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Review Article

2B4 and CD48: A powerful couple of the immune system

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ABSTRACT

The signaling lymphocytic activation molecule (SLAM) family of receptors (SLAMF) is a group of receptors belonging to the CD2 family. It is composed of several members expressed on many hematopoietic cells. Most of the receptors interact in a homophilic fashion with neighboring cells. Their distribution and binding properties, together with their ability to function as both activating and inhibitory receptors, put them as key players in the immune system regulation. Several SLAM family receptors have been extensively investigated. This review mainly focuses on CD244 (2B4 or SLAMF4,) and CD48, particularly as expressed by the key cells of allergy, mast cells and eosinophils.

1. Introduction

The SLAMF1-9 receptors are members of the signaling lymphocytic activation molecule (SLAM) family (SLAMF). Most of them are type 1 transmembrane receptors and self-ligands, with the exception of SLAMF2 (CD48, BLAST1) and SLAMF4 (2B4, CD244), which interact with each other, with SLAMF2 being a GpI anchored receptor. SLAMF1-9 receptors are predominantly composed of an intracellular, a transmembrane, and an extracellular domain. The extracellular domain includes Ig variable-like (IgV) and Ig constant 2-like (IgC2) motives; the intracellular domain is responsible for the signal transduction pathway and contains intracellular tyrosine-based switch motives (ITSM). The receptors are diverse in the number of motives found on each domain (as reviewed in ref. [1]), however, the majority are characterized by one IgV, one IgC and two ITSMs. The intracellular part interacts with molecules such as the SLAM-associated protein (SAP), Ewing sarcoma-associated transcript-2 (EAT-2) and Src homology 2 (SH2), involved in the signaling, and their presence dictates whether an activating or inhibitory signal will occur. The recruitment of Fyn protein by SAP results in cells activation (reviewed in ref. [1–3]). In the absence of the SAP the SLAM receptors have an inhibitory function, since the presence of SAP prevents the binding of SH2 domain containing protein tyrosine phosphatase-1 (SHP-1), SH2 domain containing protein tyrosine phosphatase-2 (SHP-2) and SH2 domain-containing inositol phosphatase 1 (SHIP-1) to the ITSM region on the receptors. The most known example of 2B4 displaying inhibitory function was described in X-linked lymphoproliferative diseases patients, a disease characterized by mutations in SAP [4].

The SLAM receptors are expressed mostly on hematopoietic cells including, NK cells, T cells, dendritic cells (DCs), neutrophils, macrophages and notably mast cells (MCs) and eosinophils (Eos) (reviewed in ref. [1]) and have been linked to many physiological and pathological conditions. MCs and Eos are the key cellular players in allergic diseases such as asthma, atopic dermatitis (AD), allergic rhinitis and food allergy (as reviewed in ref. [5]). Both cells contain prominent cytoplasmic granules and derive from the $CD34^+$ progenitor. MCs are tissue resident cells that can be found throughout the body mostly on mucosal surfaces and in connective tissues (as reviewed in ref. [6]), where their survival is dictated by stem cell factor (SCF) binding to cKit. Unlike MCs, Eos differentiation and maturation occurs in the bone marrow, and mature Eos circulate in the blood. The most prominent Eos differentiation, maturation and survival cytokines are IL-3, IL-5 and granulocyte colony-stimulating factor (GM-CSF) (as reviewed in ref. [6]). In allergic individuals, the allergen exposure induces the production of IgE antibodies, through a mechanism regulated by T helper (Th) 2 and/or ILC-2 cells. The IgE antibody binds to its high affinity receptor FCεRI located on the surface of MCs. During subsequent exposures, the allergen binds to the IgE bound to FCεRI and the coupling of the receptors triggers the activation of MCs and thus the initiation of the early phase of the allergic reaction. This phase is characterized by MCs degranulation and release of pre-formed mediators, production and release of lipid mediators and of cytokines. A few hours later the late phase of the reaction begins, characterized by infiltration of immune cells such as macrophages, lymphocytes and granulocytes with Eos as the most prominent ‘granulocytes. Upon stimulation, Eos degranulate and release their granular cationic proteins [such as eosinophil peroxidase (EPX) and

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major basic protein (MBP), etc.], together with several preformed cytokines, chemokines and growth factors and de novo synthesized lipid mediators (reviewed in ref. [5]).

