1. Introduction

Hodgkin’s lymphoma (HL) was the first lymphoma to be recognized as a distinct clinical entity [1] and is one of the most common malignant neoplasms in European and Western countries. However, HL stands biologically distinct from all other cancers. The neoplastic cells, Hodgkin and Reed-Sternberg (H-RS) cells, represent less than 1% of the cells in the involved lymph nodes and are surrounded by an inflammatory infiltrate, mostly of lymphocytes, plasma cells, histiocytes, eosinophils, and various degrees of fibrosis. Despite their rarity, H-RS cells appear to facilitate profound paraneoplastic effects: constitutional symptoms, including weight loss, fever, and pruritis; eosinophilia; and altered immune response [2,3].

Although the unique clinicopathological features have long been recognized, the origin of the H-RS cells and the basis for the pathogenesis of HL remained largely unknown. In the past several years, however, there has been a break-through in this research field, including 2 important findings. Identification of the cellular origin and a common molecular biological characteristic of H-RS cells. These findings have significantly advanced our understanding of HL. Owing to the rarity of H-RS cells in affected lymph nodes, efforts to understand the cellular origin have been hampered by the difficulty in obtaining pure H-RS cells. The results obtained from whole tissue extracts have remained inconsistent, probably because the background of accompanying inflammatory cells masks the nucleic expression profile of the H-RS cells.

Results obtained from immunophenotypic studies in the 1980s suggested the lymphocytic origin of H-RS cells. However, variable expression of B-cell or T-cell markers sometimes along with dendritic or myeloid markers made it difficult to clarify the detailed cellular origin [4]. Recent advances in molecular biological techniques enabled us to obtain single H-RS cells by micromanipulation. Amplification of genomic DNA and complementary DNA (cDNA) derived from single H-RS cells gave us a better understanding of their cellular origin. Accumulating evidence obtained from single-cell analyses has revealed that (1) approximately 95% of HL H-RS cells are clonal and derived from B-cells, (2) the remaining 5% of HL appear to be derived from T-cells, and (3) somatic hypermutation in the rearranged variable regions suggests a germinat center B-cell origin. These B-cells are unable to produce immunoglobulin because of crippling immunoglobulin gene mutations or lack...
of messenger RNA (mRNA) expression [5-9]. At the beginning of the 1990s light began to be shed on the biological backgrounds of H-RS cells. The most important work was the cDNA cloning of CD30 reported in 1992 [10]. Although CD30 had been recognized in the 1980s as an important marker of H-RS cells, the biological significance of this molecule remained entirely unknown for a long period [11-13]. Cloning and characterization of CD30 cDNA revealed that CD30 is a member of the tumor necrosis factor receptor (TNF-R) superfamily. Cloning of cDNA for its ligand CD30L in 1993 revealed that CD30L in turn belongs to the TNF superfamily [14]. Subsequent cloning work expanded the list of known members of this receptor-ligand superfamily. Accumulating evidence obtained from functional studies of the TNF receptor superfamily revealed that signaling events by this superfamily regulate life and death of the cells. Within a few years the yeast 2-hybrid method made it possible to identify numerous signal-transducing molecules situated downstream of the TNF receptor superfamily. This advance made it possible for us to better understand signaling events regulating life and death of cells [15,16].

In addition to expression of CD30, the initially identified H-RS cell marker, expression of other TNF-R family receptors such as TNF-R1, TNF-R2, CD40, and CD95 (Fas) was identified on the surface of H-RS cells. Triggering TNF-R family members activates NF-κB, p38 mitogen-activated protein kinase, c-Jun N-terminal kinase, and caspases. The process thus induces pleiotropic effects, including cytokine secretion, expression of adhesion molecules, and proliferation and death of cells. The results obtained from in vitro experiments are evidence that these receptors are functional and essential for H-RS cells. The pathophysiology of HL was defined as a ligand-receptor interaction between H-RS cells and surrounding reactive cells [17].

