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1. Introduction

Hodgkin’s lymphoma (HL) is currently recognized as B cell derived lymphoma with histological and biomarker-based distinction from other types of B cell derived lymphoma (Swerdlow, S.H. et al., 2008). HL had a worldwide incidence of 67,887 cases in 2008, with an age standardized rate of 1.0 per 100,000 (both genders) (http://globocan.iarc.fr/). Some of the information in this chapter has already been part of an earlier review article (Banerjee, D., 2011) and is cited again for the sake of completeness, but this chapter also provides some historical or current data that was not included that review.

2. Historical aspects of Hodgkin’s Lymphoma

The earliest description of Hodgkin’s lymphoma (HL) in an autopsy patient is attributed to Malpighi who described an 18 year old female with prominent splenic nodules in his 1666 publication (Malpighi, M., 1666). Thomas Hodgkin, whose name is now associated with this disease, was very careful to mention this fact in the published version of his paper “On some morbid appearances of the absorbent glands and spleen” (Hodgkin, T., 1832) read to the Royal Medical and Chirurgical Society of London on January 10th and 24th, 1832. The paper was read not by Hodgkin but by the Society secretary Robert Lee. This was because Hodgkin was not a member of the Society at the time and therefore was prohibited from presenting the paper in person or even being present in the room during Lee’s reading of his paper.

Although the compound microscope had been invented in 1590 by spectacle-makers Zacharias Janssen and his son Hans (Uluç, K. et al., 2009), its use in pathology was nonexistent in Malpighi’s time. It is thus impossible to verify that Malpighi had indeed described what we now recognize as Hodgkin’s lymphoma. Even Hodgkin, who actually knew about light microscopy, having used it in a study published with Lister (Hodgkin, T. & Lister, J.J., 1827), did not use a microscope to study this disease. This is due to the fact that tissue processing, staining, and histopathology were not established techniques at the time. Two of Hodgkin’s original 7 cases were subsequently proven to be true examples of Hodgkin’s lymphoma by Fox (Fox, H., 1926) and again by Poston, this time demonstrating that the neoplastic cells indeed expressed CD15 (Poston, R.N., 1999). Case IV is likely to be an example of a peripheral T cell lymphoma with rare CD15+ Reed Sternberg-like cells. It is possible the other 4 cases were also HL but no tissue was available for histology or immunohistochemistry at the time of Poston’s study.
Hodgkin’s description of his 7 cases remained in obscurity for years even after being rediscovered and attributed to him by Bright (Bright, R., 1838) and Wilks (Wilks, S., 1856). It was through Wilks’ persistence that the disease was later recognized as Hodgkin’s disease (Wilks, S., 1859). Wilks had to put the term “Hodgkin’s disease” in the title of his paper to make the point (Wilks, S., 1865).

Most of the cases that Hodgkin described were patients who died soon after admission to hospital with terminal disease. He did have an opportunity to treat one of the 7 patients with cascarilla and soda to “improve his general health” and iodine “as an agent most likely to affect the glands” but noted dryly in his report that the treatment “appeared to be productive of no advantage, on which account it is probable the patient withdrew himself from my observation” (Hodgkin, T., 1832).

The first description of the histopathological features of HL was published by Theodor Langhans, (Langhans, T., 1872). Six years later, Greenfield published the histopathological features of HL in the English language (Greenfield, W., 1878). The detailed description of the characteristic multinucleated cells in this disease was described by Carl Sternberg (Sternberg, C., 1898) and Dorothy Reed (Reed, D., 1902) and are now called Reed-Sternberg cells. Gall and Mallory established HL as a neoplastic process (Gall, E. & Mallory, T., 1942). The first definitive evidence of the neoplastic nature of HL came in 1967 with the publication about the cytogenetics of HL (Seif, G.S. & Spriggs, A.L., 1967), further supported by a 1975 publication that showed clonal growth of Hodgkin cells (Boecker, W.R. et al., 1975).

The histopathological classification of HL has undergone several changes over the years. The first attempt to classify HL was by Jackson and Parker who in 1947 proposed three categories – paragranuloma, granuloma and sarcoma subtypes (Jackson, H. & Parker, F., 1947). Smetana and Cohen published the results of a retrospective review of mortality rates of HL cases culled from the records of the Armed Forces Institute of Pathology, classified according to the Jackson and Parker classification (Smetana, H.F. & Cohen, B.M., 1956). They did not describe how these patients had been treated.

