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# CD30 in Systemic Mastocytosis

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## KEYWORDS

• CD30 • Soluble CD30 • CD30 ligand • CD153 • Systemic mastocytosis

## KEY POINTS

- Mast cells from mastocytosis patients frequently aberrantly express CD30, the detection of which can especially aid in establishing the diagnosis of well-differentiated systemic mastocytosis, although other CD30 expressing neoplasms must be considered.
- Expression of CD30 by mast cells is stronger in patients with a high mast cell load; further research is needed to determine whether analysis of CD30 expression can aid identification of advanced subtypes of mastocytosis.
- Mast cell-expressed CD30 and release of soluble CD30 can interfere with normal CD30-CD30L interactions, the effects of which need further investigation.
- Investigations are under way to determine the effects of CD30 expression on mast cell proliferation, hymenoptera venom allergy, and the effectiveness of an anti-CD30 antibody for the treatment of advanced systemic mastocytosis and mast cell leukemia.

## INTRODUCTION

The CD30 receptor is similar to mastocytosis itself, in that it constitutes one of the rare bridges between the disciplines of hematology and allergology. Originally CD30 was identified as an antigen expressed by the malignant Reed-Sternberg cells of Hodgkin lymphoma.<sup>1</sup> Expression of CD30 is still widely used in this manner, identifying and prognosticating a variety of hematologic malignancies.<sup>2,3</sup> However, after identifying CD30 as a functional receptor,<sup>4,5</sup> attention has expanded to the role of CD30 in immunity in general and allergic diseases in particular.<sup>6,7</sup> With the discovery of mast cell-expressed CD30 as a marker of systemic mastocytosis, CD30 research has come full circle, further intertwining allergology and hematology.<sup>8</sup> This article aims to

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The authors have nothing to disclose.

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summarize the basic science of the CD30 receptor in disease and health, with emphasis on translating bench research to clinical applications relevant for systemic mastocytosis.

### THE CD30 RECEPTOR AND ITS LIGAND CD30L

CD30 is encoded for by the tumor necrosis factor receptor superfamily 8 gene (TNFRSF-8).<sup>4</sup> As the name implies, CD30 is sequentially and functionally homologous to the other members of the TNFRSF, such as CD40, RANK, and CD27.<sup>9</sup> The TNFRSF-8 gene is located on chromosome 1p36, and transcription and translation of TNFRSF-8 results in the 105- to 120-kDa transmembrane receptor protein CD30.<sup>9–11</sup>

The same gene can, through alternative splicing, be translated into a 25 kDa cytoplasmic protein called CD30 variant (CD30v), which lacks the transmembrane portion.<sup>12</sup> However, the role of CD30v in health and disease is poorly understood and therefore are not extensively reviewed here. The transmembrane portion of CD30 can strongly bind its ligand CD30L, resulting in downstream signaling in the CD30-expressing cell through tumor necrosis factor (TNF) receptor associated factor (TRAF) 1, 2, 3, and 5, resulting in activation of nuclear factor (NF)- $\kappa$ B and the mitogen-activated protein (MAP) kinase kinases.<sup>13</sup> As is common in the TNF family, binding of CD30L by CD30 results in downstream signaling in the CD30L-expressing cell through reverse signaling as well.<sup>14</sup> The result of this is that both the CD30-expressing and the CD30L-expressing cells receive a transmembrane signal after ligation.

### SOLUBLE CD30 AND SCD30L

The final player known to influence CD30-CD30L interactions is the soluble forms of CD30 (sCD30). The metalloproteinases ADAM10 and ADAM17 proteolytically cleave the extracellular portion of the CD30 receptor, resulting in the 85 kDa protein sCD30.<sup>15,16</sup> There is *in vitro* evidence that cleaving of CD30 and the subsequent release of sCD30 is enhanced by binding of CD30 to CD30L, raising the possibility that sCD30 levels reflect the amount of CD30-CD30L signaling.<sup>17</sup> Levels of sCD30 are clinically relevant, as sCD30 is biologically active. By high-affinity binding to CD30L, sCD30 reduces CD30 transmembrane signaling through competitive antagonism, acting as a negative feedback loop for CD30 signaling through reduction of available CD30L.<sup>18</sup>

