Activation of Hodgkin Cells Via the CD30 Receptor Induces Autocrine Secretion of Interleukin-6 Engaging the NF-κB Transcription Factor

By Hans-Jürgen Gruss, Dawn Ulrich, Steven K. Dower, Friedhelm Herrmann, and Marion A. Brach

The CD30 surface molecule is a recently identified member of the tumor necrosis factor/nerve growth factor receptor superfamily. Within the cytoplasmic signal transducing domain, CD30 shares no significant homology to other members of this family. Signaling events engaged via CD30 are still unknown. We here identify the NF-κB transcription factor as a target of the CD30-induced signal pathway in Hodgkin's disease (HD) cells. Exposure of HD cells to CD30 ligand induces release of interleukin-6 (IL-6) that can be duplicated by cross-linking HD-cells to an agonistic anti-CD30 specific monoclonal antibody (κCD30), but not by cross-linking to an isotype-identical irrelevant monoclonal antibody. Cross-linking of HD cells to κCD30 leads to enhanced accumulation of IL-6 mRNA in a time-dependent fashion resulting from transcriptional activation of the IL-6 promoter. Transient transfection assays using a series of deleted IL-6 promoter constructs linked to the human growth hormone gene as a reporter gene furthermore indicate that transcriptional activation of the IL-6 promoter requires the presence of an intact NF-κB binding site. In addition, introduction of an NF-κB binding site appeared to be sufficient to confer inducibility of a heterologous promoter on activation of CD30 in HD cells. Cross-linking of CD30 promotes rapid and transient binding activity of nuclear proteins to the NF-κB recognition site of the IL-6 promoter. Supershift experiments using a series of monoclonal antibodies recognizing distinct members of the NF-κB transcription factor family furthermore indicate that in CD30 cross-linked HD cells p65, p50/Rel-A, and Rel-B are present, whereas the c-rel protein is not.

CD30 HAS BEEN originally identified as a cell surface antigen expressed on both, primary and cultured Hodgkin and Reed-Sternberg (H-RS) cells. CD30 is a phosphorylated membrane glycoprotein of 120 kD derived from a non-phosphorylated 84-kD apoprotein. Most primary H-RS cells, except those present in the lymphocyte-predominant subtype of Hodgkin's disease (HD), display CD30 as shown by immunohistochemistry. Subsequent studies have shown surface expression of CD30 not only on HD-derived cells but also on a variety of other malignant as well as nonmalignant cell types, including mitogen- or antigen-activated T cells, virally transformed T and B cells, and natural killer cells. Recent cloning of the CD30 cDNA has shown that CD30 belongs to the tumor necrosis factor/nerve growth factor (TNF/NGF) receptor superfamily. CD30 shares in its extracellular ligand-binding domain significant homology to other members of this family, including the type I and type II TNF receptors, CD27, CD40, 4-1BB, OX40, and CD95 (Fas/Apo-1).

More recently, the CD30 ligand (CD30L) was cloned and also characterized as a novel member of the TNF-like protein family. Like other members of this family, CD30 ligand exerts a plethora of biologic effects on its target cells. For instance, CD30L exerts mitogenic effects on activated T cells, promotes surface expression of the intercellular adhesion molecule-1 (ICAM-1/CD54), and induces secretion of secondary cytokines such as interleukin-2 (IL-2), TNF-α, or interferon-γ (IFN-γ). Cultured "T-cell-like" HD cells have been shown to proliferatively respond to CD30L or to cross-linking with κCD30 antibodies, whereas "B-cell-like" HD cells did not. CD30L enhances secretion of several cytokines such as IL-6, TNF, and LT-α by cultured H-RS cells. CD30L also upregulates surface expression of CD54 and B7 family members on activated T cells and cultured H-RS cells. These molecules are frequently overexpressed in primary H-RS cells. Increased CD30 surface expression as well as elevated serum levels of soluble CD30 (sCD30) have been associated with advanced disease and bulky tumor states and/or the presence of B-symptoms in HD patients. High levels of sCD30 have also been linked to short disease-free survival and may thus be of prognostic significance.