Further refinement of HL classification came with the publications of Lukes and Butler (Lukes, R.J. et al., 1966; Lukes, R.J. & Butler, J.J., 1966), who divided HL into 6 groups: lymphocytic and/or histiocytic, (L & H), nodular, lymphocytic and/or histiocytic (L & H), diffuse, nodular sclerosis (NS), mixed, diffuse fibrosis and reticular. This was later simplified at the Rye Conference into 4 categories: Lymphocyte predominance (LP), Nodular sclerosis (NS), Mixed cellularity (MC), and Lymphocytic depletion (LD) (Lukes, R. et al., 1966). The first system to separate nodular lymphocyte predominance from classical HL was published in 1994 as part of the Revised European-American lymphoma (REAL) classification system, including the addition of a provisional entity of lymphocyte-rich classical HL (Harris, N.L. et al., 1994). The 2001 and 2008 WHO classification systems accepted the new category which is no longer a provisional one (Jaffe, E.S. et al., 2001; Swerdlow, S.H. et al., 2008). Recently, a comprehensive update of the histopathology and immunohistochemistry findings in HL has been published (Eberle, F.C. et al., 2009).

The therapy of HL has also undergone numerous changes, starting with Thomas Hodgkin’s attempts with cascarilla and soda and iodine combination therapy on one patient (Hodgkin, T., 1832). Fowler’s solution (potassium arsenite), a panacea concocted in 1786 by Thomas Fowler (Sears, D.A., 1988) for all sorts of chronic conditions, was used to treat HL (Waxman, S. & Anderson, K.C., 2001). It turns out that this was effective. In 1937 Hendrick and Burton
from the University of Toronto published a case report of a young male patient with HL who had a remarkable response to colloidal arsenic (Hendrick, A.C. & Burton, E.F., 1937). More recently, Mathas et al. have shown that sodium arsenite rapidly down regulates constitutive IkB kinase (IKK) as well as NF-κB activity and induces apoptosis in Hodgkin Reed-Sternberg (HRS) cell lines containing functional IkB proteins and that arsenic trioxide induces tumour reduction in xenograft models of HL (Mathas, S. et al., 2003). The use of nitrogen mustard for the chemotherapy of HL was introduced by in 1946 (Goodman, L.S. et al., 1946), with reports from others on the results of nitrogen mustard on HL in the forties (Alpert, L.K. & Peterson, S.S., 1947; Dameshek, W. et al., 1949).

Immunotherapy was attempted in 1928 (Wallhauser, A. & Whitehead, J.M., 1928). Three HL patients were treated with saline extracts from affected lymph nodes by subcutaneous injections. Two of the 3 patients achieved complete remission, while the third relapsed after initial response, but responded to a second round of injections. This report encouraged Hanrahan to try the same approach in 1930 with 9 patients but with less spectacular results (Hanrahan, E.M., 1930). Hanrahan used a preservative, tricresol (a mixture of three isomeric phenols derived from toluene: ortho-, meta- or para-methylphenol), in the extract, so one could speculate that whatever the active substance was in the HL tissue extract might have been damaged by tricresol.


Modern therapy of HL has been described in recent reviews (Boleti, E. & Mead, G.M., 2007; Edwards-Bennett, S.M. et al., 2010; Eichenauer, D.A. et al., 2009; Federico, M. et al., 2009; Mendler, J.H. et al., 2008; Oflazoglu, E. et al., 2008) and not further discussed here.

3. The cell of origin and the pathobiology of HRS cells

The neoplastic cells of classical HL (cHL) (Hodgkin/Reed-Sternberg cells or HRS cells) are usually derived from germinal centre B cells, and rarely are of T cell origin; those of nodular lymphocyte predominance (NLPHL) HL (LP cells) cases are always of germinal centre B cell origin (Brauninger, A. et al., 2006; Caporaso, N.E. et al., 2009; Kuppers, R., 2009; Küppers, R., 2009; Kuppers, R. et al., 2002; Mani, H. & Jaffe, E.S., 2009; Marafioti, T. et al., 2000; Seitz, V. et al., 2000).

