, the malignant cells are referred to as Hodgkin and Reed-Sternberg (HRS) cells, and in NLPHL they are lymphocyte-predominant (LP) cells (1). These malignant cells are large, and in classical HL one may distinguish mononucleated Hodgkin cells and bi- or multinucleated Reed-Sternberg cells. In classical HL, the tumor cells are infected by EBV in about 40% of cases, which is of pathogenetic relevance.

Cellular origin of HRS and LP cells

Tumor cells usually retain key phenotypic features of the normal cells from which they originate. Therefore, the expression of various B cell markers by LP cells indicates their B cell derivation (2). Moreover, LP cells express markers typical for GC B cells, including BCL6, the key regulator of the GC B cell program (3, 4). GC B cells are antigen-activated mature B cells involved in T cell–dependent immune responses. A close relationship of LP cells to GC B cells is also indicated by the histology of NLPHL, in which LP cells grow in GC-like structures in association with follicular dendritic and follicular Th cells (1). The B cell derivation of LP cells and their monoclonality was proven by the detection of clonal Ig heavy- and light-chain variable (V) gene rearrangements in these cells (5, 6). The Ig V genes of LP cells carry somatic mutations, which are introduced during the GC reaction and hence are a hallmark of GC and post-GC B cells (5, 6). Several cases showed intraclonal diversity as a sign of ongoing hypermutation during clonal expansion (5, 6), further validating the GC B cell origin of LP cells. LP cells seem to be selected for expression of a functional B cell receptor (BCR) (7).

Previous immunophenotypic studies have not revealed the origin of HRS cells because they show a very unusual phenotype, with coexpression of markers for various hematopoietic lineages. HRS cells can express markers of T cells (CD3, NOTCH1, GATA3), cytotoxic cells (granzyme B, perforin), B cells (Pax5, CD20), dendritic cells (fascin, CCL17), NK cells (ID2), myeloid cells (CSFR1), and granulocytes (CD15) (3). HRS cells always express the activation marker CD30 (1).

The origin of HRS cells from mature B cells was clarified by the demonstration that they carry clonal and somatically mutated Ig heavy- and light-chain gene rearrangements (8–11). Surprisingly, about 25% of classical HL cases showed loss of function Ig gene mutations, including nonsense mutations, in their V genes (8–11). GC B cells acquiring such mutations normally rapidly undergo apoptosis. Thus, critical steps in HL pathogenesis most likely happen in the GC to enable the crippled HRS cell precursors to escape apoptosis. As many other unfavorable mutations are not easily identifiable, HRS cells as a rule may derive from GC B cells with unfavorable Ig gene mutations, and hence from apoptosis-prone GC B cells (9). It should, however, be stressed that HL development (like tumor development in general) is a multistep process, so that some transforming events might be carried by HRS precursor cells before they enter the GC reaction, and final transforming events might occur after the cells have left the GC.

Because of the expression of T cell markers by HRS cells in a fraction of classical HL, several such cases were studied for a potential T cell derivation, and some of them indeed turned out to carry T cell receptor gene rearrangements (12, 13). Thus, in rare instances lymphomas diagnosed as HL have a T cell origin and represent rare variants of classical HL.

The relationships between HRS cells and putative precursor or stem cells

HRS cell clones are always composed of mixtures of mononuclear Hodgkin and multinuclear Reed-Sternberg cells. The same holds true for the few existing HL cell lines (14–16). Cell fusion does not play a role in the generation of the Reed-Sternberg cells (17), rather, Reed-Sternberg cells derive from Hodgkin cells through a process resembling endomitosis, i.e., nuclear division without cellular division (14, 15). Hodgkin cells of HL cell lines give rise to new mixtures of HRS cells, but Reed-Sternberg cells are generally unable to undergo further proliferation (14).

