

Review article

The role of CD30 in atopic disease

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Introduction

Historical background

The functional role of CD30 has been a matter of debate during the last decade. This molecule has a very distinct expression on lymphoid cells, a fact which indicates a specific immunologic function. The findings that CD30 knockout mice have enlarged thymuses and that CD30 transgenic mice exhibit enhanced killing of thymocytes suggest a role for CD30 in the negative selection in the thymus. However, the function of CD30 in mature T cells is still unknown. CD30 has been associated with T helper (Th) 2 cells and with human disorders dominated by a Th2 type of immune response. This review summarizes the findings on CD30 in atopic disorders, with the focus on atopic dermatitis (AD).

The CD30 (Ki-1) surface antigen was originally identified on the tumor cells of Hodgkin's disease, i.e., Hodgkin and Reed-Sternberg cells (1). The monoclonal antibody (mAb) which was produced reacted selectively not only with the Hodgkin and Reed-Sternberg cells, but also with a small but distinct population of cells in lymph nodes and tonsils, as well as scattered CD30⁺ cells in the bone marrow (1). Further screening for CD30 expression identified CD30/Ki-1 positive non-Hodgkin's lymphoma, and anaplastic large-cell lymphomas (2). It was also found that CD30 is activation dependent, since it is virtually absent on normal resting peripheral blood mononuclear cells (PBMC), but can be induced by mitogen activation, or by infection by viruses such as Epstein-Barr virus (EBV) or human T-cell leukemia viruses (HTLV I and II) (2). Subsequently, it was demonstrated that CD30 is expressed by a subset of

CD45RO⁺ (memory) T cells (3). The CD30 molecule is a type I transmembrane protein of 120 kDa with a 90-kDa nonglycosylated precursor (4) (Table 1, Fig. 1). CD30 was cloned in 1992 and determined to be a member of the tumor necrosis factor receptor (TNF) superfamily (5). It is characterized by six cysteine-rich motifs in the extracellular domain, showing significant homology to the other TNFR family members. In the intracellular parts, however, no homology was found (5) (Fig. 1).

Soluble CD30

A soluble form of CD30 (sCD30) has been described (6) (Table 1). This 85/88-kDa molecule is generated when the membrane-bound CD30 protein is cleaved by a zinc metalloproteinase and released from the cell surface (7). The sCD30 shedding can be enhanced by certain anti-CD30 antibodies (8, 9) or by interaction with CD30L⁺ cells (10). sCD30 can be detected both *in vivo*, in serum, and *in vitro*, in cell-culture supernatants of CD30⁺ cells (6), with a highly sensitive ELISA test kit. Elevated levels of sCD30 have been found in several human disorders, such as various lymphomas and infectious diseases, including Hodgkin's disease and HIV infection (11, 12), while the levels are relatively low in normal healthy subjects. A role for sCD30 as a marker of disease activity and with prognostic significance has been suggested. Indeed, a correlation between disease spread and tumor burden has been shown in Hodgkin's disease patients (11). Furthermore, in patients with HIV infection, a faster progression to AIDS could be demonstrated in patients with elevated sCD30 levels in the early phases of infection (12). The possible