Despite the fact that cHL HRS cells are derived from germinal centre or post-germinall centre B cells, they lack B cell markers including the B cell receptor (BCR) (Schwering, I. et al., 2003) as they lose their B cell programming (Hertel, C.B. et al., 2002) through several mechanisms including promoter DNA methylation (Doerr, J.R. et al., 2005; Ushmorov, A. et al., 2006), inhibition of transcription factor E2A by HLH proteins ABF-1 and Id2 resulting in reprogramming of neoplastic B cells (Mathas, S. et al., 2006), loss of PU.1 expression associated with defective immunoglobulin gene transcription (Jundt, F. et al., 2002), down-regulation of BOB.1/OBF.1 and Oct2 (Stein, H. et al., 2001) and upregulation of NOTCH1, a negative regulator of the B cell program (Jundt, F. et al., 2008). At the same time non-B cell lineage proteins are upregulated (Atayar, C. et al., 2005; Dorfman, D.M. et al., 2005).

The LP cells in NLPHL are derived from antigen-activated germinal centre B cells (Brauninger, A. et al., 1997), express functional IgV genes with intrachlonal diversification
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(Mottok, A. et al., 2005; Schmitz, R. et al., 2009), BCL6 protein (Falini, B. et al., 1996), and GCET1 (centerin), a germinal centre B cell associated serpin (Montes-Moreno, S. et al., 2008). In contrast to H/RS cells, LP cells retain most of their B cell programming; however, LP cells also show selective loss of the B cell phenotype such as down regulation of CD19, CD37, PAG and LCK (Dogan, A. et al., 2000; Masir, N. et al., 2006; Tedoldi, S. et al., 2007). The mechanism is not related to promoter methylation of the encoding genes (Tedoldi, S. et al., 2007).

3.1 The role of the Epstein Barr virus in HL

The Epstein-Barr virus was first identified in 1964 by Epstein, Achong and Barr (Epstein, M. et al., 1964). Up to 40-60% of cHL cases may contain the EBV genome (Kapatai, G. & Murray, P., 2007), but since EBV infects 90% of the adult population worldwide (Cohen, J., 2000), and is a B lymphocytotropic virus, it may be a passenger, but not a driver in HL.

Comprehensive EBV-human protein interaction maps have been generated by Calderwood et al. (Calderwood, M.A. et al., 2007) who showed over 40 interactions between EBV proteins and over 170 interactions between EBV and human proteins.

4. Genetic defects in primary immunodeficiency disorders (PID) and HL

Mutations in the SH2D1A and ITK genes are associated with aberrant T and NK function that predisposes patients to serious EBV infections, and lymphoproliferative disease including HL in those that survive the initial fulminant infectious mononucleosis. Detailed reviews of these PIDs has been published recently (Rezaei, N., Hedayat, M., et al., 2011; Rezaei, N., Mahmoudi, E., et al., 2011) and some key points are summarized below.

4.1 SH2D1A

The small (128-amino acid) Src homology 2 domain protein 1A (SH2D1A, DSHP or SAP) is associated with X-linked lymphoproliferative disease (XLP). The patients respond to the Epstein-Barr virus (EBV) infection with a fulminant, frequently fatal infectious mononucleosis syndrome (Purtilo, D.T. et al., 1975; Rezaei, N., Mahmoudi, E., et al., 2011). Most cases of XLP are due to mutations in the SH2D1A gene, which codes for the adaptor molecule called Signaling Lymphocytic Activation Molecule (SLAM; CD150)-associated protein (SAP) (Rezaei, N., Mahmoudi, E., et al., 2011). Patients with XLP and Sap null mice have defective natural killer and CD8+ T cell cytotoxicity, impairment of T cell cytokine production, activation-induced cell death, germinal centre formation and T NK cell development (Rezaei, N., Mahmoudi, E., et al., 2011). Survivors may develop agammaglobulinemia and B cell malignant lymphomas including HL (Rezaei, N., Hedayat, M., et al., 2011; Seemayer, T.A. et al., 1995). SH2D1A has been detected in 5 of 6 EBV negative classical HL cell lines including T cell derived HL cell lines (Kis, L.L. et al., 2003) and SH2D1A mRNA found in HRS cells in HL tissue (Nichols, K.E. et al., 1998). The lack of EBV in HL cell lines expressing SH2D1A protein is unexplained (Kis, L.L. et al., 2003).