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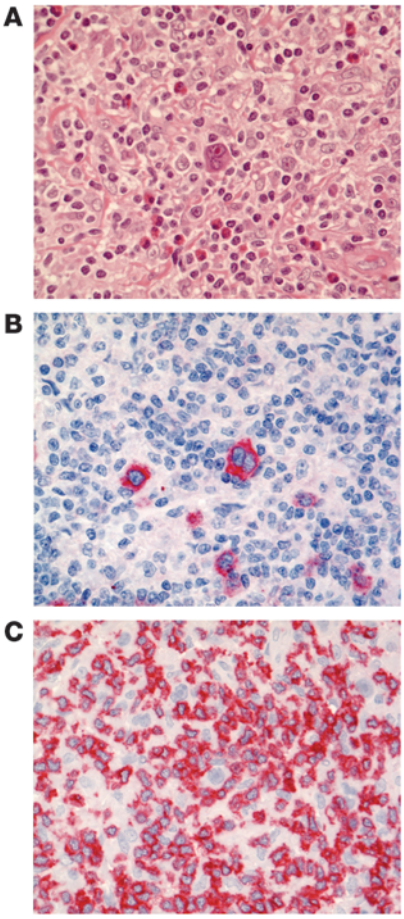

Figure 1
Morphology and immunohistochemical features of HRS cells. Typical histological and immunohistochemical picture in classical HL. (**A**) H&E staining of a case of mixed cellularity type HL. A binucleated HRS cell is visible in the middle of the image, surrounded by histiocytes, lymphocytes, and eosinophilic granulocytes. (**B**) CD30 immunostaining (red) showing some large and small CD30-positive HRS cells. A binucleated HRS cell is visible in the middle of the image. HRS cells consistently express the TNF receptor family member CD30, so that immunostaining for CD30 is often used in the diagnosis of HL. (**C**) CD3 immunostaining showing large amounts of T cells that completely or partly surround HRS cells. Rosette forming T cells around a HRS cell in the middle of the image.

A recent study reported the detection of putative HRS stem cells among $CD20^+BCR^+CD30^-$ B cells in the peripheral blood and lymph nodes of patients with HL (18). However, that work was criticized based on technical concerns, as no clear evidence was provided for a clonal relationship between the HRS cells and their putative stem cells (19), and further studies are needed to clarify this issue. Further complicating the question was the detection of side population (SP) cells in several HL cell lines (20, 21). SP cells are defined by negativity for Hoechst dye 33342 staining, due to expression of ABC transporters, which expel the dye from the cell (22). As such transporters also export various chemotherapeutic drugs, SP cells are often chemoresistant. Moreover, these cells share features with cancer stem cells (22). The rare SP cells in HL cell lines (about 0.5% of the HRS cells) were found among the mononuclear Hodgkin cells, were $CD30^+$ and $CD20^-$, showed chemoresistance, and could reestablish HRS cell clones upon subcloning (20, 21). However, SP cells were not detected in all HL cell lines (20, 21), which argues against a general role of these cells in the maintenance of HRS cell clones.

The lost B cell phenotype of HRS cells

Although HRS cells derive from mature B cells, they show a global downregulation of the B cell gene expression program (23–25), which is unique among B cell lymphomas in its extent. The initial event that causes this extensive reprogramming is unknown, but several contributing factors have been identified. HRS cells downregulate expression of numerous B cell transcription factors, such as OCT2, PU.1, and BOB1, likely causing downregulation of their respective target genes (24, 26). B cell–specific genes are also silenced by epigenetic mechanisms in HL (27, 28). Furthermore, HRS cells aberrantly express master regulators of other hematopoietic cell lineages that suppress B cell genes, in particular the T cell factor Notch1 and the NK cell factor ID2 (29–31). ID2, as well as activated B cell factor 1, which is also highly expressed in HRS cells, directly inhibit the important B cell transcription factor E2A (30–32). The transcription factors STAT5A and STAT5B are also involved in the downregulation of B cell genes in HRS cells (33).

Expression of multiple key transcription factors of HSCs may further contribute to the peculiar phenotype of HRS cells. HRS cells express multiple members of the polycomb group family 1 and 2 complexes (34–36); although some of these are expressed in normal B cells, their co-expression is not seen in normal B cells. As polycomb group factors can downregulate B cell genes, and as HSC and lymphoid progenitors show promiscuous coexpression of markers of distinct hematopoietic cell types (37–39), these factors may play a role in the downregulation of B cell genes and the expression of markers of other lineages in HRS cells.

Transforming events that are as yet unknown may contribute to the consistent downregulation of the B cell program in HRS cells. Moreover, this specific feature may be directly linked to the fact that HRS cells are derived from pre-apoptotic GC B cells. It is also possible that, for GC B cells with low-affinity BCRs or complete loss of BCR expression, the strong selection pressure to undergo apoptosis may select for loss of the B cell identity, so that these "failed" B cells escape the apoptosis (23).