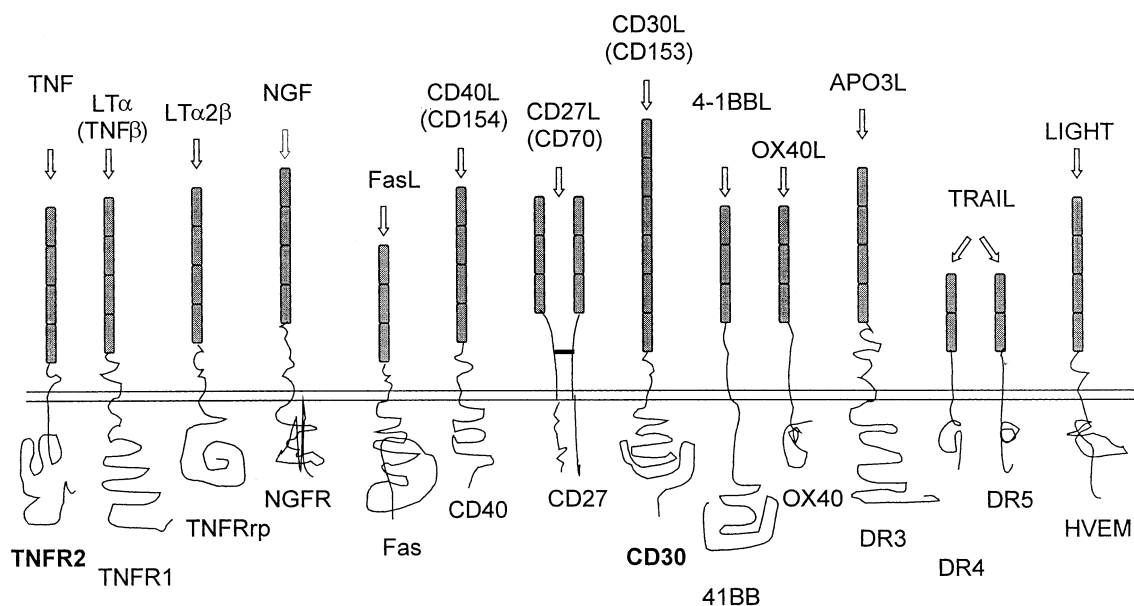


Figure 1. The rapidly expanding TNF receptor and ligand families. (modified after Herbein & O'Brien [97]).

immunologic function of sCD30 is not clear. Circulating sCD30 might reflect ongoing biologic events involved in CD30-related diseases.

The CD30 ligand

The 26–40-kDa CD30 ligand (CD30L/CD153) has been cloned and shown to be a member of the TNF ligand family (13) (Table 1, Fig. 1). This type II membrane protein is not detectable on resting T cells and macrophages, but it is expressed on both activated T cells and macrophages (13, 14). Furthermore, CD30L expression on resting B cells (15), granulocytes, eosinophils, and neutrophils (16), as well as on various neoplastic cells (17), has been reported. Signal transduction through CD30 has been found to augment proliferation under some circumstances (13), but in other cases to potentiate apoptosis (18). Interestingly, CD30L has been detected in the human thymus. A high expression of CD30L was observed in the outer wall of Hassall's corpuscles, structures in the thymic medulla containing epithelial cells, macrophages, and cell debris, and on epithelial cells in the medullary areas. In addition, CD30 expression was found on CD4⁺ CD8⁺ medullary thymocytes, indicating that an interaction between CD30/CD30L could occur in the thymic medulla (19). Indeed, CD30 knockout mice have enlarged thymuses and increased number of thymocytes compared to littermates (20). These data strongly suggest that the CD30/CD30L interaction is involved in the negative selection in the thymus.

In our laboratory, we made the novel observation of CD30L⁺ cells in the fetal part of the placenta. In all the placental specimens studied, CD30L⁺ cells were detected all over the mesenchymal part of the chorionic

villi, in villous stroma, and close to the trophoblast area. Scattered positive cells were also detected in the mesenchymal part of the chorionic plate, in the decidual region, and in umbilical cord tissue (21). From the structure of the CD30L immunoreactive cells in the villous stroma, we concluded that these cells are probably placental macrophages, i.e., Hofbauer cells (22). Indeed, the localization of these cells close to fetal vessels and trophoblasts makes a regulatory function of these cells likely. It is possible that the CD30L expression observed on these placental macrophages plays a role in immune regulation. It is also interesting that the placenta has been proposed to be a site for extrathymic T-cell development (23). Furthermore, a regulatory role for CD30 has been suggested in primary cutaneous CD30⁺ T-cell lymphomas, in which CD30L was expressed in regressing lesions, but not in growing ones (24).

CD30 expression in health and disease

CD30 expression under normal conditions

CD30 is preferentially expressed by activated lymphoid cells. In normal peripheral organs, however, CD30 expression is rather low. Resting peripheral blood lymphocytes were found to be negative for CD30. However, one recently published article showed that a variable proportion (3–31%) of circulating T cells in the normal peripheral blood are CD30⁺, and many of these are CD8⁺ T cells (25). This variability in results is probably due to the sensitivity of the staining technique. CD30⁺ cells can also be detected within the parafollicular areas and in the rim of the follicular centers in the lymph nodes (26). In addition, CD30⁺ cells are found

in the medulla of the thymus, mainly around Hassall's corpuscles (19). B cells also express CD30 to a variable extent, as do activated NK cells, endothelial cells, and decidual cells (27–30). sCD30 levels in normal individuals vary, but are usually very low (6–7, 11–12). However, in some studies in which healthy blood donors were used as controls, very high sCD30 levels have been reported (31, 32), most notably in the younger age groups (32). Since CD30 is upregulated after virus infections, the high sCD30 levels in these individuals could be explained by EBV infection (33).