In addition, sCD30 itself stimulates additional cleaving of CD30 by the metalloproteinases.<sup>19</sup> Concurrently a sCD30 homologue has been demonstrated to induce transmembrane signaling in CD30L-expressing cells through reverse signaling.<sup>20</sup> Taken together, these investigations illustrate that sCD30 possesses the unique property of being able to reduce CD30 signaling while stimulating CD30L signaling. An overview of all the players influencing the signaling cascades of CD30 is given in **Fig. 1**. Although soluble CD30L (sCD30L) can be detected in serum, its origin and biological effects have not been thoroughly investigated, and both signal-inducing and antagonistic binding has been reported for sCD30L fusion proteins depending on trimerization and immobilization.<sup>21</sup>

### EXPRESSION OF CD30 AND CD30L IN PHYSIOLOGY

Under physiologic conditions, expression of CD30 (CD30+) is restricted to a small population of cells, yet expression has been reported to be inducible in a variety of lymphocytes and leukocytes.<sup>7</sup> Mast cells do not express CD30 under these conditions. During neonatal development, transient expression of CD30 is frequent in a



large variety of embryonal tissues.<sup>22</sup> Most CD30+ cells and, subsequently, the greatest sources of circulating sCD30 in adult physiologic conditions are thought to be activated B and T cells.<sup>23</sup> Compared with CD30, expression of CD30L is more prevalent, with CD30L expression in both resting and activated cells of the myeloid and lymphoid lineage, including mast cells.<sup>24,25</sup> There is considerable controversy regarding the expression of CD30 and CD30L on cell types between investigations. This discord in findings presumably reflects differences in methodology. For instance, the initially reported expression of CD30 by macrophages was found to be due to the affinity of an Fc-receptor-like binding site for murine immunoglobulin (Ig)G3 on macrophages binding to the used Ki-1 monoclonal antibody.<sup>26</sup> The anti-CD30 IgG1 antibody Ber-H2 could not detect expression of CD30 on macrophages.<sup>27</sup> Another important consideration is that sCD30 can act as a bridging protein between CD30L and anti-CD30, thereby offering sites for anti-CD30 antibodies to bind, resulting in the possibility of a weak false-positive signal.<sup>15</sup> An overview of cells expressing CD30 and/or CD30L is given in **Table 1**. Increased expression of CD30 and release of sCD30 has been associated with various diseases.

### EXPRESSION OF CD30 AND SCD30 IN ALLERGIC AND IMMUNOLOGIC DISEASES

Immunologic diseases associated with increased levels of sCD30 have been extensively reviewed.<sup>41</sup> Traditionally, upregulation of CD30 and increased levels of sCD30 were thought to reflect a T-helper (Th)2-skewed immune system.<sup>6</sup> Accordingly, elevated levels of sCD30 have been found in various Th2-dominated diseases, such as atopic dermatitis,<sup>42</sup> hymenoptera venom allergy,<sup>43</sup> and Graves disease.<sup>44</sup> However, increase in expression and release of sCD30 have also been found in Th1-dominated diseases, such as colitis ulcerosa,<sup>45</sup> and granulomatosis with polyangiitis.<sup>46</sup> The current paradigm is that sCD30 levels in immunologic diseases reflect the activation

CD30+			CD30L+		
Cell Type	Characteristics	References	Cell Type	Characteristics	References
T cell	Activated T cells Memory T cells	7,28	T cell	Activated T cells	24
B cell	Activated B cells Epstein-Barr transformed B cells	7,27	B cell	Predominantly lymphoid cells	29,30
Plasma cells	Disputed	31	Neutrophils	—	14,25
Macrophages	Disputed	26,27	Mast cells	—	32
NK cells	Induced	33	Dendritic cells	Mostly immature DCs	34
Extrafollicular lymphoid blasts	Partial coexpression of AID	7,35	Medullary epithelial cells	Hassall corpuscles	36
Eosinophils	Low expression	37	Eosinophils	—	38
Embryonal cells	—	22,39			
Decidual cells	—	39,40			

*Abbreviations:* AID, activation-induced cytidine deaminase; DC, dendritic cell; NK, natural killer.

states of the B cells and T cells, not necessarily the Th cell differentiation stage.<sup>23</sup> Levels of sCD30 can be also be increased by aberrant expression of CD30 on malignant cells.