However, the role of CD30 in the pathogenesis of HD is still poorly understood. CD30 may provide proliferative responses either directly or may also spur proliferation of HD cells indirectly via induction of release of secondary cytokines such as IL-6, TNF, and LT-α. So far, the molecular mechanisms leading to cytokine secretion by HD cells remain enigmatic. The close association of CD30 surface expression, increased levels of sCD30 in sera of HD patients, and the presence of B-symptoms, likely to be caused by IL-6, TNF-α, and other polypeptides detectable in the sera of HD patients, suggests that activation of CD30 may play a causative role for the release of secondary cytokines by HD cells. To further substantiate this notion, we have examined the ability of various monoclonal antibodies (MoAbs) capable of binding and activating CD30L to induce release of IL-6 and have also investigated some of the underlying mechanism.

MATERIALS AND METHODS

Cell culture. The human HD-derived cell lines HDLM-2 and KM-H2 (kindly provided by Dr H. G. Drexler, DSM, Braunschweig, Germany) were maintained in RPMI 1640 medium supplemented with 10% low-endotoxin heat-inactivated fetal calf serum (Hazelton, Germany).

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from each sample was then electrophoresed on a paper (Schleicher and Schuell, Dassel, Germany) in 1.5X SSC (1.5 mmol/L NaCl and 150 mmol/L sodium citrate) using the diethyl aminoethyl (DEAE)-Deutan method as previously described.11 Cells were fixed with 1% paraformaldehyde for 5 minutes at 25°C, as detailed elsewhere.11,12,14

Assessment of cytokine levels in cell-free culture supernatants. Levels of IL-6 were determined in cell-free culture supernatants by commercially available enzyme-linked immunosorbent assays (ELISA; R&D Systems, Minneapolis, MN) according to the manufacturer’s guidelines.

RNA extraction and Northern blot analysis. Northern blot analysis of IL-6 mRNA expression was performed as previously described in detail.27,28 Briefly, cells were resuspended in guanidinium isothiocyanate (Sigma, München, Germany) and extracted with an equal volume of acetate/EDTA-equilibrated phenol (60°C for 25 minutes with frequent vortexing). The aqueous phase was recovered after centrifugation and extracted once with an equal volume of phenol/chloroform and twice with chloroform. The resulting RNA was precipitated overnight at −20°C with 2.5 vol of ethanol. The total RNA from each sample was then electrophoresed on a 1% agarose gel containing 20 mmol/L sodium borate, pH 8.3, 0.5 mmol/L EDTA, and 3% formaldehyde. The RNA was transferred to nitrocellulose paper (Schleicher and Schuell, Dassel, Germany) in 10X SSC (1.5 mmol/L sodium chloride and 150 mmol/L sodium citrate) using capillary blotting overnight. The blots were baked and prehybridized at 55°C, 2X SSC containing 1% SDS for 2 hours, hybridization at 42°C for 16 hours, filters were rinsed in 2X SSC at 55°C, and RNAase at 37°C and finally washed in 0.1X SSC and 0.1% SDS. The blots were then washed at 55°C in 1X SDS/×1 SSC and were autoradiographed with a Kodak X-omat film (Eastman Kodak, Rochester, NY) at −70°C with an intensifying screen.

Nuclear run-on assays. For nuclear run-on transcription assays, HDLM-2 cells (107) were lysed in a lysis buffer consisting of 10 mmol/L Tris-HCl, 5 mmol/L KCl, 60 mmol/L MgCl2, and 0.5% Nonidet P 40 (Sigma) and were washed in ice-cold phosphate-buffered saline (PBS). Nuclei were incubated at 26°C in 15% glycerol; 70 mmol/L KCl; 2.5 mmol/L MgCl2; 10 mmol/L EDTA; 4 mmol/L L levels each of ATP, CTP, and GTP; 0.5 mmol/L dithiothreitol; 60 U/mL RNAsin (Boehringer Mannheim, Mannheim, Germany); and in the presence of 100 µCi of [3H]UTP (3,000 Ci/mmol; Amer sham Buchler, Braunschweig, Germany). The blots were then washed at 55°C in 1X SDS/×1 SSC and were autoradiographed with a Kodak X-omat film (Eastman Kodak, Rochester, NY) at −70°C with an intensifying screen.