Role of EBV in HL pathogenesis

In about 40% of classical HL in the Western world, and in more than 90% of pediatric cases of HL in Central America, HRS cells are latently infected by EBV, a γ-herpes virus (40). HRS cells are clonally infected, suggesting that EBV infection is an early event in HL pathogenesis (41). EBV has several types of latency, and in HRS cells latency II is observed, meaning that EBV-encoded genes EBV nuclear antigen 1 (*EBNA1*), latent membrane protein 1 (*LMP1*), and *LMP2a* are expressed. EBNA1 is essential for the replication of the episomal EBV genome in proliferating cells. LMP1 mimics an active CD40 receptor, a central costimulatory molecule for B cells (42). LMP2a carries a cytoplasmic motif that resembles the signaling module of the BCR. As CD40 and BCR signaling are main regulators of survival and selection of GC B cells, it was speculated that LMP1 and LMP2a can rescue BCR-deficient B cells from apop-

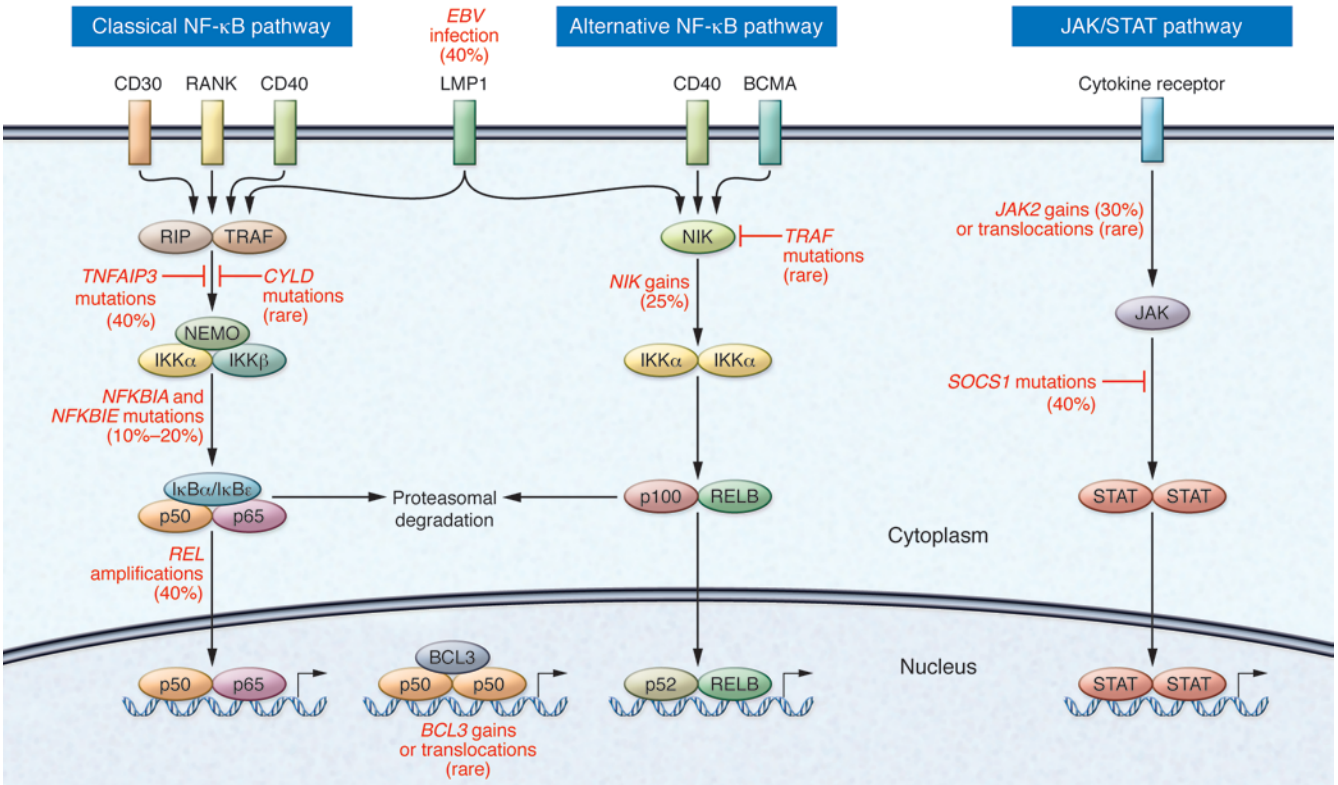

Figure 2

NF-κB and JAK/STAT activity in HRS cells. In the canonical NF-κB signaling pathway, stimulation of various receptors, which complex with TNF receptor–associated factors (TRAFs) and the receptor interacting protein (RIP), leads to activation of the IKK complex, targeting the NF-κB inhibitors IκBα and IκB for ubiquitination and proteasomal degradation. As a consequence, the NF-κB transcription factors translocate into the nucleus, where they activate multiple genes. TNFAIP3 and CYLD are further negative regulators of NF-κB signaling. In the alternative NF-κB pathway, activation of receptors such as CD40 and TACI causes stimulation of the kinase NIK (MAP3K14), which then activates an IKKα complex. NIK activity is negatively regulated by TRAF3. Activated IKKα processes p100 to p52, which translocates as p52/RELB heterodimers into the nucleus. HRS cells have constitutive activity of both NF-κB pathways. Activation of CD40, RANK, BCMA, and TACI through ligands expressed on lymphoma-infiltrating cells likely contributes to this activity. Numerous genetic lesions and signaling through the EBV-encoded latent membrane protein 1 in EBV-positive cases of HL play important roles in the deregulated NF-κB activity. The JAK/STAT pathway is the main signaling pathway for cytokines. In HRS cells, STAT3, -5, and -6 are constitutively active. In addition to activation of cytokine receptors, such as the IL-13 receptor and the IL-21 receptor, activation of this pathway is mediated by genomic gains or translocations of the *JAK2* gene and frequent inactivating mutations of the *SOCS1* gene. The frequency of genetic lesions and viral infections affecting NF-κB or STAT activity in HRS cells is indicated as percentages. Adapted with permission from *Nature Reviews Cancer* (2).