CD30 expression in malignant lymphomas and infectious diseases

In contrast to the low levels of CD30 in healthy individuals, high expression of CD30 has been demonstrated in tumors of the immune system, the malignant lymphomas. CD30 expression is important for the identification of Hodgkin's disease (HD), anaplastic large-cell lymphoma (ALCL), and CD30⁺ non-Hodgkin's lymphoma. In HD, CD30 is expressed by the giant multi- and mononucleated Hodgkin and Reed-Sternberg cells. The origin of these cells is still unknown (10). Patients with HD also have elevated levels of sCD30 in their blood, in correlation with the clinical features (11). Overexpression of CD30 has also been detected in nonhematolymphoid neoplasms, such as embryonal carcinomas (34), and in some seminomas (35, 36).

CD30 also appears to play a role in nonneoplastic diseases. The number of CD30⁺ cells/levels of sCD30 increases in patients with infectious mononucleosis (33), which is usually caused by EBV. There is overexpression of CD30 also in HIV, hepatitis B, and hepatitis C (12, 37, 38). Moreover, when the expression and release of CD30 were investigated in patients with measles infection, elevated sCD30 levels and an expansion of the CD4⁺ CD30⁺ and CD8⁺ CD30⁺ cells subsets compared to healthy controls were shown (39).

CD30 and Th2-related conditions

The identification of the two T helper subsets, Th1 and Th2, which each produce a distinct pattern of cytokines, has helped us to understand the mechanisms by which polarized immune responses occur *in vivo* in various human conditions, and in response to different pathogens. Indeed, Th1 cells are involved in monocyte/macrophage-mediated inflammatory responses, while Th2 cells promote Ig production and enhance eosinophil and mast-cell activation and proliferation (40–42). Th subsets with less differentiated cytokine profiles, designated Th0, usually mediate intermediate effects, depending on the ratio of cytokines produced and the type of target cell (41, 43). It has been shown that during early T-cell activation, the surrounding environment determines the profile of the subsequent T-cell response. IL-4 favors the development of a Th2 response, while

Table 1. Characteristics of CD30 and CD30 ligand (CD30L)

	Molecular mass (kDa)	Protein type	Soluble form	Protein family
CD30	120	Type I	85–88 kDa	TNF receptor
CD30L (CD153)	26–40	Type II	Not known	TNF ligand

IL-12 promotes a Th1 response. Furthermore, it has been suggested that the two subsets counteract each other's development and activities, since Th2-type cytokines (IL-4, IL-10) inhibit Th1 responses, and Th1-type cytokines (IFN- γ) repress the development of Th2 responses (40–42). Strongly polarized human Th1 and Th2 responses not only are involved in protection, but also cause various types of human immunopathologic reactions (44). Human disorders in which a Th1 type of response is believed to predominate include contact dermatitis, multiple sclerosis, rheumatoid arthritis, and unexplained recurrent abortions (45–48). On the other hand, a predominately Th2 type of response has been proposed to be involved in atopic disorders, progression to AIDS in HIV infection, and Omenn's syndrome, as well as in successful pregnancy (45, 49–51) (Table 2).

It has been shown that CD30 expression is dependent on activation (52, 53). Exactly what regulates CD30 expression is, however, still unknown. After analysis of CD30 expression in CD4⁺ T-cell clones, it was suggested that CD30 is preferentially expressed by those identified as Th2 (54, 55). Our own data on allergen-specific T-cell clones contradict the results of Del Prete et al., since we observed that Th1 and Th0, as well as Th2, clones had the ability to express CD30 after activation (53). However, in our data, we noted an extended expression of CD30 and a higher mean fluorescence intensity (MFI) in the clones defined as Th2. Hamann et al. have since confirmed our results by showing, in a large panel of human Th1, Th0, and Th2 clones, that no correlation existed between CD30 expression and Th phenotype (56). Thus, the correlation between CD30 expression and cytokine profile is controversial, and CD30 may not be used as a marker to define the Th2 cell subset.

Still, the higher MFI and the extended expression of CD30 in the cells defined as Th2 might suggest an association of this molecule with Th2-mediated diseases such as allergy. Indeed, increased expression of CD30 and the release of its soluble counterpart have also been found in several Th2-related diseases (57). When the presence of CD30 was assessed in the target organs of patients with diseases characterized by Th1 profiles (multiple sclerosis, Crohn's disease, and *Helicobacter pylori*-induced gastric antritis) or Th2 profiles (Omenn's syndrome, systemic sclerosis, and graft versus host disease), high CD30 expression was detected in the Th2-related, but not in the Th1-related, disorders (57).