4.2 IL-2–inducible T-cell kinase (ITK)

IL-2-inducible T-cell kinase (ITK) is a cytoplasmic non-receptor tyrosine kinase expressed in thymocytes, mature T cells, NK cells, iNKT cells, and mast cells (Au-Yeung, B.B. & Fowell, D.J., 2007; Au-Yeung, B.B. et al., 2006; Gadue, P. & Stein, P.L., 2002; Gomez-Rodriguez, J. et al.,

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2007; Grasis, J.A. et al., 2003; Iyer, A.S. & August, A., 2008; Qi, Q. et al., 2011). ITK mutations lead to fatal EBV induced lymphoproliferative disease characterized as hemophagocytic lymphohistiocytosis (HLH) and HL (Huck, K. et al., 2009; Stepensky, P. et al., 2011).

5. Prognostic indicators derived from transcriptome, genome and host response patterns

5.1 Gene copy number variation in HRS cells

Complex chromosomal and genomic alterations occur in HRS cells of HL. My laboratory reported novel gains and losses of 9 novel regions in Hodgkin Lymphoma cell lines L428 and KMH2, which shared gains in chromosome cytobands 2q23.1-q24.2, 7q32.2-q36.3, 9p21.3-p13.3, 12q13.13-q14.1, and losses in 13q12.13-q12.3, and 18q21.32-q23. The genes located in these regions include cell cycle associated genes, MAPK signaling pathway genes, those encoding tight junction proteins, Jak/Stat signaling pathway genes and tumour suppressor gene ING3 (Fadlelmola, F. et al., 2008).

Steidl et al. compared patients that had failed primary treatment with those that responded as usual (Steidl, C., Telenius, A., et al., 2010). Gains of 16p11.2-13.3 were associated with treatment failure and shorter disease-specific survival. One of the genes mapping to this region is the multidrug resistance gene ABCC1 encoding multidrug resistance protein MRP1 (Leslie, E. et al., 2001; Rosenberg, M. et al., 2001), and functional studies indicate that this does play a role in chemoresistance (Steidl, C., Telenius, A., et al., 2010).

5.2 Gene expression studies

Devillard et al. using whole cells including the microenvironment, found a signature that can distinguish between good outcome Hodgkin’s disease and bad outcome cases (Devillard, E. et al., 2002). Good outcome was associated with overexpression of genes involved in apoptotic induction and cell signaling pathways, including cytokines, whereas bad outcome was associated with overexpression of genes associated with fibroblast activation, angiogenesis, extracellular matrix remodeling, cell proliferation, and the down regulation of tumor suppressor genes.

Sánchez-Aguilera et al. identified 145 genes predictive of outcome (Sánchez-Aguilera, A. et al., 2006). Four different signatures were obtained by supervised hierarchical clustering, 2 of which were associated with the host immune response of tumor microenvironment and the other 2 with the HRS cells based on known expression in HL cell lines and normal germinal centre B cells.

Chetaille et al. studied 63 cHL cases (not enriched for HRS by microdissection, thus including cells from the microenvironment) using full transcriptome coverage and found 47 genes associated with adverse outcome, and 403 genes associated with favorable outcome (Chetaille, B. et al., 2009). Favorable outcome was associated with expressed genes of the “B-cell” cluster, whereas genes associated with unfavorable outcome were in the “extracellular matrix” cluster.

Global gene expression analysis of microdissected LP cells (L&H cells) from 5 cases of NLPHL has been reported by Brune et al. (Brune, V. et al., 2008). The gene expression
signatures were closer to T cell-rich B cell lymphoma and classical HL than to diffuse large B cell lymphoma, Burkitt lymphoma, and follicular lymphoma. There is increased expression of ABCC1 in LP cells, which as already discussed, encodes multidrug resistance protein MRP1 (Leslie, E. et al., 2001) and is also amplified and overexpressed in primary treatment refractory cHL (Steidl, C., Telenius, A., et al., 2010).

5.3 Host microenvironment/immune response
An increased number of CD68+ macrophages is associated with a shortened progression-free survival, an increased risk of relapse after HDCT/ASCT, and shortened disease-specific survival. In multivariate analysis, CD68+ cells as a prognostic factor is superior to the International Prognostic Score for disease-specific survival. The absence of an increased number of CD68+ cells in patients with limited-stage disease predicted long-term disease-specific survival of 100% in cHL patients treated with current treatment protocols (Steidl, C., Lee, T., et al., 2010). The immunohistochemistry (IHC) assay for CD68, which is widely available in clinical laboratories, can identify patients with HL who are likely to be refractory to first line therapy and was noted to be the first predictive in-vitro test for cHL (DeVita, V.T., Jr. & Costa, J., 2010).