The most studied SLAM receptors expressed on MCs and Eos are CD48 and 2B4. Nevertheless, also SLAMF5 (also known as CD84) is expressed on both the cells, while SLAMF1 (also known as CD150) and SLAMF3 (also known as CD229), are both weakly expressed only on MCs [7]. Moreover, SLAMF8 (also known as CD353/BLAME) expression was detected on LAD2 and HMC1.2 MC leukemia cell lines. More importantly, SLAMF8 was found to be involved in the oncogenic pathway of the mutated c-kit that characterizes MC leukemia cells and therefore it was suggested as a specific therapeutic target for mastocytosis [8]. In this review we emphasize the role of the CD48 and 2B4 receptors on MCs and Eos and particularly in allergy.

2. 2B4 and its role in different conditions

2B4, also named SLAMF4/CD244, was first described on NK cells as a stimulatory receptor that initiates cytokine release and cytolytic activity [9]. Subsequently, it was also described on monocytes, basophils, Eos, γ δ T cells and on a subpopulation of $CD8^+$ T cells. 2B4 is also expressed on murine DCs, MCs and weakly on macrophages (as reviewed in ref. [10]). Like most of the SLAM family members, 2B4 extracellular region is made of one IgV and one IgC domain while unlike most of them its intracellular part is composed of four ITSMs (as reviewed in ref. [1]).

2B4 could function as an activating (AR) and inhibitory receptor (IR) (Fig. 1) [11]. The inhibitory function of 2B4 is due to the ability of the third ITSM to bind SHIP, SHP-1, SHP-2 and C-Terminal Src Kinase (CsK). while the first, second and fourth ITSMs can bind only SAP (Fig. 1) [11]. The murine 2B4 exists in two isoforms resulting from a splicing variant which produces a short (2B4-S) and long (2B4-L) one that differ in the intracellular domain. These two isoforms were first described to act as an AR and IR respectively, on RNK-16 cell line. [12,13]. However, both isoforms were found to function as ARs on CD8+ T cells [14]. In murine MCs, an inhibitory role for 2B4 was described when bone marrow derived MCs (BMMCs) were activated by IgE- dependent mechanisms [15] but they have not been correlated to short or long isoform. On the other hand, on murine and human Eos, 2B4 is an AR [15,16]. As mentioned above the high affinity ligand of 2B4 is CD48 and the binding between the two initiates the phosphorylation of all four ITSMs.

In the last few years 2B4 has been investigated in the context of several diseases. Upregulation of 2B4 expression was observed on NK cells following their first exposure to influenza virus [17] and a direct binding between 2B4 and the viral hemagglutinin protein of the virus was reported [18]. Hepatitis C infection induced the expression of 2B4 on virus specific CD8+ T cells. In this case 2B4 functions both as AR and IR, depending on the 2B4 expression levels and the availability of the SAP molecule [19]. Decreased expression of 2B4 on NK cells was described in multiple myeloma (MM) patients [20], and on platelets, monocytes, and NK cells in systemic lupus erythematosus [21,22]. On the contrary, in human immunodeficiency virus positive patients, $CD4^+$ invariant natural killer T (iNKT) cells highly express 2B4. In this case 2B4 expression negatively correlates with INFγ secretion from these cells [23]. Remarkably, 2B4 is highly expressed also on $CD4^+$ T cells in septic patients and blockade of 2B4 by anti-2B4 mAb results in increased survival rate in a cecal ligation and puncture mouse model, thus