### EXPRESSION OF CD30 AND SCD30 IN MALIGNANCY

Aberrant expression of CD30 and elevated levels of sCD30 has been reported in a large variety of malignancies. Mastocytosis has recently been added to the list of CD30-expressing neoplasms. Initially, CD30 expression on mast cells was reported to indicate advanced forms of mastocytosis, such as aggressive systemic mastocytosis and smoldering systemic mastocytosis.<sup>8</sup> Follow-up studies report more widespread expression of CD30, with CD30-expressing mast cells being frequently found in cutaneous mastocytosis (CM) and indolent systemic mastocytosis (ISM) as well.<sup>47–49</sup> Moreover, the authors have found mastocytosis to be associated with marked elevations of sCD30 in serum for both patients with advanced systemic mastocytosis and those with ISM, correlating with the mast cell load (article in preparation). For further details, see the section “Soluble CD30 and mastocytosis.” Determination of CD30 expression and levels of sCD30 have proved to be clinically relevant for other malignancies as both diagnostic and prognostic tools. For instance, CD30 expression is used for establishing the diagnosis of Hodgkin lymphoma and anaplastic large-cell lymphoma.<sup>50,51</sup> In addition, CD30 identifies a subcategory of diffuse large B-cell lymphoma, with a better disease-free and overall survival.<sup>51</sup> In contrast to CD30, aberrant expression of CD30L is not used as a marker for malignancy and has not been associated with a clinical phenotype. Expression of CD30L in malignancy is therefore not reviewed here.

The soluble form of CD30 has been successfully used as a parameter of tumor burden in Hodgkin lymphoma, and a high level of serum sCD30 is an independent predictor for lower survival in Hodgkin lymphoma and CD30+ cutaneous lymphomas.<sup>52–54</sup> **Table 2** shows malignancies associated with frequent expression of

CD30 Clinical Relevance			CD30 of Unknown Relevance	
Tumor Type	Clinical Importance	References	Tumor Type	References
Classic Hodgkin lymphoma	Diagnosis sCD30 predicts survival	54,55	Enteropathy-associated T-cell lymphoma	56
Anaplastic large cell lymphoma	Diagnosis	50	Follicular lymphoma	57
Lymphomatoid papulosis	Diagnosis	58	Primary mediastinal B-cell lymphoma	59
Embryonal carcinoma	Diagnosis	60	Primary effusion lymphoma	61
Mastocytosis	Diagnosis	48,49,62	Acute myeloid leukemia	63
Diffuse large B-cell lymphoma	Prognosis	51		
NK/T-cell lymphoma	Prognosis	64		
Mycosis fungoides	Prognosis	65		
Adult T-cell lymphoma/leukemia	sCD30 predicts prognosis	66,67		

CD30 and the clinical significance of CD30. The expression of CD30 can provide information on the etiology of malignant cells. The Epstein-Barr virus (EBV) and human T-cell leukemia virus types 1 and 2 are capable of transforming and inducing CD30 expression on human lymphocytes. Both are implicated in the pathogenesis of CD30+ neoplasms, and the EBV genome is preferentially found in CD30+ non-Hodgkin lymphoma.<sup>68–70</sup>