tosis by replacing these signals (43). Indeed, EBV-immortalized B cell lines can be established from BCR-deficient GC B cells (44, 45). This suggests that EBV might play a major role as an initial event in HL pathogenesis by rescuing crippled GC B cells from apoptosis. Interestingly, all HL with null BCR mutations are EBV positive, strongly supporting an essential role of EBV in the pathogenesis of such lymphomas (46). However, the function of LMP2a in the established HRS cell clone is uncertain because most components of BCR signaling are downregulated.

Somatic genetic lesions and germline alterations

HRS cells usually show multiple chromosomal abnormalities and are aneuploid (47). In addition to clonal abnormalities, multiple subclonal aberrations are found, indicating chromosomal instability of the tumor (47). Chromosomal translocations involving the Ig loci, a hallmark of many B cell non-Hodgkin lymphomas, were detected in about 20% of classical HLs (48). Some of them involve the known oncogenes *BCL1*, *BCL2*, *BCL3*, *BCL6*, *REL*, and *MYC*, but for most cases the partner genes are unknown (48, 49). Considering the general silencing of the Ig loci in HRS cells, it is intriguing to ask whether oncogenes linked to the Ig loci through translocations show deregulated expression in the established HRS cell clone. Alternatively, these translocations might be important during early stages of HL development, when the HRS precursor cells still have a B cell phenotype, but become irrelevant later when additional transforming events are acquired.

The detection of constitutive activity of the transcription factor NF-κB in HRS cells (50) prompted numerous studies to search for gene mutations that contribute to this activity (Figure 2). Genomic gains of *REL*, encoding an NF-κB factor, are present in about 30% of cases (51, 52). The positive regulator of the alternative NF-κB pathway, *NIK*, is also frequently affected by genomic gains in HRS cells (53, 54). Mutations in the genes of the NF-κB inhibitors IκBα and IκBε were found in about 10%–20% of cases (55–58). A20, which is encoded by the *TNFAIP3* gene, and which is an inhibitor of NF-κB activity, is

inactivated in about 40% of classical HL cases (59, 60). Notably, most *TNFAIP3*-mutated HLs are EBV negative, suggesting that A20 inactivation and EBV infection are largely mutually exclusive transforming events in classical HL (60). *TNFAIP3* reconstitution in A20-deficient HL cell lines impairs survival of the cells, establishing *TNFAIP3* as a tumor suppressor gene (60). Other regulators of NF-κB, i.e., *BCL3* and the tumor suppressor genes *CYLD* and *TRAF3* are rarely mutated in HRS cells (53, 61, 62). Hence, multiple genetic lesions in the NF-κB pathway contribute to its dysregulation in HRS cells. Remarkably, HL cell lines often carry mutations of several NF-κB regulators, indicating that HRS cells may require distortions of more than one factor of this pathway to obtain the strong NF-κB activity that is essential for their survival and proliferation.