To date many researchers have focused on the molecular mechanisms driving constitutive NF-κB activation. In 1996, Bargou et al showed high-level nuclear NF-κB and Oct-2 activity in various H-RS cell lines and primary tumor cells. These authors proposed that this high-level nuclear NF-κB was a unifying and characteristic property of H-RS cells that might explain the deregulated expression of various cytokines leading to the clinical and pathological manifestations of HL [18]. Recent work has revealed the presence of defective IkBα in a certain proportion of H-RS cell lines and H-RS cells from patients. Thus some researchers have proposed that defective IkBα is responsible for deregulated NF-κB activation [19-23]. However, the fact that most cell lines derived from H-RS cells and those from patients apparently have at least 1 wild-type allele and express wild-type IkBα protein suggests the existence of another common mechanism that drives NF-κB activation. To understand the mechanisms of constitutive NF-κB activation in H-RS cells, we investigated the signal transduction pathway of CD30 and recently identified a novel mechanism, namely, ligand-independent signaling by overexpressed CD30. CD30, when overexpressed, can transduce signals leading to activate NF-κB without interaction with its ligand CD30L. This finding led us to combine 2 common characteristics of HL, overexpression of CD30 and constitutive NF-κB activation at the molecular level [24].

In this review we focus on the molecular mechanisms that drive constitutive NF-κB activation in H-RS cells and extensively examine recent data on this issue. First, for better understanding, we present a brief review of recently attained knowledge about CD30 and NF-κB, 2 characteristic molecules of H-RS cells, in reference to HL.

2. CD30 and HL

CD30 was initially reported as “a molecule specific for H-RS cells” that was recognized by monoclonal antibody Ki-1 on the cell surface of H-RS cells. Ki-1 was generated by immunization of mice with the HL cell line L428 derived from pleural effusion of HL patients [11,12]. Expression of CD30 on H-RS cells was extremely strong; however, later study revealed that CD30 was expressed not only on H-RS cells but also on a subset of large cell non-Hodgkin’s lymphoma, activated peripheral blood lymphocytes, and virus-infected lymphocytes [13]. Today CD30 is recognized as a “lymphocyte activation associated antigen” [25-39]. Contrary to the restricted expression pattern of CD30 on lymphocytes, expression of its ligand CD30L is broader, being expressed on lymphocytes, neutrophils, and eosinophils as well as activated monocytes/macrophages. However, H-RS cell lines lack expression of CD30L [40-44].

CD30 cDNA was cloned and characterized in 1992. CD30 is a transmembrane glycoprotein with a molecular mass of 120 kd and is generated from a 85-kd precursor. CD30 is a member of the TNF-R superfamily. Structurally, CD30 consists of 595 amino acids and retains 6 cysteine-rich repeats in the extracellular domain characteristic of TNF-R superfamily members [10]. Cleavage by a zinc metalloprotease generates the soluble form of CD30, the serum level of which is increased in various disease conditions, especially in HL, and reflects the total number of CD30-bearing cells in the body [45-53]. CD30 ligand (CD30L) was cloned and characterized in 1993. It was revealed that this protein is a type II transmembrane protein consisting of 234 amino acids and forms a trimer on the cell surface [14]. Thus CD30L and CD30 are shown to belong to the TNF/TNF-R superfamily.

Evidence underscoring the functional importance of CD30 was gradually accumulated after the initial cloning reports of CD30 and CD30L [27,33,54-63]. Biological functions of CD30 for lymphocytes have been referred to as “pleiotropic” by many researchers. CD30 can mediate proliferative or antiproliferative, even proapoptotic, signals for lymphocytes depending on the types of cells and differentiation or activated status. Effects of CD30 ligation on H-RS cell lines have reported to differ depending on cell lines. CD30 signals stimulate proliferation of H-RS cell lines with T-cell phenotype such as L540 and HDLM-2, whereas they show no effects on H-RS cell lines with B-cell phenotype, such as L428 and KMH-2 [63]. These results appeared to reflect the heterogeneity of HL cell lines. However, in view of the self-signaling by overexpressed CD30 in H-RS cells described in detail later, these results apparently need to be reevaluated. The results of in vitro experiments by other researchers suggested that CD30 is functional and essential for H-RS cells and that the pathophysiology of HL was thought to be ligand-receptor interaction between H-RS