5.4 Mechanisms of chemoresistance
The multidrug resistance gene ABCC1 in overexpressed in LP and HRS cells and HRS cells contain increased copy number of the ABCC1 gene (Brune, V. et al., 2008; Steidl, C., Telenius, A., et al., 2010). HL tumor samples contain a population of cells that increase efflux of Hoechst 33342 dye and are resistant to gemcitabine, a commonly used drug for the treatment of refractory HL. These cells have the phenotype of HRS cells and express multidrug resistance genes ABCG2 and MDR1 (ABCB1) (Shafer, J.A. et al., 2010).

Genes encoding cytokine receptors (IL5RA, IL13RA1), markers expressed on antigen-presenting cells (CD40, CD80), as well as genes with known association to chemoresistance, such as myristoylated alanine-rich protein kinase C substrate, and PRAME (preferentially expressed antigen in melanoma) are upregulated in chemoresistant cells (Staege, M.S. et al., 2008).

Chemoresistance in HL is also related to XIAP (X-linked inhibitor of apoptosis) an NF-kappaB-independent target of bortezomib. Bortezomib sensitizes HL cells against a variety of cytotoxic drugs independent of NF-kappaB (Kashkar, H. et al., 2007).

6. How the HRS cell, an abnormal B cell clone, survives the normal apoptotic process and immune destruction
Normally B cells that fail to achieve productive or high affinity Ig gene rearrangements or lack BCR are destroyed during the germinal centre reaction (Gordon, J. et al., 1993; Guzman-Rojas, L. et al., 2002; Hollowood, K. & Goodlad, J.R., 1998; Zhang, Q.P. et al., 2005). There are several excellent reviews on the topic of the germinal centre reaction and mechanisms of B cell apoptosis and survival during a normal antigen driven reaction (Elgueta, R. et al., 2010; Goodnow, C.C. et al., 2010; Nutt, S.L. & Tarlinton, D.M., 2011; Oracki, S.A. et al., 2010;
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Vikstrom, I. & Tarlinton, D.M., 2011; Vinuesa, C.G. et al., 2010), so only a brief summary is provided in this chapter.

6.1 The germinal center reaction

The biologic or physiologic purpose of the germinal centre reaction is to generate long-term humoral immunity in the adaptive immune system against antigens expressed by pathogens, while, at the same time, eliminating autoreactive clones. The end result is the generation of long-lived antibody-secreting plasma cells and memory B cells which can rapidly trigger subsequent waves of plasma cell production when the same antigen/s are encountered again. The germinal centre reaction is a complex cascade of events, highly regulated, requiring crosstalk and collaboration between B cells, follicular helper T cells and antigen presenting cells including dendritic cells, macrophages and follicular dendritic cells (Cattoretti, G. et al., 2005; Elgueta, R. et al., 2010; Guzman-Rojas, L. et al., 2002; Jardin, F. et al., 2007; Kosco-Vilbois, M.H., 2003; Park, C.S. & Choi, Y.S., 2005; Phan, R.T. & Dalla-Favera, R., 2004; Schenka, A.A. et al., 2005; Siepmann, K. et al., 2001; Spender, L.C. et al., 2009; Tarlinton, D.M. & Smith, K.G., 2000; Zhang, Q.P. et al., 2005).

6.2 The primary lymphoid follicle

Primary lymphoid follicles appear in the second trimester of fetal life in humans and are composed of antigen-naive recirculating B cells that migrate through meshworks of follicular dendritic cells (FDC) with a transit time of 24 hours (Howard, J.C. et al., 1972). These antigen-naive B cells have already undergone recombination of gene fragments, with a theoretical repertoire of >10^10 antigen binding receptors (Berek, C. & Milstein, C., 1988). When these B cells encounter an antigen, they increase their expression of the chemokine receptor CCR7 which facilitates their migration to the interface between T and B cells zones (Cyster, J.G., 2005; Okada, T. & Cyster, J.G., 2006). Here they can contact antigen-primed T cells, triggering a burst of proliferation of the activated B cells in the outer follicle, ultimately forming a germinal centre (Coffey, F. et al., 2009). HRS cells of cHL also express CCR7 which may explain why HRS cells tend to be located in interfollicular zones (Höpken, U.E. et al., 2002). LP cells are CCR7- and therefore remain in germinal centers.