### FUNCTIONAL ROLE OF CD30 IN PROLIFERATION AND APOPTOSIS

The role of CD30 in neoplastic and immunologic diseases is not limited to CD30 as a marker of malignancy or activation. The signals provided by interaction between CD30 and CD30L have been mechanistically implicated in several physiologic and pathologic processes. Initially it was discovered that ligation of CD30 expressed on Hodgkin lymphoma cell lines resulted in increased proliferation and survival of the malignant cells,<sup>71,72</sup> although results varied depending on the cell line used.<sup>72,73</sup> Dissimilarly, in anaplastic large-cell lymphoma cell lines, CD30 signaling resulted in inhibition of proliferation and increased apoptosis.<sup>73,74</sup> Signaling through CD30 has a potent effect on eosinophils, inducing rapid apoptosis.<sup>37</sup> Antagonistic binding of CD30L by Hodgkin lymphoma-derived sCD30 has been speculated to be responsible for the correlation between sCD30 and eosinophilia in Hodgkin lymphoma.<sup>37,75</sup> Eosinophilia is common in mastocytosis as well, and it is tempting to speculate on a possible inverse association between mast cell-derived sCD30 and concomitant eosinophilia. The observation that mastocytosis-associated mast cells express both CD30 and CD30L raises the question whether autocrine signaling plays a part in the pathogenesis of mastocytosis.<sup>8</sup> At present, an investigation by Valent at the Medical University of Vienna is under way to address this question, using CD30-expressing human mastocytosis cell models to determine the effect of CD30 signaling on proliferation and apoptosis.

### FUNCTION OF CD30 IN THE ADAPTIVE IMMUNE SYSTEM

In murine and human studies, CD30 and CD30L signaling between B and T lymphocytes has been found to be an important signaling event in the maintenance of the adaptive immune system by regulating memory antibody responses and Ig class switching to IgE and IgG.<sup>76–78</sup> In mice, abrogation of CD30-CD30L signaling using knockout models or antagonistic antibodies for CD30L reduced allergic lung inflammation, allergic rhinitis, and specific IgE levels.<sup>79–81</sup> In vitro experiments with human cells found a similar effect for CD30-CD30L signaling on isotype switching.<sup>82</sup> Studies with natural killer cells found an increase in the production of interferon- $\gamma$  and TNF- $\alpha$ .<sup>32</sup>

### FUNCTIONAL ROLE FOR CD30L SIGNALING IN MASTOCYTOSIS

When interpreting the literature it is important to consider the difficulty of differentiating between effects of CD30 and CD30L transmembrane signaling. For instance, some previous reports should be interpreted with care, as the human mast cell line HMC-1 was used as CD30L+ cells to stimulate CD30+ cells, whereas it is now known that this cell line also expresses CD30, opening up the possibility of CD30L reverse signaling in the cells under investigation.<sup>15,34</sup> Reverse CD30L signaling has been found to stimulate dendritic cell cytokine secretion and maturation.<sup>34</sup> Important for mastocytosis is the report that reverse signaling through human mast cell-expressed CD30L stimulates degranulation-independent release of chemokines, raising the question as to whether these signals are responsible for part of the mediator release symptoms of mastocytosis.<sup>83</sup> The authors have found no correlation between sCD30, a possible



inducer of CD30L reverse signaling, and mediator release symptoms such as flushing, pruritus, and diarrhea in a pilot investigation in 79 patients with systemic mastocytosis (van Anrooij and colleagues, unpublished data, 2013).

### EFFECTS OF MASTOCYTOSIS-EXPRESSED CD30 ON IMMUNE HOMEOSTASIS

The effect of CD30 expression in mastocytosis on its environment, such as CD30- and CD30L-expressing B/T cells, could be profound. Expression of CD30 by Hodgkin lymphoma cells has been shown to suppress T-cell proliferation, contributing to an ineffective antitumor response.<sup>84</sup> A similar immune escape mechanism could be present in mastocytosis. Antibody production and IgE biology specifically may be profoundly affected, the latter being of importance considering the frequent IgE-mediated anaphylactic reactions in ISM patients. The induced expression of CD30 on T cells found in (B-cell) chronic lymphocytic leukemia impairs isotope switching through reverse signaling in CD30L-expressing B cells.<sup>85</sup> Furthermore, sCD30 derived from CD30-expressing malignancies reduces the availability of CD30L by antagonistic binding.<sup>18</sup> These antagonistic properties of sCD30 may mimic the earlier mentioned specific IgE-suppressing effects of antagonistic anti-CD30L antibodies.<sup>81,86</sup> The authors have found that levels of sCD30 inversely correlate with hymenoptera venom-specific IgE levels (article in preparation). For further details, see the section "[Soluble CD30 and mastocytosis.](#)" Antagonistic binding of CD30L by mastocytosis-derived sCD30 downregulating CD30-CD30L interactions may partially explain the lower levels of specific IgE found in allergic mastocytosis patients compared with allergic nonmastocytosis patients.<sup>87</sup>