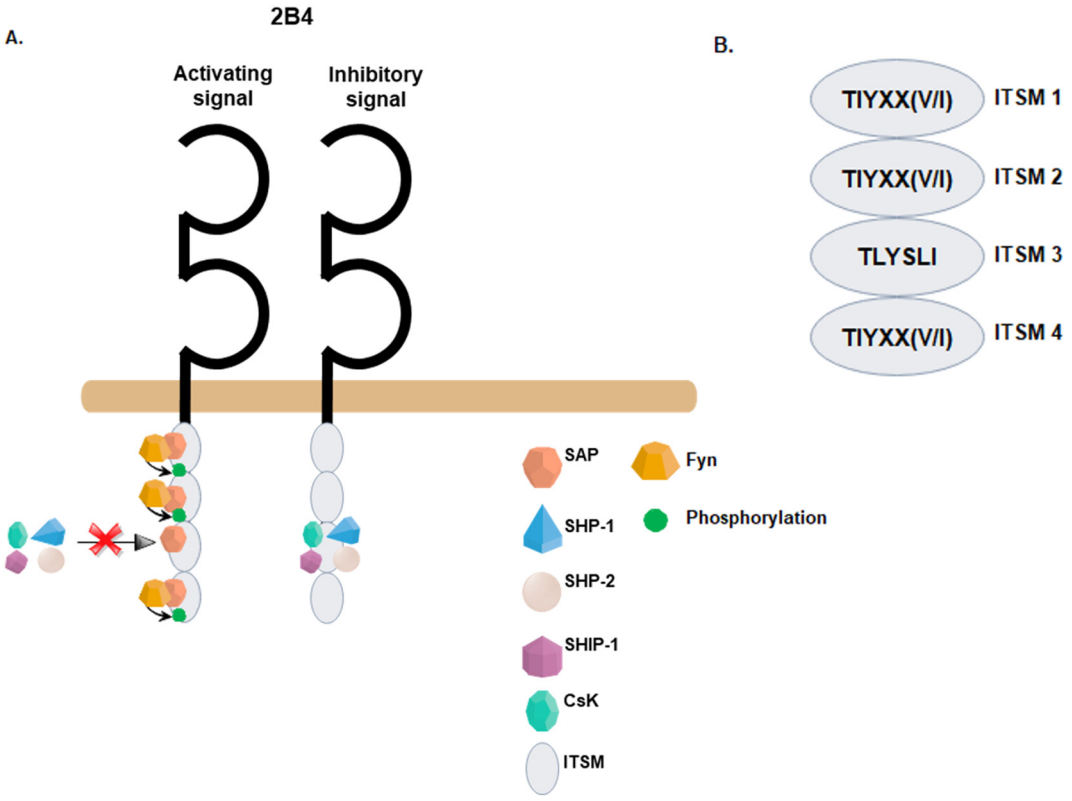

Fig. 1. 2B4 can be Dr. Jekyll and Mr. Hyde.
Representation of the mechanism behind 2B4 ability to function as both inhibitory and activator receptor on the same cell and different cells: (A) The extracellular portion is composed of one IgV and one IgC domain. The intracellular moiety is composed of four ITSM domains which, by binding SAP, deliver the activating signal. On one hand binding of SAP to the first, second and fourth ITSMs, recruits Fyn which phosphorylates the domains, while on the other hand SAP binding to the third ITSM prevents the ability of the inhibitory SHP-1,2, SHIP-1 and CsK to be recruited by the ITSM. When SAP is found at low concentration or it is absent, SHP-1,2, SHIP-1 and CsK bind to the ITSMs, triggering the inhibitory signal. (B) Representation of the consensus sequences in 2B4 ITSMs. The different sequence in the third ITSM might be the explanation for the inhibitory function shown only by this domain.

indicating that this receptor might be an interesting pharmacological target in this situation [24]. Importantly, Zhang et al. showed that silencing 2B4 in leukemia cell lines and primary leukemia initiating cells (LICs), also known as leukemia stem cells, caused impairment of tumor cell proliferation. Most interestingly, this effect is not seen upon 2B4 silencing in hematopoietic stem cells although, as LICs, they highly express 2B4 [25]. From all these studies, a potential role of 2B4 as a possible therapeutic target in some diseases, depending on its expression and function, has emerged.

3. CD48 and its role in different conditions

CD48 is expressed on all the hematopoietic cells, both in human and mice, except for murine neutrophils and long term-HSC. Two isoforms of CD48 exist due to alternative splicing, a long and a short one. However, no functional differences between the two are known. Moreover, as a number of GpI receptors do, also CD48 exists as both a membrane bound (mCD48) and a soluble (sCD48) form (reviewed in ref. [10]). Being a GpI anchored receptor lacking an intracellular domain molecule, CD48 is considered as a co-activating receptor rather than a bona fide AR. In addition, CD48 is not a "typical" member of the SLAM family, although it has an extracellular domain similar to the one possessed by other members of the family, (reviewed in 26). CD48 is anchored to the plasma membrane in the lipid raft region through an Ethanolamine-Mannose-Glucosamine linked to Inositol that is embedded to the membrane [26]. The known high affinity ligand for CD48 is 2B4, and vice versa, whereas CD2 is an additional ligand with lower affinity. CD2 is expressed on $CD4^+$, $CD8^+$ and γ δ T cells, NK cells, murine B cells and weakly expressed on human DCs (reviewed on ref. [10]). CD48 was found to bind heparan sulfate expressed on epithelial cells as well [27].

