Molecular Pathogenesis of Hodgkin’s Lymphoma

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ABSTRACT

According to the WHO classification, Hodgkin’s lymphoma (HL) is subdivided into a classical variant and a nodular lymphocyte predominant variant which are characterized by the presence of Hodgkin’s and Reed-Sternberg (H-RS) cells or lymphocytic and histiocytic (L&H) cells, respectively. This article reviews genetic characteristics and transcriptional changes of H-RS and L&H cells, including recent knowledge about transforming mechanisms and signaling pathways that contribute to the antiapoptotic phenotype displayed by H-RS and L&H cells. We also discuss major cellular and molecular mediators contributing to the establishment and maintenance of a reactive background in HL-affected tissues. We believe that an in-depth understanding of the pathogenesis of HL will eventually lead to the development of novel biologically based therapeutic strategies in the near future.

INTRODUCTION

Hodgkin’s lymphoma (HL) is characterized by the presence of giant multinuclear Hodgkin’s and Reed-Sternberg (H-RS) cells in the classical variant of HL (cHL), while lymphocytic and histiocytic (L&H) cells are pathognomonic for the nodular lymphocyte predominant HL (nLPHL). According to the WHO classification, which was presented in 1999, four subtypes of cHL can be subdivided: nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte-rich cHL. In these subtypes, the malignant cells are surrounded by a variable degree by reactive nonclonal hematopoietic cells that form a complex network in tissues affected by HL. It now becomes evident that signaling is not unidirectional but bi-directional, in that other cells in the lymphoma microenvironment both support survival of neoplastic cells and are modulated themselves by the malignant cells.

This article reviews genetic characteristics and transcriptional changes of H-RS and L&H cells, including recent knowledge about transforming mechanisms and signaling pathways that contribute to the anti-apoptotic phenotype displayed by H-RS and L&H cells. We also discuss major cellular and molecular mediators contributing to the establishment and maintenance of a reactive background in HL-affected tissues. We believe that an in-depth understanding of the pathogenesis of HL will eventually lead to the development of novel biologically based therapeutic strategies in the near future.

MALIGNANT CELLS IN HL

The Cell of Origin

The cellular origin of the H-RS cells in classical HL was unclear for a long time. This was mainly due to the scarcity of these cells in the tumor tissue, which hampered their molecular analysis, and to the unusual immunophenotype of the H-RS cells, which does not resemble any normal cell in the hematopoietic system. Indeed, H-RS cells show coexpression of markers normally expressed by different cell types, such as dendritic cells (fascin, the chemokine thymus- and activation-regulated chemokine [TARC]), granulocytes and monocytes (CD15), B cells (Pax-5), plasma cells (MUM-1, CD138) and activated T-cells (CD25).
lymphocytes (CD30). A few other B-cell markers (such as CD20) and T cell markers (CD3, granzyme B and perforin) were detected also in a fraction of cases. The origin of the H-RS cells was finally established when single H-RS cells, microdissected from immunostained tissue sections, were analyzed for rearranged immunoglobulin (Ig) variable (VAR) region gene rearrangements. Such rearrangements occur only in B lineage cells and hence represent a molecular marker for B cells. VAR gene rearrangements were found in nearly all cases of cHL, demonstrating that these cells derive from B cells. With few exceptions, the rearrangements were somatically mutated. Since the process of somatic hypermutation, which introduces mutations into rearranged VAR genes, is specific to germinal center (GC) B cells, this indicated that H-RS cells derive from mature B cells that had participated in immune responses involving the GC. Surprisingly, in about 25% of cases mutations were identified that destroyed the functionality of the VAR gene rearrangements originally expressed. Normally, GC B cells acquiring such destructive mutations would quickly undergo apoptosis. Since only a fraction of disadvantageous mutations that result in apoptosis of GC B cells can be easily identified (eg, stop codons and deletions causing frameshifts), the process of somatic hypermutation would quickly destroy the functionality of the VAR gene rearrangements.

The GC B-cell origin of H-RS cells was further supported from the analysis of rare combinations of classical HL and B-cell non-Hodgkin’s lymphoma in the same patients. In most of these composite lymphomas it was determined that the two lymphomas were clonally related, and the pattern of somatic VAR gene mutations indicated that these lymphomas often derive from distinct members of a proliferating and mutating GC B-cell clone.