Another signaling pathway activated in HRS cells for which genetic lesions have been found is the JAK/STAT pathway (Figure 2). *JAK2* shows chromosomal gains in about 20% of HL, and in rare cases is translocated (63, 64). JAK2 functions in HRS cells as an activator of STAT signaling and is also involved in epigenetic regulation, as it can phosphorylate histone H3 (65). SOCS1, a main inhibitor of STAT activity, is affected by inactivating mutations in about 40% of classical HL cases (66).

The genomic region on chromosome 9p24, which shows gains in HRS cells and in which the *JAK2* gene is located, also encompasses the gene *JMJD2C* and the programmed death 1 ligand (PD-1L) genes *PD-L1* and *PD-L2* (65, 67). PD-1Ls can inhibit PD-1–expressing T cells and thereby may contribute to an immunosuppressive microenvironment in HL (67). *JMJD2C* encodes a histone demethylase, and downregulation of its expression in HL cell lines is toxic (65). Thus, a single genetic event — gains of chromosomal region 9p24 — may contribute to HL pathogenesis by the concurrent deregulation of at least four genes.

Translocations involving the MHC class II transactivator gene *CIITA* have been detected in about 15% of classical HL cases (68). These translocations seem to impair CIITA function and hence dampen MHC class II expression. Downregulation of MHC class II expression by HRS cells is an adverse prognostic factor (69), but the reasons for this association are unclear. Other genes that were examined for mutations in HRS cells, including *TP53*, *CD95*, and *ATM*, were only rarely mutated (3).

By comparison, little is known about genetic lesions in LP cells. Translocations of the *BCL6* protooncogene are found in about 30% of NLPHL cases (70). *SOCS1* is inactivated in LP cells by somatic mutations in 40% of cases (71). Although LP cells show strong NF-κB activity (72), genetic lesions of *TNFAIP3* and *NFKBIA* are rare, if they occur at all, in these cells (73). As LP cells also appear to lack *REL* gains and are not infected with EBV (40), the mechanisms for NF-κB activation in HRS and LP cells seem to be strikingly different.

Several recent studies addressed the issue of whether germline alterations or polymorphisms contribute to HL pathogenesis; indeed, HL is one of the lymphomas with the strongest familial association (74). *KLHDC8B* was found as a constitutional translocation partner in the germline of a family with several HL patients (75). Moreover, a gene polymorphism causing reduced KLHDC8B translation occurs at increased frequency in other families with HL. The function of KLHDC8B is largely unknown, but its downregulation in a cell line results in increased frequency of binucleated cells (75). In another study, a germline frameshift mutation of the *NPAT* gene was found in a family with four members affected by NLPHL (76). Moreover, a replacement mutation in *NPAT* was observed at significantly increased frequency in sporadic NLPHL and classical HL patients than in healthy controls. The consequences of *NPAT* mutations in HRS cells remain to be clarified. A genome-wide association study of HL identified risk loci at 2p16.1, 8q24.21, and 10p14 (77). Although the odds ratios are relatively low, it is remarkable that the risk loci involve *REL* (discussed above), *PVT1* (involved in translocations in lymphoid malignancies), and *GATA3* (a T cell transcription factor that shows aberrant expression and activity in HRS cells) (78).

Deregulated signaling pathways and transcription factors

As discussed above, HRS cells show constitutive activity of the NF-κB and the JAK/STAT signaling pathways. These two pathways are usually only transiently activated in B lymphocytes. Also, as mentioned, HRS cells show constitutive activity of polycomb group proteins and of Notch1. Activation of Notch1 is mediated by its ligand Jagged1, which is expressed by cells in the HL microenvironment (79). Moreover, HRS cells have downregulated the Notch1 inhibitor Deltex (29).