Table 2. Th2-related conditions with enhanced expression/release of CD30

Disorder
Atopic allergy (Refs. 69–72, 74, 77–80)
Omenn's syndrome (50)
Human immunodeficiency virus (HIV) infection (12)
Systemic sclerosis (101)
Graft versus host disease (GVHD) (57)
Systemic lupus erythematosus (SLE) (102)

It has been suggested that there is an alteration to a Th2-type pattern in HIV-infected individuals (58). Moreover, large numbers of CD8⁺ T-cell clones with a Th2-type cytokine pattern were established from the blood and skin of patients with advanced HIV infection (59). In view of the overexpression of CD30 in HIV infection, this might also imply an involvement of CD30 in Th2 responses occurring *in vivo*.

It has also been shown that CD30 is expressed by decidual cells (30). We confirmed these findings when we analyzed placenta specimens from atopic and nonatopic mothers for the presence of CD30 by immunohistochemistry. As previously reported, CD30 expression was found on the decidual stromal cells, but nowhere else in the placenta or umbilical cord (21). However, the expression of CD30 in human decidual cells might mirror the Th2-skewed environment in the fetal-maternal interface, and/or have the function of maintaining the Th2 response. The mechanism correlating CD30 to Th2 cells and Th2-type of responses is still unknown. However, experiments performed in mice have revealed relevant results on the regulation of CD30 expression. Nakamura et al. showed that IL-4 induced CD30 expression on activated CD4⁺ T cells, while IFN- γ antagonized this induction (60). This could explain the preferential and sustained expression of CD30 on Th2 cells (53, 55). Furthermore, Gilfillan et al. demonstrated that CD30 expression on activated T cells required exogenous IL-4 or costimulation via CD28 (61).

The role of CD30 in allergy

Atopic dermatitis (AD)

AD is a chronically relapsing inflammatory skin disease that often precedes respiratory allergy. It is a worldwide health problem, affecting around 5–20% of children (62). The first symptoms of AD are present early in life, before 1 year of age in approximately 60%, and before 5 years in 90% of the patients (63). Many factors have been thought to contribute, in a complex interrelationship, to the development and severity of AD; e.g., genetic, environmental, dermatologic, pharmacologic, psychologic, and immunologic factors (64). The diagnosis of AD is based on the presence of major and associated clinical features, including severe pruritus, a chronically relapsing course, typical structure, and distribution of the skin lesions, as well as a history of atopic disease (65). The immunopathology of AD is not fully understood. However, most patients with AD have elevated levels of serum IgE and elevated numbers of circulating eosinophils, reflecting an increased expression of Th2 cytokines (66). Indeed, a number of studies have demonstrated increased frequency of allergen-specific T cells producing increased IL-4, IL-5, and IL-13, but little IFN- γ , in the peripheral blood of patients with AD (67). Various forms of therapy, including corticosteroids, UV therapy, and immunosuppressants, are now used in the management of this complex disease (64, 68). However, further studies are needed to develop strategies to prevent the initiation of AD. Reduction of Th2 responses by blocking the actions of the different molecules involved, as well as trying to restore a balance between Th1 and Th2 cytokine responses, will be essential.

CD30 in AD

To elucidate the role of CD30 in AD, we analyzed serum samples from patients diagnosed with AD for the presence of sCD30. We measured significantly higher levels of sCD30 in the serum of the AD patients than

Table 3. Allergic disorders with and without involvement of CD30 *in vivo*

Allergic disorder	CD30 involvement	Correlation between CD30 and clinical symptoms
Atopic dermatitis (AD)	CD30 ⁺ infiltrating T cells in lesions (70, 72, 74) Elevated levels of sCD30 (31, 69, 70–72, 107) Increased numbers of circulating CD30 ⁺ cells (76, 78)	Eczema score (70, 71, 78, 87–88, 107) Serum IgE (78) ECP* (78)
Atopic asthma	Elevated levels of sCD30 (77) Spontaneous expression of CD30 mRNA in PBMC (79) Surface expression of CD30 on BAL $\gamma\delta$ ⁺ T cells (81)	IgE (79)
Rhinoconjunctivitis	Elevated levels of sCD30 (80)	
Allergic rhinitis	Spontaneous expression of CD30 mRNA in PBMC (79) CD30 expression in sinus mucosa (82)	IgE (79)
Food allergy	No (80)	
Allergic contact dermatitis	No (70, 74)	
Urticaria	No (71)	