The expression of T-cell markers by H-RS cells in some cases prompted the analysis of such cases for a potential T-cell derivation. Indeed, a few cases of classical HL with a T-cell derivation were identified, accounting for 1% to 2% of classic HL. Notably, most cases expressing T-cell–specific molecules nevertheless were B cell–derived, showing that the expression of B- or T-cell markers by H-RS cells is not informative regarding their cellular origin.

In nLPHL, the suspected tumor cells, the L&H cells, show an immunophenotype that indicates their B-cell origin. The cells express general B-cell markers such as CD20 and CD79a, the B cell–specific transcription factors Pax-5, Oct-2, and Bob-1, and Ig expression was detected both at the RNA and protein level. Moreover, L&H cells also express the GC B cell–specific transcription factor BCL-6, and the enzyme activation-induced cytidine deaminase, which is expressed mainly by GC B cells.

All these features strongly suggested a mature B-cell derivation of the L&H cells, possibly a GC B cell. This derivation was confirmed when single, microdissected L&H cells were analyzed for Ig gene rearrangements. L&H cells were found to consistently carry clonal and somatically mutated VAR gene rearrangements. Interestingly, a fraction of cases showed intracranial VAR gene diversity, suggesting somatic hypermutation activity in the expanding L&H clones. Since somatic hypermutation is a hallmark of GC B cells, this finding further supports the concept that L&H cells represent transformed GC B cells.

### Loss of B-Cell Phenotype in H-RS Cells

As described in the preceding paragraphs, immunophenotypic studies indicated that H-RS cells usually lack expression of molecules that are characteristic for B-lineage cells. Gene expression profiling studies of HL cell lines substantially extended this finding by showing that there is a global downregulation of the B-cell phenotype in H-RS cells. This downregulation affects surface molecules (CD22, CD52), components of several

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**Table 1. Genotypic and Phenotypic Features of H-RS and L&H Cells Relating to Their B-Cell Origin**

<table>
<thead>
<tr>
<th>Feature</th>
<th>H-RS Cells of cHL</th>
<th>L&amp;H Cells of nLPHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatically mutated Ig VAR genes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Presence of destructive somatic mutations*</td>
<td>Yes (25% of cases)</td>
<td>No</td>
</tr>
<tr>
<td>Ongoing somatic mutation</td>
<td>No</td>
<td>Often</td>
</tr>
<tr>
<td>Proposed cellular origin</td>
<td>Pre-apoptotic GC B cell</td>
<td>Antigen-selected, mutating GC B cell</td>
</tr>
<tr>
<td>Expression of a BCR</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Expression of B-cell-specific transcription factors (Oct-2, Bob1, Pu1)</td>
<td>Very rarely</td>
<td>Yes</td>
</tr>
<tr>
<td>Expression of B-lineage commitment and maintenance factor Pax-5</td>
<td>Yes (low level)</td>
<td>Yes</td>
</tr>
<tr>
<td>Expression of B-cell surface markers (CD20, CD79)</td>
<td>Very rarely</td>
<td>Yes</td>
</tr>
<tr>
<td>Expression of GC B-cell markers (bcl-6, activation-induced cytidine deaminase)</td>
<td>Rarely</td>
<td>Yes</td>
</tr>
<tr>
<td>Expression of plasma cell markers (Mum-1, CD138)</td>
<td>Often</td>
<td>No</td>
</tr>
<tr>
<td>Expression of molecules involved in antigen presentation (MHC class II, CD40, CD80, CD86)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Expression of markers for non-B cells (eg, TARC, granzyme B, perforin)</td>
<td>Occasionally/ frequently</td>
<td>No</td>
</tr>
<tr>
<td>Rare cases with a T-cell origin</td>
<td>Yes (&lt; 2% of cases)</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: H-RS, Hodgkin’s and Reed-Sternberg; L&H, lymphocytic and histocytic; cHL, classic variant of Hodgkin’s lymphoma; nLPHL, nodular lymphocyte predominant HL; Ig, immunoglobulin; VAR, variable; GC, germinal center; BCR, B-cell receptor; MHC, major histocompatibility complex; TARC, thymus and activation-regulated chemokine.*This refers to obviously crippling mutations that can be easily identified (eg, stop codons and deletions causing frameshifts).
signaling pathways (eg, Syk, Blk), and transcription factors (Spi-B, A-myb). The downregulation of several B cell–specific transcription factors (ie, Oct-2, Bob1, and Pu.1) has been described previously, and it is likely that this contributes to the lost B-cell phenotype of H-RS cells and the downregulation of Ig expression in these cells. However, as reconstitution of Oct-2 and Bob1 in HL cell lines does not lead to significant expression of the endogenous Ig loci, it is likely that an inactive chromatin structure also contributes to the absence of Ig transcripts in H-RS cells.