Preparation of nuclear proteins and electrophoretic mobility shift assays (EMSA). EMSA were performed essentially as previously described.27 Briefly, nuclear extracts were prepared from HDLM-2 cells which had (or had not) been cross-linked to M44 according to the Dignam method. Protein concentrations were determined by the Bradford assay. Double-stranded oligodeoxynucleotides (NF-κB sense, 5'TCGAGGAAATGTGGGATTTCCAGGCG-3'; NF-κB antisense, 5'TCTGGGAAATCCCCACATTTCCTCTC-GAGGC-3' [the binding sites are underlined]; mutated NF-κB sense, 5'TCGAGGAAATGTGGGATTTCCAGGCG-3'; NF-κB antisense, 5'TCTGGGAAATCCCACTTCCTCTC-GAGGC-3' [mutated bases are in small letters]) corresponding to the NF-κB binding site of the IL-6 promoter were synthesized, annealed, and end-labeled. The NF-κB binding site in the IL-6 promoter (position −84 to −72) was excised as a 66-bp fragment (position −115 to −49) by Sau96I/Stylp digestion and subcloned. The end-labeled oligodeoxynucleotides or isolated DNA fragments (1 ng; approximately, 10,000 cpm) were incubated with 10 ng nuclear proteins in an incubation buffer, as previously described,27 for 20 minutes at room temperature. For competition assays, incubation was performed in the presence of 25-fold molar excess of unlabeled double-stranded oligomers containing the NF-κB recognition sequence or a mutated binding sequence. The reaction products were analyzed by electrophoresis in a 5% polyacrylamide gel followed by autoradiography. In selected experiments, antibodies to p50-NF-κB, p50-NF-κB, c-Rel, and Rel-B (Santa Cruz Inc, Santa Cruz, CA) were used to further identify the nature of the proteins bound to the NF-κB recognition sequence. These supershift assays were performed with an incubation buffer containing 20 mmol/L HEPES, pH 7.9, 20% (vol/vol) glycerol, 300 mmol/L KCl, 0.5 mmol/L EDTA, 10 mmol/L dithiothreitol (DTT), 100 mmol/L phenylmethylsulfonyl fluoride (PMSF), 40% (vol/vol) Ficoll, 1 µg BSA (10 mg/mL), and 0.1 µg polydeoxyinosinic-deoxyctydilic acid (poly-dIdC; 1 mg/mL).

Transient transfection assays. Promoter constructs used for transient transfection assays have been described before.27 In addition, the 66-bp fragment containing the NF-κB binding site of the IL-6 promoter was cloned into the same vector (pTKGH) containing the heterologous thymidine kinase promoter linked to the human growth hormone gene as reporter gene. Transient transfections were performed using commercially available liposomes (Boehringer Mannheim) as detailed by the manufacturer. Cells were cultured in the presence of liposome-complexed DNA for 24 hours, split, and cultured on plates coated with the M44 MoAb or an irrelevant isotype-matched monoclonal antibody for additional 24 hours followed by analysis of human growth hormone activity (hGH) in cell-free culture supernatants using an hGH-specific EIA (Eurogenetics, Tessenderlo, Belgium).

RESULTS

In the first set of experiments we have investigated whether activation of CD30 is associated with secretion of IL-6. To this end, HDLM-2 cells and KM-H2 cells were either exposed to CD30L or cross-linked to either an agonistic anti-CD30 MoAb M44 or an irrelevant isotype-matched antibody for up to 96 hours. As shown in Fig 1, both M44 as well as CD30L were capable of inducing secretion of IL-6 by HDLM-2 cells and KM-H2 cells in a time-dependent fashion, whereas cross-linking to the isotype-identical control MoAb failed to promote IL-6 synthesis during the time period investigated (Fig 1). U-937 leukemia cells that do not express CD30, failed to respond to M44 or CD30L with release of IL-6 (data not shown).

Secretion of IL-6 by HDLM-2 cells after stimulation with M44 was preceded by enhanced synthesis of IL-6 transcripts.
CD30 ENHANCES IL-6 SECRETION BY HODGKIN CELLS

Fig 1. Activation of CD30 induces release of IL-6 by HD cells. HDLM-2 cells or KM-H2 cells were cross-linked to M44 or to an isotype-matched irrelevant control antibody (Control MoAb) or were cultured in the presence of paraformaldehyde-fixed CV-1 cells that had been transfected either with vector alone (CV-1/HAV) or with the full-length CD30L cDNA (CV-1/CD30L) for the time period indicated. IL-6 protein was quantitated by ELISA in cell-free culture supernatants. Results are expressed as the means ± SD of three independent experiments. Comparable results were also obtained when HDLM-2 cells or KM-H2 cells had been cross-linked to another agonistic antibody directed against CD30 designated M67 (data not shown).