BAL: bronchoalveolar lavage; ECP: eosinophil cationic protein; PBMC: peripheral blood mononuclear cell.

the nonatopic controls (31). These results are in agreement with other research groups who have found increased concentrations of sCD30 in both adult (69, 70) and juvenile AD patients (71, 72). On the other hand, nonelevated levels of sCD30 were observed in patients with allergic contact dermatitis (ACD) (69), a finding which might reflect the Th1-dominated response in this disease (45). Similarly, when investigating sCD30 levels in psoriasis patients, we did not detect any significant differences compared with the healthy controls (31). This finding is interesting, since it has been suggested that psoriasis is a Th1-related disease (73). High proportions of CD30⁺ skin-infiltrating cells in AD have been reported (70, 72), whereas virtually no CD30⁺ cells were found in the skin of patients with ACD (70, 74) (Table 3). When Dummer et al. compared the CD30 expression in the inflammatory infiltrate of acute and subacute/chronic AD lesions, CD30⁺ cells were found in all biopsies from acute lesions, while CD30 expression was absent or very weak in the subacute/chronic specimens (74). Interestingly, both Th1 and Th2 cytokines have been shown to contribute to the pathogenesis of skin inflammation in AD, depending on the duration of the skin lesion. The acute phase is associated with a predominance of IL-4 and IL-13 expression (Th2), while in the chronic inflammation IL-5, GM-CSF, IL-12, and IFN- γ are also expressed (Th1) (75). Moreover, increased levels of cutaneous lymphocyte-associated antigen (CLA)⁺ T cells expressing CD30 were found in patients with AD (76). The increased serum levels of sCD30 in AD might reflect its release by CD30⁺ skin-infiltrating cells or by circulating CLA⁺ CD30⁺ T cells. According to previously published work, the number of CD30⁺ cells in the circulation, as analyzed by flow cytometry, has been undetectable or very low, in both normal and atopic subjects (2, 50, 55, 77). Still, in a recent paper by Yamamoto et al., a mean value of 4.6% of CD30⁺ CD4⁺ CD45RO⁺ PBMC from AD patients was detected, a percentage significantly higher than for the nonatopic controls (78). It was also demonstrated that the number of CD30⁺ cells correlated significantly with the number of IL-4-producing cells in the AD patients. Interestingly, there was an inverse correlation between the proportions of CD30-expressing cells and IFN- γ -producing cells (78).

CD30 in asthma, uncharacterized respiratory disorders, rhinoconjunctivitis, and food allergy

Elevated sCD30 levels have also been found in patients with asthma (77), but not in patients with uncharacterized respiratory disorders (69). Leonard et al. showed that a larger number of CD4⁺ T cells from atopic asthmatics than atopic nonasthmatics or healthy nonatopic controls express CD30. They also demonstrated an inverse correlation between IFN- γ produc-

tion and the percentage of CD4⁺ CD30⁺ cells in stimulated PBMC from both atopic and nonatopic subjects (77) (Table 3). Moreover, Del Prete et al. reported a small number of CD4⁺ CD30⁺ cells in the circulation of four of six atopic donors during the pollen season, while virtually no CD4⁺ CD30⁺ cells were detected before the pollen season. These CD4⁺ CD30⁺ cells were allergen specific and produced Th2-type cytokines upon stimulation (55). Dummer et al. did not find any significant differences in sCD30 levels when comparing a group of patients with atopic respiratory disorders with controls (69). Esnault et al. investigated the expression of CD30 mRNA PBMC from patients with asthma and/or allergic rhinitis and compared it with that of nonatopic controls. A significant spontaneous expression in the majority of the atopic patients was demonstrated. Interestingly, a correlation between CD30 and serum IgE levels was also shown, a finding which might imply a functional role for CD30 in the IgE response in allergic patients (79). In a study of 20 pollen-sensitized children (all with rhinoconjunctivitis and 11 also with asthma), the authors found significantly higher sCD30 levels than in nonatopic controls, while the levels of IL-12 measured in serum were not significantly different from controls (80). In this study, sCD30 levels were also analyzed in 22 children with food allergy. However, the sCD30 levels in these patients were not significantly higher than in controls. In contrast, they had significantly elevated levels of serum IL-12 (80). When investigating bronchoalveolar lavage (BAL) fluid from patients with chronic asthma, Spinazzi et al. found a significant number of $\gamma\delta$ ⁺ T cells coexpressing CD30 (81). Furthermore, Suzuki et al. reported a significantly higher number of CD30-expressing cells in the sinus mucosa of patients with allergic rhinitis than in nonallergic controls (82).