Several additional signaling pathways show deregulated activity in HRS cells. These include the PI3K/AKT pathway and the MAPK/ERK pathway (80, 81). Inhibition of these pathways in HL cell lines has apoptotic and/or anti-proliferative consequences (80, 81), suggesting their critical role in HRS cell survival and proliferation. HRS cells also show aberrant expression and activity of multiple receptor tyrosine kinases that are not normally expressed by B cells (82, 83). Receptor tyrosine kinases have multiple functions in the regulation of cell growth, survival, and differentiation. The aberrant expression of the myeloid cell receptor and protooncogene CSF1R in HRS cells is mediated through activation of an endogenous long terminal repeat located upstream of the *CSF1R* gene (83).

Deregulated microRNA expression in HRS cells

MicroRNAs (miRNAs) are small, non-coding RNAs that bind to complementary sequences in the 3′ end of mRNAs and have multiple important physiological functions. Binding of a miRNA to an mRNA induces either degradation of the mRNA or translational silencing. Molecular studies have revealed a number of miRNAs with deregulated expression in HRS cells as compared with normal B cells (84, 85). For most of these, it is unclear whether their deregulated expression is of pathophysiological relevance. However, the diminished expression of miR135a appears to contribute to high expression of its target gene JAK2 (86), and the increased expression of members of the miR17/106b seed family negatively regulates p21, an inhibitor of cell cycle progression (87). Moreover, miR155, which is highly expressed in HRS cells, has oncogenic properties in B lineage cells (88), pointing to a pathogenic role.

Microenvironmental interactions

The microenvironment that surrounds the malignant cells of HL is a critical determinant of its initiation and progression. HRS cells interact with $CD4^+$ and $CD8^+$ T cells, B cells, plasma cells, macrophages, mast cells, dendritic cells, neutrophils, eosinophils, and fibroblasts and indeed actively attract them via the secretion of cytokines and chemokines (Figure 3). The microenvironment in HL is unique among lymphomas both in the complexity of cell types involved and its size, with the non-tumor cells often accounting for 99% of cells in the tumor.