HDLM-2 constitutively accumulate IL-6 mRNA that is further enhanced by threefold 12 to 24 hours after cross-linking of HDLM-2 cells to M44 and decreased to starting levels within the following 24 hours (Fig 2). Cross-linking to an isotype-identical irrelevant MoAb failed to enhance IL-6 mRNA accumulation in these cells over the 48-hour observation period (data not shown). Enhanced IL-6 mRNA accumulation was also observed in HDLM-2 cells cultured in the presence of CV-1/EBNA cells transfected with the full-length human CD30-ligand cDNA, but not in cells transfected with the vector only (Fig 2). Similarly, KM-H2 cells also responded to either αCD30 cross-linking or CD30L stimulation with enhanced accumulation of IL-6 mRNA transcripts (data not shown).

Transcriptional run-off assays furthermore indicated that IL-6 mRNA accumulation after cross-linking of HDLM-2 cells to M44 was, at least in part, due to transcriptional activation of the IL-6 gene (Fig 3). Cross-linking HDLM-2 cells to M44 for 30 minutes was sufficient to enhance the transcriptional rate of the IL-6 gene by twofold to threefold, whereas the transcriptional activity of the GAPDH-gene remained unaffected (Fig 3).

To further delineate the molecular mechanism responsible for transcriptional activation of the IL-6 gene induced by cross-linking to CD30, a series of deleted IL-6 promoter constructs was instrumental.27 These constructs were transiently transfected into HDLM-2 cells followed (or not) by cross-linking to M44 and quantitation of human growth hormone activity as a reporter gene product in cell-free supernatants. The results summarized in Fig 4 indicate that cross-linking of CD30 to M44 resulted in transcriptional activation of the IL-6 promoter in HDLM-2 cells by fourfold to fivefold. Deletion of the IL-6 promoter up to position -107 did not significantly interfere with the capacity of CD30 activation to promote transcriptional activity. This deleted construct still harbors the recognition site for the NF-κB transcription factor that has previously been shown in several studies to be essential for IL-6 gene activation.27-31 Deletion of the AP-1 binding site (position -283 to -277) or deletion of the NF-IL6 binding site (position -158 to -145) did not prevent transcriptional activation of the IL-6 promoter in HDLM-2 cells on cross-linking to M44 antibody (Fig 4). Deletion of the IL-6 promoter up to position -49, which eliminates the NF-κB binding site as well as deletion of the NF-κB transcription factor binding site in the context of the intact IL-6 promoter resulted in complete loss of transcriptional activation of the promoter by CD30 in HD cells (Fig 4). To exclude that the deleted 66-bp fragment contained binding sites for additional transcription factors that may also contribute to the transcriptional activation of the IL-6 promoter by CD30 activation, gel mobility shift experiments were performed using this fragment as a probe. DNA-protein complexes formed by nuclear extracts obtained from cells which had or had not been cross-linked to CD30 did not differ from those obtained when probed with the oligonucleotide that contains the NF-κB binding site only. Moreover, DNA-protein complex formation was relieved by excess unlabeled NF-κB oligonucleotide, suggesting that the 66-bp DNA fragment deleted is targeted by NF-κB only (data not shown).

The capacity of CD30 to promote functional activation of the NF-κB transcription factor was also shown by demonstrating that a heterologous promoter construct carrying the NF-κB recognition site responded to cross-linking of M44 with enhanced activation in HDLM-2 cells, whereas a control construct, not containing the NF-κB recognition sequence, failed to do so (Fig 5). Similarly, the deleted 66-bp fragment of the IL-6 promoter containing the NF-κB recognition site (position -115 to -49) conferred a sixfold to eightfold enhanced activation in HDLM-2 cells after CD30 cross-linking of the heterologous thymidine kinase promoter (Fig 5).

Moreover, gel mobility shift assays showed that cross-linking of M44 to HDLM-2 cells was sufficient to promote binding activity of NF-κB, whereas cross-linking of an isotype-identical MoAb had no effect on NF-κB binding activ-
Enhanced binding activity was detectable within 15 minutes upon cross-linking to CD30, peaked after 1 to 2 hours and decreased to starting levels within 24 hours (Fig 6). DNA binding activity was specific as shown by competition assays. To further ascertain the nature of the NF-κB transcription factor subunits involved in DNA-protein complex formation, supershifts were performed with antibodies to single members of the c-rel/NF-κB transcription factor family. Although in the presence of αp50, αp65/Rel-A, and αc-Rel supershifted bands became readily detectable, no supershift was observed in the presence of αRel-B. An irrelevant antibody directed against the c-jun component of the AP-1 transcription factor also failed to supershift any protein bound to the NF-κB recognition sequence.