Correlation between CD30 and clinical findings in AD – a biologic marker?

There is still no reliable laboratory marker available to identify AD. The meaningfulness of CD30 as a biologic tool to monitor disease activity in AD or as a predictor of atopic disease has been discussed. Since the levels of CD30⁺ cells in the circulation of both atopic and nonatopic individuals are very low, the level of sCD30, which are readily detected in sera, has been used to investigate the association with clinical manifestations in atopic disease. In our laboratory, we investigated the relation between the concentration of sCD30 and total IgE serum levels in a group of AD patients. However, we found no significant correlation. Nor did we discover any relationship between sCD30 levels and the AD patients' clinical condition, which was evaluated by the calculation of a severity index according to the SCORAD scoring system (83). In agreement with

our data, Dummer et al., like Cavagni et al., observed no relationship between sCD30 and IgE in patients with AD (69, 72). Nor was any correlation found between sCD30 and IgE levels in patients with other atopic diseases (32). In contrast, a relation between the concentration of sCD30 and disease activity in AD has been described (70, 71). Yamamoto et al. reported a correlation between the number of CD30⁺ CD4⁺ CD45RO⁺ circulating T cells in AD patients and clinical symptoms (eczema severity, serum IgE, and peripheral eosinophil count). However, they did not detect a relationship between sCD30 levels and clinical findings (78).

Among the allergens that can trigger AD, various microbes have aroused significant interest, including *Staphylococcus aureus* (84). The yeast *Pityrosporum orbiculare*, now designated *Malassezia furfur*, has also gained interest as a potential pathogen in AD. When 20 AD patients, with *P. orbiculare*-specific IgE, were treated for 5 months with the antifungal drug ketoconazole, there was an improvement in the patients' clinical picture (85), along with decreased levels of total and *P. orbiculare*-specific IgE, as well as eosinophil cationic protein (ECP). However, no significant difference in sCD30 concentration was noted in sera collected at the different time points during treatment. No correlation between concentration of sCD30 and serum IgE, *P. orbiculare*-specific IgE antibodies, disease activity, or ECP levels was found (31).

However, the correlation with disease activity was further studied in 43 AD patients, who completed a 12-month avoidance study, by using encasings for bedding to avoid contact with house-dust mites (86). Half of the AD patients received placebo covers as a control. The eczema severity decreased significantly in both groups, with a more pronounced decrease in patients with active covers. Interestingly, sCD30 serum levels followed the severity scores in both groups, with a significant reduction after 12 months (86). This may indicate that 5 month's treatment is too short a period to see a shift in sCD30 levels, but that after 12 months these levels do reflect the clinical picture. Moreover, Bottari et al., like Caproni et al., demonstrated reduced serum sCD30 levels in patients with severe AD that were treated with cyclosporin A, along with significantly improved clinical symptoms (87, 88). Similarly, it has been reported that in AD patients treated with combined UV-A and UV-B treatment for 2 months the eczema scores decreased along with the numbers of CD30⁺ cells within the CLA⁺ T-cell subset (89).

In conclusion, the results from different laboratories clearly demonstrate that patients with AD have elevated levels of sCD30 in their blood compared to healthy nonatopic controls. Still, the correlation between CD30 expression/release and clinical symptoms is a controversial subject. In some cases, the levels

of sCD30 correlate with disease activity, while a correlation with serum IgE has not been shown. sCD30 may, in combination with other parameters, be helpful as a marker in the diagnosis of AD, and to monitor disease activity.

sCD30 in pregnancy and in early childhood

The question of whether high levels of sCD30 in cord blood can predict the development of atopy or AD in early childhood has been discussed. However, when Øymar et al. investigated the levels of sCD30 in the cord blood of 35 children who, at the age of 3 years, had developed allergic disease, they found no relation between sCD30 in cord blood and the subsequent development of allergic disease (90). In a recent study, we have investigated sCD30 levels in 59 serum samples from cord blood; 23 from children with atopic mothers and 36 from children with nonatopic mothers (21). The results showed no significant difference in sCD30 concentration between the two groups of children. However, the serum levels of sCD30 in cord blood, irrespective of maternal atopy, were relatively high compared to the concentration of sCD30 in the mothers' serum (21). Interestingly, sCD30 in cord blood correlated with maternal sCD30 levels. To our knowledge, transplacental transfer of sCD30 has not been shown. However, one explanation could be that the factor(s) enhancing maternal sCD30 levels also influence the fetus.