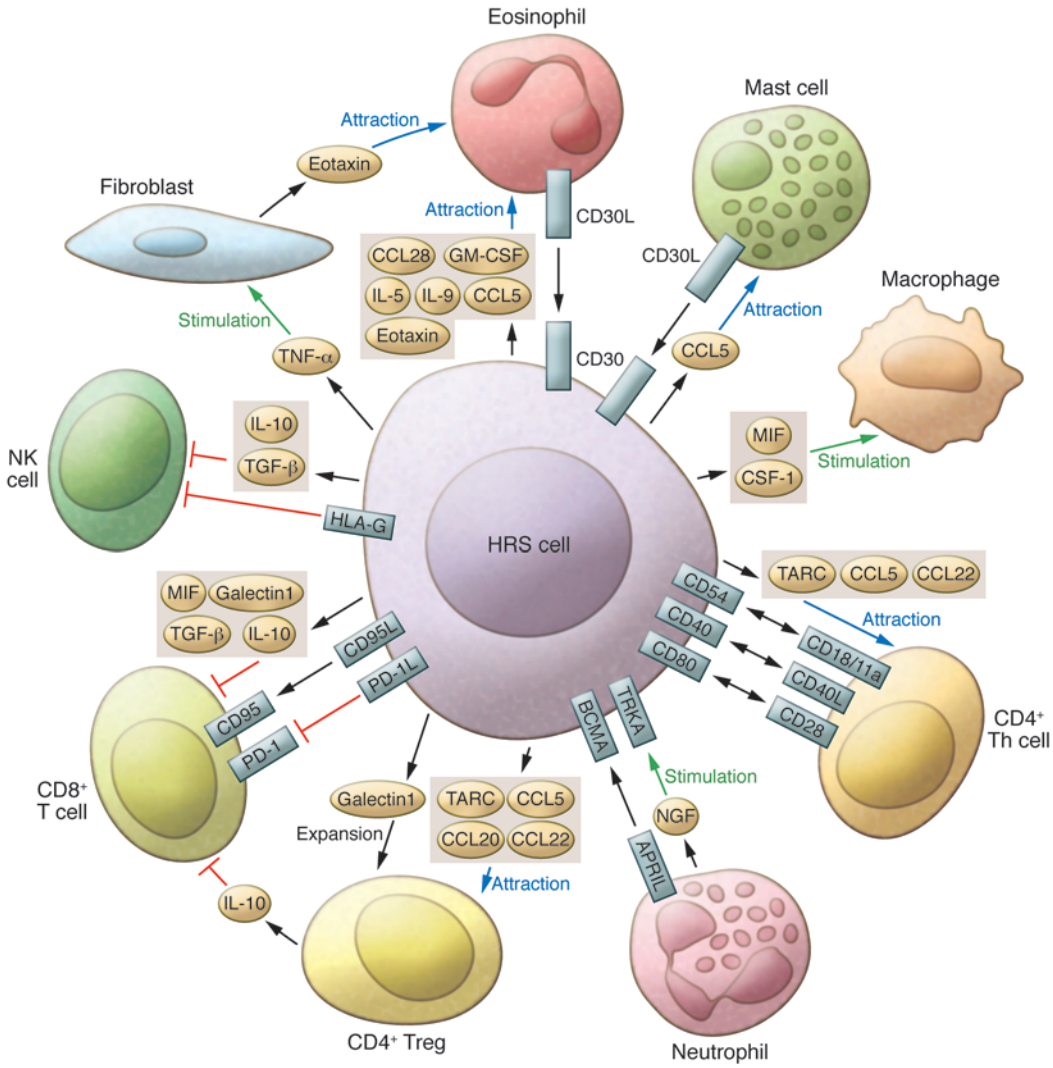

Figure 3

Cellular interactions in the HL microenvironment. HRS cells orchestrate the infiltration and activation of multiple cell types into the lymphoma microenvironment by secretion of cytokines and chemokines. Eosinophils and mast cells may stimulate HRS cells through CD30-CD30L interactions, whereas neutrophils may stimulate HRS cells through APRIL-BCMA interactions and the secretion of nerve growth factor (NGF), which binds to the receptor tyrosine kinase TRKA on HRS cells. The cellular interactions between CD4+ Th cells likely involve adhesion molecules (CD54-CD18/11a) and key molecules of B cell–T cell interaction, i.e., CD40-CD40L and CD80-CD28. Cytotoxic T cells and NK cells are inhibited through Tregs by secretion of IL-10, and perhaps additional mechanisms, and directly by the HRS cells though secretion of immunosuppressive mediators (IL-10, TGF-β). Cytotoxic T cells are furthermore inhibited by galectin1, secreted by HRS cells, and expression of PD-1L by HRS cells. CD95 ligand–expressing HRS cells may induce apoptosis of CD95+ cytotoxic T cells. Macrophage infiltration is of prognostic relevance, but the interactions between HRS cells and macrophages are only partly understood. Adapted with permission from *Nature Reviews Cancer* (2).

The attraction of many of these cells and their interaction with HRS cells is presumably a very important factor for the survival and proliferation of HRS cells. Indeed, HRS cells are usually not found in the peripheral blood, and it is very difficult to grow HRS cells in culture or in immunodeficient mice (89, 90). Numerous interactions can be envisioned. For example, CD4+ Th cells, which are often in close contact with HRS cells, express CD40L and CD28, the ligands for CD40 and CD80/CD86, which are expressed by HRS cells (91, 92). CD40 stimulation leads to NF-κB activation, and signaling through CD80 is an important costimulatory signal in B cell–T cell interaction. Other factors and interactions help to rescue HRS cells from an immunological attack, including inhibition of cytotoxic T cells by Tregs (93). Cytotoxic T cells are also inhibited through expression of the PD1 and CD95 ligands and secretion of IL-10, TGF-β, and galectin1 by the HRS cells (94–97).

Current and developing treatment options

With the introduction of multi-agent chemotherapy and improved radiation techniques, the prognosis of patients with HL has substantially improved. Depending on stage and clinical risk factors, 65%–90% of patients can be rendered disease-free after five years (98). Patients are usually divided into early

