Hodgkin's Lymphoma: An Appraisal of Its Biology and Clinical Manifestation

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The 175-year-old history of the disease carrying the name of Thomas Hodgkin teaches us humility about what we think we understand about this complex biological phenomenon. As Hodgkin's disease became Hodgkin's lymphoma (HL), our understanding of its underlying biology underwent regular revisions. During its long history, the disease has been regarded as, among other things, a reactive disorder, a type of leukemia, a special type of tuberculosis and, more recently, a neoplastic disorder. On the other hand, it is a pleasant surprise to realize how fast our understanding of this 'enigmatic disease' has grown in recent years. It took roughly 10 years from the first epidemiological evidence of a link between Epstein-Barr virus and HL [1, 2] to prove the presence of viral proteins and DNA in the Hodgkin and Reed-Sternberg (HRS) cell [3, 4]. It was again a long way to finally defining the very nature of the Reed-Sternberg cell. The origin of this cell unique to HL has been attributed to various cells of the body, including those of the immune system, before definitely establishing its B lineage origin in 1999 [5, 6]. With this historical background in mind, it follows that a critical review of our current position is always a useful exercise.

In the present issue of *Pathobiology*, the state-of-the-art of HL is reviewed by a group of clinicians and a group of pathologists. Given the important advances in both treatment and biology of HL the reader will easily realize that we have still a lot of blank spaces to fill in on our

map of HL. In the large groups of patients with various immunodeficiency states (i.e. AIDS patients, organ recipients), we do see HL-like lesions that need to be more clearly defined [7]. As highlighted in the review by Tzankov and Dirnhofer [8], morphological and immunological characteristics suggest that once again, HL can be profoundly influenced by the host's immune system. In this sense, immunodeficiency-related HL is the ideal case study to assess the relationship of HL with the immune system within which it develops. A second field of further study is the role of 'inflammatory-type' mechanisms in the pathogenesis of HL [9]. Again, it is well known that the HRS cells are only a minority in the tissue of HL. The infiltrate mostly consists of cells such as lymphocytes, eosinophils, neutrophils and macrophages, reminiscent of an inflammatory process. Both HRS and their numerous 'bystander' cells are known to produce a plethora of cytokines and cytokine receptors [10]. Many of the cytokines detected in HL appear to depend upon NF κ B activity. This transcription factor is essential in inflammatory and neoplastic processes and has been shown to take part in the development of inflammation-associated cancer [11]. The inflammatory and immunological changes that precede the development of HL as well as their role during the disease process is still a wide field for translational research linking clinical observations to the recent advances in the molecular biology of HL.

What are the consequences of basic research on the present day standard therapeutic protocols? In this issue of *Pathobiology*, Fuchs et al. [12], who have extensive experience with the management of HL patients, describe the recent advances and further challenges. HL counts among those human neoplasms that constitute ‘success stories’ in oncology, as over 89% are cured. But these positive results are fraught with serious secondary effects and the search for other treatment modalities is going on. While therapy using anti-CD20 antibodies has led to a revolutionary change in the treatment of non-Hodgkin’s lymphoma [13], only nodular lymphocyte-predominant HL benefits from anti-CD20 antibody treatment; the other forms of HL do not. The usefulness of anti-CD30 an-

tibodies has yet to be demonstrated. In this context small molecules could provide another way to interfere with HL cell survival. Given the central role of NF κ B, it is known that this factor can be inhibited by targeting the proximal signaling proteins responsible for its activation as well as the downstream signaling molecules and the proteasome-mediated degradation of the inhibitor proteins (I κ B and casein kinase 2).

HL is an excellent example of the progress that can be made when research translates into therapy and finally changes the lives of the patients. Those patients who advocated for HL such as Bill Allen (to mention only one), co-founder of Microsoft together with Bill Gates, are major partners in pushing forward our work on HL.

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