The mechanisms that enable the mother to accept the implanting fetus – a genetically foreign tissue – and carry it through pregnancy to term, are still not fully explained. However, recent studies in this field suggest that a combination of factors contribute to a successful pregnancy. One of them is the local production of certain cytokines (IL-4, IL-5, and IL-10) and hormones (progesterone and prostaglandins) in the placental-maternal interface, which has been shown to promote a shift in the balance of cytokine profiles away from a Th1- and toward a Th2-type reactivity (91–94). One might speculate that the Th2 environment surrounding the fetus during pregnancy is the cause of the elevated sCD30 levels observed in neonates. Indeed, Krampera et al. have earlier shown that a polarization toward the Th1 pattern occurs when the immune system matures in the growing child, and that this shift is inversely correlated with sCD30 levels (95). In addition, sCD30 levels were significantly lower in a group of healthy adults than in a group of healthy children (72). Since pregnancy seems to be a condition with a Th2-biased immune response (91–94) and since recurrent spontaneous abortions might be due to a Th1 bias (48, 51), the concentrations of sCD30 were determined in sera from women with normal pregnancy and from women with recurrent spontaneous abortion. However, no signifi-

cant difference was shown between the groups (96), a finding which suggests that sCD30 cannot be used as a reliable marker to predict pregnancy outcome.

The biologic function of CD30 in allergy

CD30 and CD30L belong to the rapidly expanding TNF receptor and ligand families that are involved in immune regulation. Among the members of the TNFR family are TNFR1 and TNFR2, TNFRp (TNFR-related protein), the low-affinity nerve growth factor (NGF) receptor, the Fas antigen (CD95), CD40, CD27, CD30, 4-1BB, OX40, DR3, DR4, DR5, and HVEM (herpesvirus mediator) (Fig. 1). The family members are very similar in their extracellular domains, but are more diverse in the intracellular signal-transducing domains. The family of TNF ligands includes TNF- α , lymphotoxin (LT), nerve growth factor (NGF), Fas ligand, CD40 ligand, CD27 ligand, CD30 ligand, 4-1BB ligand, OX40 ligand, APO3 ligand, TRAIL, and LIGHT (Fig. 1). It is believed that the members of the TNF ligand family are trimeric proteins, and mediate their effects by causing trimerization of the corresponding receptor at the cell surface (97). It has been shown that the ligand family members can induce pleiotropic biologic responses, including differentiation, proliferation, activation, and cell death (98).

To investigate the function of CD30-CD30L interaction in human allergen-specific Th cells, we used agonistic anti-CD30 mAbs (M44, Immunex Corp). It has been shown that immobilized M44 antibody has agonistic characteristics, i.e., the ability to trigger a response in a cell, and mimics CD30 ligand-induced receptor cross-linking (13). In our studies, we activated human allergen-specific Th clones of Th1 and Th2 type with immobilized M44 antibodies, or, as a control, with isotype-matched mAbs. We observed an increased production of IFN- γ in the Th1 clones, and of IL-4 and IL-5 in the clones defined as Th2, after CD30-cross-linking, compared to cytokine production after culturing with the isotype-matched control antibodies (8). Our observations demonstrate that the anti-CD30 mAb M44, by ligating CD30, can act as a positive regulator in activated T cells by enhancing the effector functions in both Th1 and Th2 clones (8).

These data seem to conflict with those presented by Del Prete et al. (99), who described an enhancement in cytokine production only in Th2 cells, and not in Th1 cells. These authors also demonstrated a preferential development of antigen-specific Th2 cells after CD30 costimulation, whereas blockade of CD30-CD30L interaction induced a shift toward the Th1 phenotype (99). It has previously been demonstrated in various CD30-expressing cells that activation with anti-CD30 antibodies, or with fixed cells expressing recombinant CD30L on their surface, can induce miscellaneous

effects, ranging from proliferation to cell death (14). The mechanisms by which CD30 mediates these cellular processes are unclear. However, the pleiotropic effects have been ascribed to the nature of the target cell, its state of differentiation and transformation status, etc. (14). The pleiotropic effects may also be explained by divergent pathways of CD30 signal transduction through a family of adapter molecules called TRAFs (TNFR-associated factors) (100).