Because plasma cells downregulate numerous B-cell markers, and because H-RS cells often express the plasma cell markers MUM-1 and CD138, some have speculated that the phenotype of H-RS cells reflects a plasma cell differentiation. While such a differentiation process may be partly involved in the H-RS cell phenotype, it should be stressed that the lack of Ig expression and the retained expression of Pax-5 and MHC class II argue against a simple plasma cell differentiation of the H-RS cells. The reason for the downregulation of most B-cell molecules by H-RS cells is uncertain. Interestingly, H-RS cells express the transcription factor Notch-1, which is normally not expressed by B cells and suppresses a B-cell differentiation in lymphoid precursors in favor of T-cell differentiation. Thus, the aberrant expression of this master regulator for T-lineage development may play a role in the suppression of the B-cell phenotype of H-RS cells.

**Transforming Mechanisms in HL**

H-RS cells in classic HL show chromosomal abnormalities in virtually all cases. These are mostly numerical chromosomal alterations, indicating chromosomal instability of the H-RS cells. There is also evidence from cytogenetic studies that H-RS cells carry chromosomal translocations in a fraction of cases, but the proto-oncogenes \( BCL-2, BCL-6, C-MYC \) and \( MALTL1 \), which are involved in specific types of B-NHL, were found to be affected in H-RS cells only rarely. Mutations in the tumor suppressor genes \( p53 \) and \( CD95 \) or the proto-oncogene \( n-ras \) occur rarely, if at all. As H-RS cells appear to be resistant to CD95-mediated apoptosis induction, other members of the CD95 signaling pathway were analyzed for inactivating mutations, but none were identified.

A hallmark of H-RS cells in classical HL is constitutive activity of the transcription factor NFκB that functions as an important survival signal in these cells. Although this activity may be due in part to signaling through members of the tumor necrosis factor (TNF) receptor family (CD30, CD40), there is also evidence that genetic aberrations may be involved causally. Somatic mutations of the NFκB inhibitor IκBα may occur in up to 30% of cases, and a few cases show mutations in another NFκB inhibitor, IκBε. In addition, genomic amplifications of the \( c-Rel \) gene, a component of NFκB, are frequently present in H-RS cells.

Genomic amplifications affect not only the \( c-Rel \) gene, but frequently also the Jak2 and MDM2 loci. Jak2 is involved in cytokine signaling through the Jak/STAT (signal transducer and activators of transcription) pathway, and MDM2 is an inhibitor of p53, which plays a central role in the regulation of apoptosis.

In about 40% of cases of classical HL, the H-RS cells are infected by Epstein-Barr virus (EBV). Since EBV can transform human B cells in vitro, and since one of the virally-encoded genes expressed in H-RS cells, the latent membrane protein 1 (\( LMP1 \)), is an oncogene, it is likely that EBV contributes to the pathogenesis of classic HL. One of the main functions of \( LMP1 \) is activation of NFκB, so that \( LMP1 \) expression by EBV-infected H-RS cells represents a further mechanism for constitutive NFκB activity in these cells. Interestingly, the latent membrane protein 2a (\( LMP2a \)) which is also expressed by EBV-infected H-RS cells, mimics a B cell receptor, and it has been speculated that \( LMP2a \) may therefore play an important role in the rescue of an EBV-positive H-RS cell precursor that acquired destructive VAR gene mutations from apoptosis. Indeed, in mouse models, \( LMP2a \) transgenic B cells can survive without a B-cell receptor.