Table 1
New antibodies and molecules: clinical trials in HL

Drug name	Class	Company	Phase	Reference
Brentuximab vedotin (SGN-35; ADCETRIS)	Anti-CD30 monoclonal antibody	Seattle Genetics, Takeda	I–III	114, 115
AFM13	Anti-CD16/CD30 bispecific antibody	Affimed	I	116
Ofatumumab (ARZERRA)	Anti-CD20 monoclonal antibody	GlaxoSmithKline	II	117
Lenalidomide (Revlimid)	Immunomodulatory drug	Celgene	II	118
Resminostat (4SC-201)	HDAC inhibitor	4SC	I	119
4SC-202	HDAC inhibitor	4SC	I	120
Everolimus (RAD001; Affinitor)	mTOR inhibitor	Novartis Pharmaceuticals	II	121

favorable, early unfavorable, and advanced-stage risk groups. For early favorable patients with classical HL, two cycles of ABVD chemotherapy followed by involved field radiotherapy (IFRT) with 20 Gy are considered standard of care (99). Early unfavorable patients usually receive four cycles of ABVD chemotherapy followed by IFRT with 30 Gy (100, 101). Treatment of patients with advanced-stage HL is more controversial: six to eight cycles of ABVD have been regarded standard of care for many years (102, 103), but this regimen is being challenged by the more effective but also more toxic $BEACOPP_{escalated}$ approach (99). Direct comparisons between ABVD and $BEACOPP_{escalated}$ confirmed that better tumor control is achieved with $BEACOPP_{escalated}$ but failed to prove differences in overall survival due to the low number of patients included (104, 105). The HD15 trial of the German Hodgkin Study Group (GHSG) demonstrated that six cycles of $BEACOPP_{escalated}$ are less toxic and more effective than the old standard of eight cycles and thus represent the new GHSG standard of care (106). In stage IA NLPHL, patients are usually treated with IFRT alone, whereas classical HL is treated with combined modality. All other NLPHL patients receive the same treatment as those with classical HL (107). In addition, anti-CD20 monoclonal antibodies have been shown to be effective when used as single agents in relapsed NLPHL patients (108, 109).

The current goal in the treatment of HL patients is to reduce toxicity but maintain efficacy. The rationale for attempting dose reduction is the high risk of acute and long-term toxicity including secondary neoplasia, organ toxicity to heart and lung, fatigue, and infertility (110). Based on retrospective, nonrandomized studies, positron emission tomography is currently being explored to identify high-risk patients early in the course of chemotherapy (111, 112).

Another approach to reduce toxicity of treatment while maintaining efficacy is the development of less toxic, targeted drugs. Here, the CD30 antigen has been a focus of interest due to the strong expression on HRS cells. Several monoclonal antibodies targeting CD30 have been evaluated in various formats (113). Recently, a new antibody drug conjugate targeting CD30, brentuximab vedotin, demonstrated very good efficacy and tolerability in a phase I study (114). Brentuximab vedotin was subsequently registered for the treatment of relapsed HL and $CD30^+$ anaplastic large cell lymphoma. A number of other promising new drugs targeting pathways active in HL are currently being evaluated in clinical trials (Table 1) and might further improve the treatment of HL.

Conclusions and perspective

Whereas most lymphomas, including NLPHL, retain key features of their cell of origin, the GC B cell–derived HRS cells of classical HL are unique in the extent to which they have downregulated their B cell–specific gene expression program and have gained expression of numerous markers typical for other hematopoietic cell types. Perhaps this reprogramming is an essential strategy for the survival of HRS cells as failed GC B cells unable to express high-affinity BCRs. The genetic lesions involved in the pathogenesis of HL are only partly understood and appear to be heterogeneous. However, transforming events are frequent in members of the NF-κB and JAK/STAT signaling pathways, suggesting that they have a critical role in HL development. Numerous other signaling pathways and transcription factors also show deregulated activity in HRS cells. The activation of these pathways is presumably to a large extent mediated by interactions of HRS cells with other cells in their microenvironment. Indeed, HRS cells actively attract many cells into the lymphoma tissue, and thereby orchestrate the typical inflammatory microenvironment. This environment probably promotes the survival of HRS cells and helps them to escape attack from cytotoxic T or NK cells. Considering the dependency of HRS cells on multiple deregulated signaling pathways and numerous cellular interactions, these features may offer novel strategies for targeted therapies, e.g., by specific inhibition of signaling pathways or the interaction of HRS cells with other cells in the lymphoma tissue.

Note added in proof. A recent global gene expression study of isolated HRS cells and other normal and malignant B cells revealed, among other findings, that EBV infection has surprisingly little specific influence on gene expression of HRS cells, that the lost B cell phenotype of HRS cells is not linked to acquisition of a plasma cell–like gene expression program, and that HRS cells and HL cell lines differ extensively in gene expression (122).

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