When we analyzed the surface expression of CD30 by flow cytometry in the anti-CD3 preactivated TCC, after 24-h exposure to the immobilized anti-CD30 M44 mAb, there were minor changes in the number of CD30⁺ cells after cross-linking. However, the CD30 mean fluorescence intensity (MFI) was clearly reduced in all the clones after exposure to M44 mAb compared to the isotype-matched control antibody. Earlier studies have made it clear that some anti-CD30 antibodies induce the release of sCD30, whereas others actually inhibit it (9). This could be explained by the allosteric effects induced by a certain antibody, making the CD30 more accessible to membrane-associated proteases, while another antibody may block the proteolytic cleavage site at the membrane-associated CD30 and thus inhibit cleavage. Since our results indicate elevated levels of sCD30 in culture supernatants after CD30 cross-linking, it is likely that M44 induced cleavage of the membrane-bound CD30 also in our system. The immunologic function of sCD30 is still not clear. It is not known whether the elevated sCD30 levels associated with several human disorders (12, 31, 50, 101, 102) mirror the activated state of these patients' immune systems, or whether sCD30 actually plays an active role in the immune response. It has been shown that sCD30 can bind to the CD30L present on peripheral blood lymphocytes (103). sCD30 may not be sufficient to cross-link CD30L and induce a signal, but blocking of the CD30-CD30L interaction by sCD30 could prevent CD30 signaling.

It has been shown in human T-cell lines that cross-linking of CD30 elicits the activation of nuclear factor- κ B (NF- κ B). Several studies indicate a role for CD30 in HIV infection (59, 104). It has been reported that ligation of CD30 on HIV-infected CD4⁺ T cells leads to NF- κ B activation and enhanced HIV transcription (104).

The role of CD30-CD30L interaction in the pathogenic mechanisms in AD is still an enigma. Does CD30 or sCD30 actually have a role in the allergic mechanisms, by enhancing or initiating the Th2 responses in allergic disease, or does the overexpression of CD30 and the release of its soluble counterpart reflect the dominate Th2 response in AD and asthma? Th2 cells are believed to play an important role in the induction and maintenance of the allergic response by the production of certain cytokines. IL-4 and IL-13 promote the production of IgE antibodies by B cells;

IL-5 causes the differentiation and activation of eosinophils; and, finally, IL-4, IL-9, and IL-10 induce the growth of mast cells and basophils (105).

The expression of CD30 on CLA⁺ cells and the CD30 expression on CD4⁺ cells infiltrating AD lesions suggest an involvement of CD30 in the allergic reaction (74, 76).

Our results showing enhanced cytokine production after CD30 stimulation suggest that CD30 plays a role as a positive regulator of late T-cell immune responses (8). Indeed, the function of CD30 as an important costimulatory molecule in later immune responses has previously been suggested (61).

Concluding remarks

The prevalence of allergic diseases is, for unknown reasons, steadily increasing (106). Among the atopic diseases are eczema, hay fever, and asthma. The allergic phenotype is dependent not only on genetic predisposition, but also on environmental interactions, before and after birth (106). The cellular mechanisms involved in the allergic reactions are only partly elucidated; much is still unknown. It is believed, however, that the cytokines produced by Th2 cells, IL-4, IL-13, IL-5, IL-9, and IL-10, play an important role in the allergic reaction, as they promote the production of IgE antibodies by B cells, cause the differentiation and activation of eosinophils, and induce the growth of mast cells and basophils (105).

The CD30 molecule has been considered to be preferentially expressed by T cells producing type-2

cytokines (55). However, the correlation between CD30 and a certain cytokine profile is still controversial (52, 56), and the conclusion must be that CD30 cannot be used as a marker to distinguish Th2 cells. Still, increased expression of CD30, and the release of its soluble counterpart, has been found in several Th2-related diseases (57), among them, the atopic allergies (31–32, 69–72, 76–80). Several research groups have independently reported elevated serum levels of sCD30 and increased expression of CD30⁺ cells in the lesional skin of AD patients (31, 69–72, 74, 76, 78). In some of the studies, a relation between the levels of sCD30/numbers of CD30⁺ cells and clinical symptoms has been shown. More seldom has a correlation between CD30 and serum IgE been demonstrated. As there is still no reliable laboratory marker to assess disease activity in AD, analysis of sCD30/circulating CD30⁺ cells could be a way to verify the diagnosis of AD, and the levels of sCD30 may function as an additional serologic marker for evaluation of disease activity before and after treatment.

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