Little is known about the transforming events involved in the pathogenesis of lymphocyte-predominant HL. The L&H cells are always EBV-negative, and few cytogenetic or molecular mutation studies have been reported for this rare subtype. The only well-described aberration concerns the \( BCL-6 \) gene, which is involved in chromosomal translocations in a considerable fraction of cases.

**Antia apoptotic Phenotype of H-RS Cells**

Apoptosis, defined as caspase-mediated cell death, is the result of several partly overlapping caspase activation pathways, including the death receptor pathway, the mitochondrial pathway, the endoplasmic reticulum pathway, and the granzyme B–mediated direct activation of caspase 3. Activation of caspase 3 is the convergence point of the extrinsic receptor mediated pathway and the intrinsic mitochondria-associated pathway.

Although H-RS cells lack the expression of a B-cell receptor, they survive the germinal center reaction reflecting apoptosis resistance of these cells. Caspase 3 is expressed by H-RS cells but not by L&H cells in most cases. Nevertheless, functional analyses of cell lines indicate that caspase 3 is not active. The major inhibitory molecules that prevent proper caspase 3 activation in H-RS cells through the extrinsic and intrinsic pathway are c-FLIP and X-linked inhibitor of apoptosis proteins (XIAP), respectively.

The relevance of the CD95 pathway for the pathogenesis of HL came from the observation that H-RS cells are...
apoptosis resistant and harbor clonal somatic CD95 mutations in some instances. Interestingly, patients suffering from autoimmune lymphoproliferative syndrome carrying inherited CD95 gene mutations have a 51% higher risk of developing HL than expected. This observation indicates a further role of CD95 gene mutations for the HL lymphomagenesis. Additional evidence for the role of the extrinsic pathway for the pathogenesis of HL is provided by the fact that c-FLIP expression has been shown to inhibit CD95 and TNF receptor apoptosis-inducing ligand (TRAIL)-induced apoptosis in H-RS cells. Accordingly, siRNA-mediated downregulation of c-FLIP expression restored the extrinsic apoptosis pathway. As c-FLIP is a downstream target gene of NFκB, it might be speculated that constitutive NFκB activity confers an apoptosis resistant phenotype to H-RS cells. However, alternative molecular events responsible for c-FLIP regulation in the absence of B-cell receptor signaling remain elusive.

The intrinsic apoptosis pathway is dependent on a balanced activity of mitochondrial pro- and antiapoptotic bcl-2 family proteins. Upon release of cytochrome C from mitochondria, a cascade of molecular events leads to the formation of the apoptosome and finally to the sequential activation of caspases 9 and 3, resulting in DNA cleavage. A defect in the activation of the proapoptotic BCL2 family protein BAX has been associated with mitochondria-dependent apoptosis resistance of H-RS cell lines but the in vivo relevance of this finding is unclear.

Similar to the imbalance of BCL-2 family proteins, deregulated expression of members of the IAP family could also confer apoptosis resistance to H-RS cells. In cHL, the role of upregulated XIAP is best characterized, although functional data are missing. Besides XIAP, cIAP1, cIAP2, and survivin are reported to be expressed to a variable extend in H-RS cell lines and primary tissue, while other family members have not been analyzed so far. cFLIP and XIAP are NFκB target genes. Thus, the anti-apoptotic phenotype of H-RS cells might be a consequence of constitutive NFκB activity in H-RS cells. Alternative signaling pathways that are known to be deregulated in H-RS cells are the mitogen-activated protein kinase extracellular receptor kinase extracellular receptor kinase/extracellular receptor kinase (MEK/ERK) pathway, and the PI3K signaling cascade, which may also contribute to apoptosis resistance of H-RS cells.

The frequency of each of these cell types varies among the four subtypes of cHL. In most cases, CD4+ lymphocytes represent the majority of the reactive cell population.

For a number of years the majority of the infiltrating T cells were thought to display a Th2 subtype. It is now understood, however, that most of these T cells have regulatory capacity in that they suppress efficient immune responses in HL affected tissue and protect H-RS cells from immunologic clearance through cytotoxic T cells. This was shown for CTLA-4–positive CD4+CD10+ and CD4+CD25+ T lymphocytes and is likely to be applicable also to transforming growth factor beta (TGFβ)-producing Th3 cells.