Moreover, CD48 can also bind exogenous molecules. A direct binding between *M. tuberculosis* and CD48 on murine MCs resulting in MCs degranulation was found by Muñoz et al. [28]. CD48 on BMMCs also interacts with FimH-expressing type 1 fimbriated *Escherichia coli*, leading to TNF-α release [29]. Our group found that CD48 and TLR2 expressed by human cord blood MCs (CBMCs), bind *S. aureus* that subsequently invades the cells, where it also replicates. Moreover, binding of *S. aureus* or its exotoxins [i.e. staphylococcal enterotoxin B (SEB), Protein A (PtA) and Peptidoglycan (PGN)] [30] to CD48 causes the release of TNF-α and IL-8 [31]. Furthermore, *S. aureus* and its exotoxins were shown to similarly bind to human Eos CD48, causing cell activation and degranulation as detected by EPX, β-hex and ECP release, and IL-8 and IL-10 release. Bone marrow-derived Eos (BMEos) incubated with either one of the toxins released EPX in a CD48-dependent manner. Moreover, incubating human Eos with the toxins led to phosphorylation of the signal transduction molecules Fyn, ERK 1 and 2. PGN and SEB increased also the phosphorylation of Lyn. Interestingly, blockade of CD48 resulted in decreased phosphorylation of all signaling proteins examined except for ERK1, 2 when cells were treated with PGN, indicating that different signaling pathways occur following Eos activation by *S. aureus* toxins [30].

In another study it was shown that SEB induces a time-dependent release of sCD48 from human Eos due to a cleavage of mCD48 by intrinsic phospholipase C and D with no significant change in mCD48 levels because of CD48 *de-novo* synthesis and the presence of intracellular reservoirs [32]. In a peritonitis model induced by SEB intraperitoneal injection an increase in sCD48 was found in the peritoneal cavity indicating that the presence of sCD48 is an event elicited by *S. aureus* toxins also in an in vivo setting [32]. As for function, sCD48 was found to be a decoy receptor both when injected in the SEB peritonitis model and in vitro when Eos were activated with SEB [32] or with anti-2B4 mAb [33]. This would suggest that sCD48 is a decoy receptor for both the exogenous *S. aureus* toxins and the endogenous 2B4 receptor.

S. aureus is known to be the most important bacterium involved in allergic diseases, including AD and asthma [34–36], further linking this receptor, as expressed by MCs and Eos, to allergic scenarios. In a study carried out to understand the possible role of CD48 in asthma we found that in moderate asthma patients, peripheral blood Eos mCD48 is upregulated, although it is decreased on these cells in severe asthma. Moreover in the severe asthma group mCD48 was significantly increased on B cells, T cells, NK cells and monocytes [33]. In moderate asthma patients sCD48 levels were found to be increased but they were decreased in the severe asthmatics. These findings might imply that Eos represent the main source of sCD48 [33]. Decreased levels of sCD48 in severe asthma patients seem not to be due to corticosteroids (CS) treatment since incubation of Eos with dexamethasone did not significantly decrease either sCD48 formation or mCD48 expression levels [33]. sCD48 was also unrelated to smoking, BMI, gender, atopic state, IgE levels and Eos numbers or percentage. Noteworthy, in a recent retrospective work we reported increased levels of sCD48 specifically in non-allergic asthma patients' sera that did not correlate with serum levels of IgE, IL-5, eosinophilia and INFγ, classical Th_2 markers [37]. sCD48 could not be detected in the sera of patients with AD possibly due to its atopic origin and/or the limited skin area involved in the studied mild/moderate patients [38]. Therefore, from our studies we can hypothesize that the asthma severe phenotype could be characterized by lower sCD48, therefore lacking protective mechanisms, and that sCD48 is an independent marker of mild-moderate asthma.