**DISCUSSION**

CD30 serves as a marker antigen to detect the H-RS cells in HD-involved tissue sections. CD30 expression has been proven as a useful pathologic and clinical marker for HD. However, the functional role of CD30 in the pathogenesis of HD is still poorly understood. We show here in cultured H-RS cells that activation of CD30 by cross-linking with a specific agonistic MoAb results in nuclear translocation of the NF-κB transcription factor. This leads to transcriptional activation of the IL-6 gene, resulting in enhanced accumulation of IL-6 mRNA known from previous studies to be constitutively transcribed by H-RS cells and finally in enhanced release of the IL-6 protein. This response appeared to be specific in that it could be duplicated by another agonistic antibody (M67) or by CD30L, whereas an isotype-matched irrelevant antibody failed to promote IL-6 release by these cells. Truncation of the IL-6 promoter up to the NF-κB site in the intact IL-6 promoter prevented transcriptional activation of the IL-6 promoter upon CD30 activation. As shown in gelmobility shift assays, this 66-bp fragment did not harbor any other binding sites apart from that recognized by members of the NF-κB protein family.

Moreover, the NF-κB recognition site or the 66-bp fragment containing the NF-κB DNA-binding site of the IL-6 promoter 5' of a heterologous thymidine kinase promoter was also sufficient to confer transcriptional activation through CD30. Activation of CD30 enhanced NF-κB binding activity time-dependently. Supershifts performed in the presence of MoAbs recognizing distinct members of the NF-κB/c-Rel transcription factor family furthermore showed that the NF-κB complex induced by the CD30 signaling pathway consists of p65/Rel-A, p50, and c-Rel subunits; the Rel-B protein was not detectable upon CD30 activation in HDLM-2 cells.

Previous studies have shown that primary and cultured H-RS cells constitutively transcribe the IL-6 gene. In addition, both transcript and surface protein expression of the IL-6 receptor p80 (IL-6R) molecule have also been detected on both primary and cultured H-RS cells. Coexpression of IL-6 and IL-6R in HD-derived cell lines and...
primary H-RS cells may thus point to a role for IL-6 in the pathophysiology of HD, such as autocrine/paracrine growth regulatory loops. In line, herewith, we have observed that transient suppression of IL-6 and IL-6R gene expression by antisense-oligonucleotides reduces in vitro survival of H-RS cells (H.J.G. unpublished results). In addition, IL-6 participates in the regulation of several acute-phase genes that may contribute to the evolution of clinical “B”-symptoms seen in HD patients. Elevated IL-6 serum levels in HD patients correlate with increases of acute-phase reactants such as C-reactive protein (H.J.G. manuscript in preparation).

In line with several other studies exploring the transcriptional regulation of the IL-6 gene, our data also indicate that the NF-κB recognition sequence is of crucial importance for the regulation of this gene. Although several other transacting molecules have been identified in the promoter of the IL-6 gene, including an AP-1 or an NF-IL6 site..

**Fig 4.** Activation of CD30 transcriptionally activates the IL-6 promoter through the NF-κB site. HDLM-2 cells were transiently transfected with a series of deleted IL-6 promoter constructs linked to the hGH as a reporter gene. Twenty-four hours after transfection, HDLM-2 cells were split and either cross-linked to M44 or to the control MoAb, were cocultured with CV-1/HAV or CV-1/CD30L cells, or were cultured in standard culture medium (Control) for an additional 24 hours. Thereafter, hGH activity was quantitated in cell-free culture supernatants by a commercially available EIA. The fold-induction of hGH activity in M44-cross-linked cells is expressed as the mean values ± SD of three independent experiments.