CD4+ T cells with a Th1 subtype and CD8+ cytotoxic T cells are under-represented in HL-affected tissue and usually not detected in the vicinity of H-RS cells. This could be explained by the strong expression of both Th2 associated cytokines (interleukin [IL] -4 and IL-13) and Th1 or CD8 inhibiting cytokines (IL-10 and TGFβ) by H-RS cells themselves. In concert with the regulatory T cells, this specific cytokine profile of H-RS cells might help to create a uniquely favorable microenvironment protecting H-RS cells from cell-mediated apoptosis.

In HL, eosinophils are attracted by the cytokine IL-5 and the chemokine eotaxin whose expression in turn can be induced by TNFα or IL-13. The biologic relevance of eosinophilia might be indicated by the observation that this histomorphologic parameter correlates with prognosis in the nodular sclerosis subtype of cHL.

Cytokines, Chemokines, and Members of the TNF Receptor Family

Soluble factors and membrane bound receptors related both to the malignant cells and the reactive cells explain some of the inflammatory characteristics of the HL affected tissue (Fig 1). Whereas cytokines are low-molecular weight proteins that regulate a variety of biologic processes, chemokines represent cytokines that are specifically involved in migration of leukocytes. TNF receptors play a role for co-stimulation of lymphatic cells during inflammatory responses. This latter group of receptors represents the most important family of cell surface molecules that is involved in the pathogenesis of HL.

Cytokines. The cytokine network in HL-affected tissue is important for both the proliferation of the H-RS cells themselves (eg, IL-13) and the maintenance of a favorable environment characterized by specific immune cells such as eosinophils (eg, IL-5) or regulatory T cells (eg, IL-10).

IL-4, IL-6, IL-7, IL-9, and IL-15 are among the many cytokines that are expressed by and thought to influence survival of H-RS cells. With the exception of IL-13, there is little evidence that supports a relevant role of these factors for survival or apoptosis resistance of H-RS cells.

### Reactive Cellular Infiltrate

H-RS cells in cHL represent only a minority of the cell population in HL-affected tissue. The composition of the inflammatory-like cellular infiltrate in HL-affected tissue is heterogeneous, consisting of lymphocytes, macrophages, eosinophils, plasma cells, stromal cells, and fibroblasts.

 ROLE OF THE MICROENVIRONMENT IN HL

**Cytokines, Chemokines, and Members of the TNF Receptor Family**

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Initially, functional IL-13 expression was identified in H-RS cell lines using RNA microarrays. It was subsequently demonstrated, that IL-13 and its respective receptor, the IL-13Rα1, are also expressed in primary HL tissue but not in most other lymphoma entities. Functional experiments in H-RS cells lines showed that IL-13 indeed is an important autocrine growth factor for H-RS cells.

The specific cellular environment in HL-affected tissue is characterized by the presence of regulatory T cells. Cytotoxic T cells might be inhibited by the secretion of anti-inflammatory cytokines such as IL-10 or TGFβ. IL-10 is found in approximately one third of cHL cases; it is detected more often in EBV-positive than in EBV-negative cases. The strong immunosuppressive TGFβ is another cytokine that is detected mostly in the nodular sclerosis subtype of cHL, in which it is believed to induce fibrosis. TGFβ might also contribute to the inhibition of IL-2 dependent T-cell proliferation, whereas it can be speculated that H-RS cells themselves are protected from TGFβ because they lack a functional TGFβ receptor.

Chemokines. In humans, the four chemokine superfamilies CC, CXC, C, and CX3C comprise more than 40 chemokines and 18 functional chemokine receptors. On the basis of a screen of H-RS cell lines for the expression of 16 cytokines, Maggio et al performed immunohistochemistry in primary HL samples for the analysis of five chemokines. It was found that expression of TARC (CCL17) is specific for cHL, whereas expression of macrophage-derived chemokine (MDC; CCL22) is found both in cHL and nLPHL. Both chemokines bind to CCR4 on Th2 cells, whereas CXCR3, which is expressed on activated T cells and Th1 cells, is the corresponding receptor for interferon (IFN) -γ-inducible protein-10 (IP-10; CXCL10), detected predominantly in H-RS cells of EBV-positive cases of cHL. These results suggest that differences in distinct subtypes of HL are related to the attraction of specific lymphocytic subsets to the HL environment by chemokines.