Regarding other diseases with non-allergic etiology, sCD48 was suggested as a disease biomarker in primary Sjogren's syndrome, since it was found to be increased in sera from patients [39]. sCD48 levels were upregulated also in sera from patients with cutaneous T-cell lymphoma, mycosis fungoides and Sézary Syndrome. In addition, mCD48 expression was found to be high on multiple myeloma (MM) plasma cells but low on normal plasma cells, thus suggesting that this disease can be potentially targeted by an anti-CD48 mAb treatment. Indeed, treatment with mAb against CD48 specifically induced MM cells death by triggering complement dependent cytotoxicity (CDC) [40]. Moreover, in in vivo experiments in which OPM2 cells were injected to the flank of both SCID and NOD/SCID mice, treatment with anti-CD48 mAb significantly reduced tumor volume. Notably, the effect in SCID mice was stronger than in NOD/SCID mice, bolstering the notion that CDC mechanism is involved [40]. Noteworthy, the acute myeloid leukemia (AML) oncogenic fusion proteins PML-RARA and AML1-ETO were found to downregulate CD48, resulting in impaired NK cells cytotoxicity [41]. In experimental autoimmune encephalomyelitis (EAE), a model disease for multiple sclerosis (MS), pathogenic $CD4^+$ T cells highly express CD48, highlighting its potential role as a biomarker and target for treatment of MS [42]. CD48 overexpression in several diseases with different etiopathologies and the role of sCD48 as a decoy receptor could indicate this receptor as a key player in the immune response regulation. Thus, this receptor might be a high potential target for immunotherapy. However, as an AR, the downregulation of CD48 on immune cells, such NK cells, results in impaired function. Therefore, careful finetuning of the possible treatments and extended understanding of the CD48 role is needed.

4. CD48 and 2B4 interaction and its importance in the Allergic Effector Unit (AEU)

The 2B4-CD48 high affinity binding is conserved between species and higher than 2B4-CD2 binding, indicating the evolutionary significance of this interaction [43]. The interaction between the two molecules is based on the presence of charged amino acids on 2B4, particularly Lys68 and Glu70, which are essential for CD48 mediated activation [44]. Noteworthy, Claus et al., found that the aforementioned amino acids seem not to have a role in 2B4 and CD48 binding and subsequent activation. However, they substituted three different amino acids with alanine (K54A, H65A and T110A), resulting in impaired 2B4-CD48 interaction [45].Functional outcome of CD48-2B4 binding can vary among different cell couples. For example, CD48 and

Table 1
The effect of trans interaction between 2B4-CD48 on different cell types.

Interacting cells	2B4 induced effects	CD48 induced effects	Ref
NK cells-NK cells	Inhibition of fratricide activity, activation of cell expansion, stimulation of cell activation and activation of cytotoxic activity	Not done	[46,47]
T cells-T cells	Activation of cytotoxic activity and activation of cell proliferation	Not done	[14,49]
MCs- Eos	Eos: Activation of cell survival	MCs: increased cell activation, degranulation and cytokine release.	[50,51]
NK cells-T cells	Not done	Activation of T cell proliferation	[48]

2B4 interaction on NK cells induces cells expansion and activation [46,47]. Moreover, binding between 2B4 on NK cells and CD48 on T cells increases T cells proliferation [48]. In addition, 2B4-CD48 binding on T cells results in T cells increased proliferation and cytotoxic activity [14,49] (Table 1).

Most interestingly, 2B4 and CD48 were reported to interact with each other not only on different cells (trans interaction) but also on the same cell (cis interaction). The latter interaction was described on NK cells for example and it was shown to downregulate 2B4 expression and NK cytotoxicity by limiting the trans binding. Notably, the binding site involved is the same in both trans and cis interaction, and the cis binding is made possible via linking domain in 2B4. [45]

Regarding MCs and Eos, CD48-2B4 interaction is a main component of the "Allergic Effector Unit" (AEU) [50] and important for the initiation and continuation of the allergic reaction. The "AEU" is a pro-inflammatory soluble mediator and physical cross-talk between MCs and Eos (Fig. 2) [50,51]. The physical interaction requires 2B4 and, to a lesser extent, Nectin-2 and Intracellular adhesion molecule 1 (ICAM-1) on Eos. MCs physically interact with Eos mostly via CD48 but also with DNAM-1 and Lymphocyte function associated antigen 1 (LFA-1) [51] (Fig. 2), with other ligand/receptor interactions being also feasible. In the physical AEU increased MCs activation and MCs and Eos survival are highly dependent on CD48-2B4 binding while not dependent on Eos activation [50,51].