6.3 Somatic hypermutation – Generation of higher affinity antibodies

Activated B cells undergo a process of affinity maturation in the germinal center reaction. Rearranged immunoglobulin (Ig) variable region genes undergo random point mutations by a process called somatic hypermutation (SHM) in which single nucleotide substitutions are introduced at a rate of one mutation per 1000 base pairs per generation (Berek, C. & Milstein, C., 1988). Both LP cells of NLPHL and HRS cells of cHL show evidence of SHM of Ig variable region genes (Liso, A. et al., 2006) and are therefore considered to be derived from antigen-activated B cells.

6.4 Selection of high affinity B cells

Since SHM is a random process, a wide range of antigen-binding affinities may result. A mechanism for ensuring that high affinity antigen receptor positive cells are preferentially
selected is required for optimal function. The default event seems to be death by apoptosis through the Fas/CD95 pathway unless the cells are rescued by signals from other cell types. Fas/CD95 triggers elimination of low-affinity and self-reactive B cell clones that arise during the germinal centre reaction through apoptosis (Defrance, T. et al., 2002). Prior to apoptosis, rapid activation of caspase-8 occurs in association with CD95 death-inducing signaling complex (DISC). c-FLIP(L), which protects B cells from Fas/CD95 triggered apoptosis is rapidly lost from the CD95 DISC unless the B cells are exposed to the survival signal provided by CD40L from follicular T helper cells (Hennino, A. et al., 2001). In cHL, over 80% of cases show constitutive expression of c-FLIP which protects the HRS cells from Fas/CD95 triggered apoptosis without the need for CD40L survival signals (Mathas, S. et al., 2004; Thomas, R. et al., 2002; Uherova, P. et al., 2004).

6.5 The role of the follicular helper T cell (T\textsubscript{FH})

The localization of T cells coexpressing HNK-1 (CD57) in the germinal centers (GC) of lymph nodes and spleens was reported by my laboratory (Banerjee, D. & Thibert, R.F., 1983). Although expressing HNK-1 (CD57), which was initially thought to be human natural killer cell specific, these cells were not cytotoxicity active. Under certain circumstances, we found that these cells could either suppress or enhance immunoglobulin production by pokeweed mitogen-activated tonsillar B cells (Banerjee, D. et al., 1988). Such cells are now recognized to be specialized CD4+ T cells called follicular helper T cells (T\textsubscript{FH}) that home to the germinal center and play a pivotal role in regulating the fate of B cell in the germinal centre reaction. They express cell surface antigens CD4, CD57, and CXCR5, produce IL-21, IL-6, IL-27, BCL-6, ICOS, CD40L, and PD-1 (Crotty, S., 2011). While germinal centre CD57+ CD4+ T cells have been shown to be a major T helper cell subset for GC-B cells in Ig synthesis, and have the capacity to induce activation-induced cytosine deaminase (AID) and class switch recombination (Kim, J.R. et al., 2005), the most effective subset of capable of inducing IgG production is the CXCR5\textsuperscript{hi} ICOS\textsuperscript{hi} CD4+ T cell. The presence or absence of CD57 does not appear to affect this function (Rasheed, A.U. et al., 2006).

Cells with the phenotype of T\textsubscript{FH} are usually found in contact with of NLPHL LP cells (Nam-Cha, S.H. et al., 2009) forming characteristic rosettes. The expression of PD-1 is more frequent than that of CD57 by the T cell rosettes around LP cells (Churchill, H.R. et al., 2010). PD-1+ T cells are also reported in cHL and HRS cells express both ligands for PD-1 (CD279), B7-H1 (PD-L1; CD274) and B7-DC (PD-L2; CD273) (Yamamoto, R. et al., 2008). The function of PD-1+ T cells in HL is unknown. In normal germinal center reactions, PD-1 signals enhance B cell survival (Good-Jacobson, K.L. et al., 2010), thus it is possible that PD-1+ T\textsubscript{FH} cells in both NLPHL and cHL provide additional survival signals. Another protective effect of PD-1 could be mediated through its inhibition of cytotoxic T cells via overexpressed PD-1 ligands CD273 or CD274 by the target cells of cytotoxic T cells (Norde, W.J. et al., 2011).