### THE DIAGNOSTIC APPLICABILITY OF CD30 IN MASTOCYTOSIS

The limited expression profile of CD30 makes it attractive both as a marker of disease and as a therapeutic target. Using flow cytometry, identification of CD30 expression on mast cells has sensitivity of 80% and specificity of 95% for diagnosing systemic mastocytosis.<sup>62</sup> In addition, the CD30 marker improves on the performance of the standard flow-cytometric mast cell markers for mastocytosis, CD2 and CD25, by reliably identifying the well-differentiated subcategory of mastocytosis.<sup>62</sup> For the identification of CD30 expression in mastocytosis, flow cytometry has proved to be more sensitive than immunohistochemistry.<sup>62</sup> Nevertheless, immunohistochemical staining for CD30 can aid in supporting the diagnosis of mastocytosis. As discussed previously, CD30+ cells in bone marrow or skin tissue are rare, and CD30 expression is not seen in related diseases such as monoclonal mast cell activation syndrome.<sup>49</sup>

### CD30 AS A MARKER OF ADVANCED SYSTEMIC MASTOCYTOSIS

At present the classification of systemic mastocytosis relies on evidence of organ dysfunction, as markers identifying the advanced and potentially life-threatening forms of systemic mastocytosis are unavailable.<sup>88</sup> As the authors have previously described, the applicability of CD30 as a marker of advanced forms of systemic mastocytosis is not yet clear. Initially CD30 expression was reported in 85% of patients with advanced systemic mastocytosis, compared with 27% with indolent systemic mastocytosis.<sup>8</sup> Follow-up investigations found CD30 expression in 50% of patients with cutaneous mastocytosis and in 23% to 100% of ISM patients using immunohistochemistry.<sup>48,49,49-69,68-81</sup> Differences in grading criteria and methodology explain these conflicting results and make comparison of data difficult. For instance, the initial investigation revealing expression of CD30 in 12 of 45 ISM patient samples used



expression of CD30 on more than 10% of mast cells as a cutoff point,<sup>8</sup> whereas in a small follow-up study using expression of CD30 on greater than 5% of mast cells it appeared that all (3 of 3) ISM patients expressed CD30.<sup>49</sup> Similarly, the original investigation revealed no expression of CD30 in bone marrow for CM patients,<sup>8</sup> whereas a follow-up investigation found CD30 expression in 6 of 12 CM patients when investigating skin biopsy samples.<sup>49</sup> **Table 3** displays the results of CD30 immunohistochemistry per category of mastocytosis. Taken together, these preliminary results suggest that CD30 is not a reliable marker for advanced systemic mastocytosis. One common finding in these reports is that CD30 expression seems to be higher in patients with greater mast cell burden, which is in accordance with the authors' own findings with sCD30.