5. Conclusion

2B4 and CD48 interplay has been shown to have an important role in a multitude of cell-cell interactions. At the same time, 2B4 and CD48 have been demonstrated to have a prominent role in different human pathologies. Therefore, both receptors might become targets for therapy via mAbs or small molecules. A possible strategy would involve, according to the specific case, either blockade or activation of one or both the two receptors. For example, homotypic interaction between 2B4 and CD4 on NK cells and T cells increases their cytotoxic activity against tumor cells [14,47], indicating that augmenting this pathway with an activating mAb toward 2B4 or CD48 might be a potential therapeutic approach. Moreover, the effectiveness of a blocking mAb against 2B4 in experimental sepsis or an activating anti-CD48 mAb in MM has already been shown in vivo and in vitro [24,40], sCD48 being a decoy receptor for 2B4 and SEB could also be used as a blocker of CD48 interactions with these entities [32].Further investigations are needed to unravel other potential strategies directed against 2B4 and CD48 and their interaction. Noteworthy, it must be taken in account that both CD48 and 2B4 are functional not only during some pathological conditions but also in health, for example during immune responses. Thus, while designing a therapeutic agent modulating 2B4, CD48 or their interaction, it would advisable to specifically target only the designed cell, possibly by using bi-specific mAb. Therefore, the design of specific therapies will require better knowledge of the physiopathological roles of 2B4 and CD48, and the interaction between them, in health and disease.

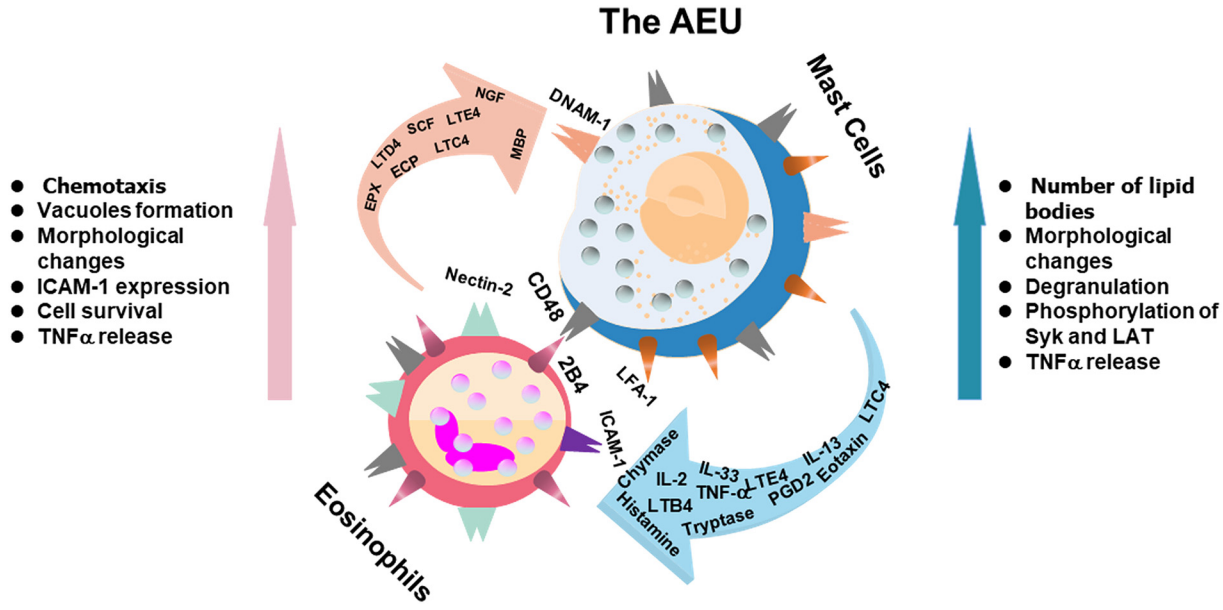

Fig. 2. The allergic effector unit: soluble and physical interactions and some of their outcomes.
Schematic representation of the physical and soluble interaction between MCs and Eos during an allergic reaction: MCs and Eos can physically interact via CD48, DNAM-1 and LFA-1 on MCs and 2B4, Necctin-2, ICAM-1 on Eos, respectively. The soluble interaction involves cytokines and mediators such as TNF-α, IL-13, exotoxin, PGD2, etc. produced by MCs and EPX, SCF, ECP, NBP, etc. produced by Eos. The interactions result in an increased number of lipid bodies, degranulation, TNF-α release, etc. on MCs and increased chemotaxis, cell survival, ICAM-1 expression, etc. on Eos.

Conflict of interests

The Authors declare no conflict of interests.

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