6.6 IL-21

HRS cells aberrantly express IL-21 and the IL-21 receptor. IL-21 activates STAT3 in HRS cells, up-regulates STAT3 target genes, and protects HRS cells from CD95 death receptor-induced apoptosis. In addition, IL-21 through up-regulation of the CC chemokine macrophage-inflammatory protein-3a (MIP-3a) attracts CCR6+CD4+CD25+FoxP3+CD127\textsubscript{lo} regulatory T cells to migrate close to the proximity of HRS cells, protecting them from immune attack (Lamprecht, B. et al., 2008).
6.7 IL-6

IL-6 is a pleiotropic cytokine (also called B-cell stimulatory factor-2, IFN-b2, 26-kDa protein, Hybridoma/plasmacytoma growth factor and hepatocyte stimulating factor HSF) with biological activities in immune regulation, hematopoiesis, inflammation and neoplasia (Kishimoto, T., 2010). HL cells express multiple cytokines, including interleukin-6 (IL-6) (Tesch, H. et al., 1992). Increased serum levels are associated with advanced disease and worse prognostic scores (Vener, C. et al., 2000). HL cells produce IL-6 through constitutional activation of the PI3K signaling pathway which promotes expression of HLXB9, an EHG homeobox gene family member, which in turn activates IL6 (Nagel, S. et al., 2005). Thus HL cells, and presumably HRS cells in vivo, do not solely depend upon T_{FH} for IL-6 supply but make their own, possibly benefiting from an autocrine loop.

6.8 BCL-6

The BCL6 proto-oncogene encodes a nuclear transcriptional repressor. It is important in germinal center (GC) formation and regulates lymphocyte function, differentiation, and survival. BCL-6 suppresses p53 in GC B-cells and protects B-cell lines from apoptosis induced by DNA damage. BCL-6 is thought to allow GC B-cells to sustain the low levels of physiological DNA breaks related to somatic mutation (SM) and immunoglobulin class switch recombination (Jardin, F. et al., 2007). BCL-6 is also an important regulator of the T_{FH} cell program, being essential for CXCR5 expression and follicular homing by T_{FH} cells (Yu, D. et al., 2009).

BCL-6 expression is usually seen in NLPHL and about 30% of lymphocyte rich classical HL (LRCHL) but not other forms of cHL (Nam-Cha, S.H. et al., 2009). However, in another study, none of the cases of LRCHL expressed BCL-6 (Brauninger, A. et al., 2003).

6.9 Bfl-1

Bfl-1 is a NF-κB target gene from the Bcl-2 family of apoptosis-regulating proteins. Bfl-1 is expressed in HRS cells in clinical biopsies and also expressed in HL cell lines. Bfl-1 can protect cultured H/RS cells from apoptosis induced by pharmacological inhibitors of NF-κB (Hinz, M. et al., 2001; Loughran, S.T. et al., 2011).

7. Next generation whole genome sequencing and new insights into the pathobiology of HL

Technological improvements now allow the analysis of entire genomes and transcriptomes at a sufficient resolution to detect point mutations at high speed and reduced cost (Cronin, M. & Ross, J.S., 2011). Two recent discoveries that are relevant to HL are highlighted in this review.

7.1 MHC class II transactivator CIITA, PD-1 and PD-1 ligands

In 15% of cHL, a gene fusion involving the major histocompatibility complex (MHC) class II transactivator CIITA (MHC2TA) and several partners has been reported (Steidl, C. et al., 2011). Not only is one of the fusions (with an uncharacterized gene BX648577) associated...
with downregulation of HLA Class II expression which could help HRS cells evade immunosurveillance, CIITA also fuses with genes encoding CD274 (PDL1) and CD273 (PDL2), leading to overexpression of both these PD-1 ligands by HRS cells. This could have two beneficial effects on HRS cell survival, the first through PD-1 survival signals from T\textsubscript{FH} cells to the neoplastic B cells and the second through inhibition of cytotoxic T cells as already discussed above.