H-RS cell–secreted chemokines are also involved in the attraction of eosinophils and plasma cells. Eotaxin (CCL11), expressed by fibroblasts, was shown to be a potent chemoattractant for eosinophils (and T cells), especially in nodular sclerosis subtypes of cHL. More recently, CCL28, which is known to attract eosinophils via CCR3 and plasma cells via CCR10 and CCR3, was also found to be expressed in H-RS cells of cHL, thus providing an explanation for the presence of plasma cells in HL-affected tissue.

TNF receptor family. Among the cell surface molecules that shape the cellular response in HL, the CD30 receptor is one of the most prominent features of H-RS cells. Although H-RS cells express both CD30 and its respective receptor, CD30L (CD153), suggesting an autocrine mechanism for autonomous proliferation of H-RS cells, it was shown that in H-RS cells CD30 activity and thus NFκB activity is mainly a CD30L-independent process. Moreover, it now appears that paracrine engagement of CD30 by CD30L induces a proliferation-inhibiting reverse signal in surrounding CD30L-bearing T cells.

CD40 and RANK (receptor activator of NFκB) are two other members of the TNF receptor family that are expressed on H-RS cells. Because CD40 expression has been reported in primary cases of HL and CD40L is found on rosetting T cells in HL affected tissue, it can be assumed that the CD40-CD40L signaling pathway is important for the survival of H-RS cells in vivo. Additional evidence for the relevance of the CD40 engagement is derived from the observation that soluble CD40L can induce proliferation in H-RS cell lines and protect H-RS cells from CD95 induced apoptosis. Coexpression of RANKL (RANK ligand) and its receptors, RANK and osteoprotegerin, in H-RS cell lines indicates an autocrine loop of this pathway. In fact, activation of RANK contributes to NFκB activation and induces several cytokines such as IFN-γ and IL-13, thus contributing to the maintenance of an inflammatory environment in HL.
Although TNFα, which is one of the most potent mediators of inflammation, has been found to be present in HL-affected tissue, its role for the pathogenesis of HL is poorly understood. A variety of other soluble factors have also been identified in HL. It was shown that stromal dendritic reticulum cells scattered around H-RS cells produce hepatocyte growth factor, which is thought to bind the transmembrane tyrosine kinase c-met, thus influencing adhesion and survival of H-RS cells. Interaction of H-RS cells with other cells in the microenvironment is also influenced by tissue inhibitor of metalloproteinase (TIMP) -1 and matrix metalloproteinase (MMP) -2 expression, which might explain some immunosuppressive and adhesive properties of H-RS cells. Another molecule that might contribute to the maintenance of the cellular network in HL-affected tissue is the endothelial growth factor vascular endothelial growth factor, which is also found to be expressed in approximately 70% of HL cases. Although it has been identified in some lymphomas in which it indicates poor prognosis, its role for survival of H-RS cells has not been established so far.

**SUMMARY AND PERSPECTIVE**

Malignant cells in HL are clonal GC-derived B cells in most instances. Despite their B-cellular genotype, they show a heterogeneous immunophenotype with lineage-aberrant expression of some cell surface molecules. These cells are further characterized by a deregulated transcriptional program resulting in a loss of B-cell identity of the H-RS cells. In addition, several cell signaling pathways are disturbed with constitutive activity of the NFκB transcription factor being the most prominent. These aberrations are reflected by an apoptosis-resistant phenotype of the H-RS cells that is mediated by several molecules, including constitutive activation of c-FLIP and XIAP, which inhibit the extrinsic and the intrinsic apoptotic pathway, respectively. The malignant cells in HL-affected tissue are embedded in a background of reactive immune cells that are attracted by specific cytokines and chemokines secreted by H-RS cells. These reactive cells not only fail to eradicate H-RS cells, but they also contribute to the survival of malignant cells by providing survival signals via cell surface receptors.

A better understanding of the pathogenesis of HL might lead to translational applications for prediction of poor-prognosis patients, thus allowing treatment adjustment dependent on individual factors. Identification of transforming mechanisms and associated aberrations (such as the antiapoptotic phenotype) may result in novel, less-toxic therapeutic strategies for HL patients.

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**Authors’ Disclosures of Potential Conflicts of Interest**

The authors indicated no potential conflicts of interest.

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