### SOLUBLE CD30 AND MASTOCYTOSIS

The authors have found that levels of sCD30 in serum are elevated in all categories of systemic mastocytosis and correlate with the mast cell burden as evidenced by baseline serum tryptase, irrespective of grading (article in preparation). Because elevated levels of sCD30 can be found in a large variety of diseases, measurement of sCD30 cannot substitute for baseline serum tryptase as a screening tool for systemic mastocytosis. Although the authors have found sCD30 levels to be significantly higher in advanced forms of systemic mastocytosis in comparison with ISM, levels of sCD30 did not predict for survival in patients with advanced systemic mastocytosis (article in preparation). Clinical significance for sCD30 may be found in the relationship with hymenoptera venom allergy. The authors previously noted that a higher mast cell load reduces the risk of hymenoptera venom anaphylaxis in systemic mastocytosis.<sup>89</sup> As a possible cause, aberrant expression of CD30 was noted. It was hypothesized that mast cell-derived CD30 and sCD30 interfering with constitutional CD30-CD30L interactions might lower the risk of hymenoptera venom anaphylaxis. The authors have found sCD30 levels to be significantly lower in ISM patients with a history of hymenoptera venom anaphylaxis than in ISM patients without such history. Furthermore, sCD30 levels were found to predict for a lower risk of hymenoptera venom anaphylaxis and to be associated with lower levels of wasp venom-specific IgE (article in preparation). The applicability of sCD30 as an identifier for patients at risk of hymenoptera anaphylaxis needs to be further investigated before clinical recommendations can be made.

### CD30 AS A TARGET FOR CYTOREDUCTIVE THERAPY

The infrequent expression of CD30 in physiologic conditions assures a high specificity for targeted treatment. In line with this, investigations using monoclonal antibodies directed at the CD30 antigen have resulted in an overall benign safety and tolerability profile.<sup>90,91</sup> However, the efficacy of these antibodies in CD30+ lymphomas was lacking.<sup>91</sup> The finding that the CD30 receptor is internalized makes it an attractive target for antibody-drug conjugates. Recently, the antibody-drug conjugate SNG-35/brentuximab vedotin has proved to be both tolerable and effective in inducing tumor regression.<sup>92</sup> These findings have resulted in the Food and Drug Administration granting accelerated approval of SGN35/brentuximab vedotin for the treatment of relapsed Hodgkin lymphoma and relapsed anaplastic large-cell lymphoma.<sup>93</sup> SNG-35/brentuximab vedotin consists of an anti-CD30 chimeric monoclonal antibody coupled to monomethyl-auristatin E, a microtubule toxin that inhibits cell division on internalization. These reports raise the question as to whether similar results for anti-CD30 monoclonal antibodies can be achieved in mastocytosis. To answer this question,

**Table 3**  
Expression profile of CD30 in mastocytosis

	Sotlar et al, <sup>8</sup> 2011	Arredondo et al, <sup>49</sup> 2011	Moonim et al, 2012	Chiu et al, <sup>48</sup> 2013	Morgado et al, <sup>62</sup> 2013	Morgado et al, <sup>62</sup> 2013
	IHC	IHC	IHC	IHC	IHC	FCM
Classification	CD30 >10% Mast Cells	CD30 >5% Mast Cells	NR	NR	CD30 >10% Mast Cells	CD30 MFI >2 rSD Background MFI
CM	0/3 (0%)	6/12 (50%)	—	—	—	—
ISM	12/45 (27%)	3/3 (100%)	10/26 (38%)	0/11 (0%)	13/57 (23%)	89/123 (80%)
SSM	2/2 (100%)	0/2 (0%)	2/2 (100%)	—	—	—
SM-AHNMD	—	6/11 (55%)	6/12 (50%)	6/19 (32%)	—	—
ASM	5/5 (100%)	3/3 (100%)	2/3 (67%)	6/11 (55%)	5/7 (71%)	8/8/(100%)
MCL	5/7 (71%)	4/4 (100%)	—	1/2 (50%)	—	0/2 (0%)

*Abbreviations:* ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; FCM, flow cytometry; IHC, immunohistochemistry; ISM, indolent systemic mastocytosis; MCL, mast cell leukemia; MFI, median fluorescence intensity; NR, not reported; rSD, robust standard deviation; SM-AHNMD, systemic mastocytosis with an associated hematologic non-mast cell lineage disorder; SSM, smoldering systemic mastocytosis.

a single-arm open-label trial for SGN-35 in aggressive systemic mastocytosis and mast cell leukemia is under way ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01807598) number NCT01807598).

## SUMMARY

In physiologic conditions, CD30 is a receptor with an expression profile limited to activated B and T cells, and is implicated in the regulation of proliferation and antibody production. The expression of CD30 by mastocytosis mast cells may influence the clinical phenotype and (future) management of mastocytosis.

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