7.2 EZH2
Mutations in \textit{EZH2}, a polycomb group oncogene which encodes a histone methyltransferase, have been described in follicular lymphomas and diffuse large B cell lymphomas of germinal centre type. These mutations involve a single tyrosine (Y641) in the SET domain of the EZH2 protein reducing its enzyme action (Morin, R.D. et al., 2010). While HL cases were not included in this study, this protein may have a role in HL. Whereas the expression of the polycomb group gene encoded proteins BMI-1 and EZH2 genes is associated with resting or proliferating germinal centre B cells, respectively and not coexpressed, Hodgkin/Reed-Sternberg (H/RS) cells co-express BMI-1 and EZH2 (Dukers, D.F. et al., 2004; Raaphorst, F.M. et al., 2000).

8. New targets for potential therapeutic approaches
CD20, a B cell expressed phosphoprotein, is usually expressed by LP cells in NLPHL but variably positive in a minority of cHL cases as recently reviewed by Saini and others (Saini, K.S. et al., 2011). Despite CD20 negativity in most cases of cHL, patients refractory to all conventional HL therapies have responded to rituximab (Younes, A. et al., 2003). An excellent review of the myriad of potential targets for novel therapies for treatment refractory HL has been published by Younes (Younes, A., 2009), and some of these, and the rationale for their use have been summarized in one of my recent review articles (Banerjee, D., 2011).

My laboratory recently reported that a 21 kDa protein (Zhou, M. et al., 2008), which we subsequently identified as CYB5B, an outer mitochondrial membrane protein, is overexpressed in the cytoplasm and plasma membrane of HRS cells but not at the plasma membrane of normal reactive lymphocytes or bone marrow precursor cells (Murphy, D. et al., 2010). Gains in the CYB5B locus in HL cell lines KMH2 and L428 were detected. HL cell lines show increased CYB5B mRNA but reactive lymphocytes and bone marrow precursor cells show no increase in CYB5B mRNA in comparison to housekeeping genes. Due to its location at the plasma membrane of only neoplastic cells in cHL, diffuse large B cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL), CYB5B might be an attractive target for antibody based therapy as toxicity should be minimal since we have determined that normal, reactive lymphocytes and CD34+ bone marrow precursor cells do not express the protein at the plasma membrane (Murphy, D. et al., 2010). We are in the process of creating chimeric antibodies to determine whether they are effective in killing HRS cells in pre-clinical models.

9. Discussion
From Hodgkin’s first report in 1832 on what we now call Hodgkin’s Lymphoma, to this day, the pathobiology of HL continues to intrigue and surprise us with the myriad ways in
which the LP and HRS cells defy all physiologic rules of B cell survival by exploiting the very signals that would normally stop undesirable B cells from surviving. The vast network of crosstalk and redundancy of pathways the tumour cells have successfully utilized keeps growing in complexity. These observations challenge our preconceived notions of cell lineage fidelity as defined by expressed cell surface proteins and other biomarkers. Indeed reprogramming and plasticity of B cells is a reality, thus neoplastic B cells derived from the germinal centre can assume various “identities” and confuse regulatory cells and pathways (Mathas, S., 2007). Eventually, classification of B cell lymphomas including HL will require, not just lineage determination and morphology-based classification and grading, but also the detailed mapping of aberrant pathways in sufficient resolution for us to understand all the potential nodes that could be novel therapeutic targets.

10. Conclusion

HL is a unique set of B cell lymphomas that are characterized by the exploitation of redundant pathways, and crosstalk between regulatory cells that promote the growth and survival of defective B cells which, under normal conditions, would die during the germinal centre reaction. While this may seem an insurmountable level of complexity, the potential for effective novel targeted therapies to deal with refractory disease will be possible to attain when a comprehensive map of pathway pathology is feasible in the future.

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Hodgkin's Lymphoma is the book consisting of 11 chapters: Recent insights into the biology of Hodgkin's lymphoma, including historical aspects, epidemiology, pathophysiology, genetic defects, and prognostic indicators are explained in the intro chapters. After a translational chapter from tumor microenvironment to immunotherapeutic approach, treatment of early stage, advanced, and refractory Hodgkin's lymphoma are explained in the following chapters. MALT lymphoma and adverse effects of chemotherapy and radiotherapy in the affected patients are discussed in the subsequent chapters, while the final chapter is focused on survivorship in Hodgkin's lymphoma. The book is intended to present recent advances in the pathophysiology of Hodgkin's lymphoma as well as practical approach to diagnosis and management in clinical practice, which is hoped to be welcomed by the physicians, who wish to learn more about Hodgkin's lymphoma.

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