![Insertion of the NF-KB binding site 5' of a heterologous promoter is sufficient to confer inducibility by CD30. A double-stranded oligodeoxynucleotide harboring the NF-KB recognition sequence of the IL-6 promoter was inserted (pNF-kappaB/TKGH) or not (pTKGH) 5' of a heterologous herpes thymidine kinase (TK) promoter linked to the hGH gene as a reporter gene. In addition, the 66-bp fragment of the IL-6 promoter containing the NF-κB binding site was fused to the TK promoter/hGH reporter gene construct (p66bp-NF-kappaB/TKGH). HDLM-2 cells were transiently transfected with either construct, split 24 hours after transfection, and cross-linked to M44 or control MoAb for an additional 24 hours. Thereafter, hGH activity was quantitated in cell-free culture supernatants using a commercially available hGH EIA. Results are expressed as mean ± SD of three independent experiments.](image)

**Fig 5.** Insertion of the NF-κB binding site 5' of a heterologous promoter is sufficient to confer inducibility by CD30. A double-stranded oligodeoxynucleotide harboring the NF-κB recognition sequence of the IL-6 promoter was inserted (pNF-kappaB/TKGH) or not (pTKGH) 5' of a heterologous herpes thymidine kinase (TK) promoter linked to the hGH gene as a reporter gene. In addition, the 66-bp fragment of the IL-6 promoter containing the NF-κB binding site was fused to the TK promoter/hGH reporter gene construct (p66bp-NF-kappaB/TKGH). HDLM-2 cells were transiently transfected with either construct, split 24 hours after transfection, and cross-linked to M44 or control MoAb for an additional 24 hours. Thereafter, hGH activity was quantitated in cell-free culture supernatants using a commercially available hGH EIA. Results are expressed as mean ± SD of three independent experiments.

**Fig 6.** Activation of CD30 results in enhanced binding activity of NF-κB. (A) HDLM-2 cells were cross-linked to M44 for the time-period indicated followed by preparation of nuclear proteins and gel mobility shift assays as detailed in the Materials and Methods using a double-stranded oligodeoxynucleotide that contains the NF-κB recognition sequence as a probe. Specificity of complex formation was confirmed by competition assays using 25-fold molar excess of unlabelled double-stranded oligodeoxynucleotide containing the NF-κB binding sequence (wt Comp) or a mutated NF-κB binding sequence (mt Comp) as detailed in the Materials and Methods. (B) Supershift experiments depicted in the right panel were performed by incubating nuclear extracts with the radiolabeled probe in the presence of the antibodies indicated.
these molecules do not appear to play a major functional role for IL-6 gene regulation in response to CD30 in cultured HD cells. The pivotal role of the NF-κB transcription factor for regulation of the IL-6 gene has previously been shown in “knock out” mice.5,9,32

The signaling events leading to nuclear translocation and activation of NF-κB by CD30 are still unknown. Within the intracellular signal-transmitting domain of CD30, no significant homology to other members of the TNF/NGF receptor superfamily or other cytokine receptor families exists.19 Nevertheless, several members of the TNF-receptor superfamily share common biologic activities, including activation of the NF-κB transcription factor.26 The type I TNF-receptor has been shown to mediate NF-κB activation through a stretch of 40 AA in the distal cytoplasmatic tail.27 This region is also involved in activation of acidic sphi- nomyelinase and in TNF-α-mediated cytotoxicity.35,36 The type II TNF-receptor has more recently been shown to induce NF-κB activation through recruitment of two novel TNF-receptor–associated factors (TRAF) 1 and 2.29 These molecules appear to constitute a growing family of signal transducing proteins involved in signaling of the TNF-receptor family. A homologous protein, designated CRAFI/CD40BP/ LAP-1 (TRAF 3), has recently been identified to be associated with the CD40 receptor.40 It is tempting to speculate that similar molecules are involved in transmitting signals from the CD30 receptor and are also involved in activation of the NF-κB transcription factor.

Besides regulating IL-6 gene expression, the NF-κB transcription factor also significantly contributes to the transcriptional regulation of several other cytokine genes such as TNF, IFN-γ, or IL-2; cytokine receptor genes; and adhesion molecules.41-43 It is therefore tempting to speculate that the activation of NF-κB in response to CD30L leads to the release of other cytokines, surface expression of cytokine receptors and adhesion molecules, and may thus represent an important factor in the promotion of cellular activation and development of B-symptoms associated with HD.

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CD30 ENHANCES IL-6 SECRETION BY HODGKIN CELLS
Activation of Hodgkin cells via the CD30 receptor induces autocrine secretion of interleukin-6 engaging the NF-kappabeta transcription factor

HJ Gruss, D Ulrich, SK Dower, F Herrmann and MA Brach