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Allergic Contact Dermatitis: Novel Mechanisms and Therapeutic Perspectives

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Abstract: Allergic contact dermatitis is a common eczematous skin disease that occurs in sensitized individuals at the site of contact with small chemicals penetrating the skin barrier. The onset of the disease is mostly due to the rapid recruitment of chemical-specific CD8⁺ T cells, which induce apoptosis of keratinocytes. Additionally, CD4⁺ Th1 and Th17 contribute to the extension of the inflammatory reaction by releasing pro-inflammatory cytokines that activate keratinocytes and other skin resident cells. The immune reaction is tightly regulated through multiple mechanisms. In particular, T cell population with regulatory function, such as T regulatory cells 1 and CD4⁺CD25⁺ T regulatory cells have a critical role in preventing the development of allergic reactions to innocuous chemicals contacting the skin, and in limiting the magnitude of the inflammatory process in already sensitized individuals.

Allergic contact dermatitis is a chronic disease, which lasts, in most cases, for the entire life of the affected individual. Thus, prevention and avoidance of contact with the sensitizer are critical factors in the management of affected patients. The gold standard therapeutic approach for the disease remains the local and/or systemic immunosuppression, aimed to block T cell functions and keratinocyte responsiveness to pro-inflammatory stimuli. However, alternative approaches that aim at preventing T cell accumulation in peripheral tissues are under investigation. Most recently, disclosure of mechanisms regulating allergic contact dermatitis have provided new therapeutic perspectives for the disease, mostly based on immunomodulatory interventions, as in the case of induction of specific oral tolerance to the causative allergen.

Keywords: Allergic contact dermatitis, T lymphocytes, Immunomodulators, Oral tolerance.

INTRODUCTION

Allergic contact dermatitis (ACD) is the consequence of an undesired immune reaction to small chemicals -namely the haptens- contacting the skin [1, 2]. Acquisition of skin sensitization is dependent upon a complex series of events which include the capacity of haptens to activate and mobilize cutaneous dendritic cells (DCs), the generation of hapten-epitopes for T cell recognition, and, finally, the capacity of the hapten-DC complex to prime effector T lymphocytes with skin homing properties [3]. Once recruited at the site of skin challenge, hapten-specific effector T cells are rapidly activated and induce tissue damage through the release of pro-inflammatory cytokines and by killing hapten-loaded keratinocytes.

Attitude of hapten molecules to act as skin sensitizers mostly depends on their chemical properties, which affect their transit through the stratum corneum and their capacity to bind covalently to proteins to generate immunogenic epitopes. Small molecular size (less than 500 dalton) and the lipophilic nature facilitate skin penetration and increase the amount of the chemical molecule that can interact with skin dendritic cells. Conditions that alter the skin barrier integrity and/or serve as co-factors for DC activation such as infections, may increase the risk to develop ACD, even in the presence of weak sensitizers [4, 5]. Typical example is the augmented frequency of nickel allergy in ear pierced individuals [6]. Indeed, piercing provides both a rapid access to the dermal compartment of nickel eventually leaked from ear rings, and an inflammatory state that increase DC maturation and mobilization towards regional lymph nodes, where T cell priming occurs. Current therapeutic targets in ACD include the local administration of barrier creams together with local or systemic immunosuppressive interventions aimed to block T cell activation. Attempts to dampen DCs migration to regional lymph nodes or specific T cell recruitment into the skin are under investigation, but have not been translated into clinical use, so far.

Albeit ACD to haptens is a frequent disease, development of skin sensitization to skin applied chemicals has to be considered as an exceptional event. Most individuals continuously contact a variety of potential sensitizers in everyday life without developing un-

desired immune reactions. Moreover, although reversal of hapten sensitization is uncommon, the magnitude of the allergic reaction in each individual may fluctuate with time. These observations suggested that both sensitization and expression of ACD are highly regulated events. In the last decade, evidence has been provided that multiple mechanisms are involved in the regulation of both human ACD and murine contact hypersensitivity (CHS), this last the most valid experimental model to investigate contact dermatitis mechanisms [7]. These mechanisms vary from non specific events, such as induction of T cell anergy and apoptosis of effector T lymphocytes due to activation-induced T cell death, to the highly specific induction of specialized T cells with regulatory function (Treg). The disclosure of the mechanisms governing ACD expression is leading to promising new therapeutic approach based on the induction of specific tolerance through desensitization protocols.

MECHANISM OF HAPTEN SENSITIZATION AND EXPRESSION OF ACD

Hapten entry into the epidermal compartment is followed by the diffusion into the extracellular spaces and interaction with cellular components of the epidermal and dermal compartments. Current dogma holds that protein reactivity of the potential sensitizer strongly affect its capacity to induce ACD reactions, being required for the generation of hapten-peptides complexes which are mounted on major histocompatibility complex (MHC) class I and class II of professional antigen presenting cells (APC) and recognized by specific T cell receptors (TCR) on CD8⁺ and CD4⁺ T lymphocytes, respectively [8, 9]. Hapten interaction with extracellular or membrane-bound proteins is followed by internalization into skin antigen presenting cells, mostly Langerhans cells and dermal DCs, and processed into MHC class II compartments to generate appropriate hapten-peptide complexes fitting in the groove of MHC molecules. Alternatively, haptens may directly interact with peptides displayed by membrane MHC molecules, and stimulate T cells without the requirement of antigen processing. Poor reacting sensitizers, called pro-haptens, require p450-dependent metabolic transformation, prior to acquiring antigenic properties [10]. Skin DCs reside in the skin in an immature state, characterized by the high capacity to capture antigens penetrated through the stratum corneum, but very low antigen presenting capacity [11, 12]. Both Langerhans cells and dermal DCs are susceptible to environmental stimuli, such as irritants, toxic stimuli, bacterial and viral products, which promote

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their migration to regional lymph nodes and the acquisition of antigen presenting capacity for naïve T cell priming and differentiation. Cytokines released by skin resident cells, in particular interleukin (IL)-1, tumor necrosis factor (TNF)- α and IL-18, critically regulate both DC migration and functional maturation [13]. Once migrated into the paracortical zone of draining lymph nodes, skin DCs prime hapten-specific naïve T lymphocytes, which differentiate into memory/effector T cells and acquire defined migratory behavior. The majority of skin homing T cells display the cutaneous lymphocyte associated antigen (CLA), the addressin that bind to e-selectin expressed on activated endothelial cells [14]. Additionally, chemokine receptor repertoire of T lymphocytes is critical for their migration into peripheral tissues. The majority of skin T cells express functional CC chemokine receptor (CCR)4 chemokine receptor, which binds to the CC chemokine ligand (CCL)27 expressed on the surface of activated skin endothelial cells, and CCR10, ligand for CCL27, a chemokine constitutively released by keratinocytes [15]. T cell differentiation is paralleled by the acquisition of defined cytokine profile. T cell differentiated towards a Th1 and Th17 phenotypes are strongly involved in ACD reactions. Strong experimental evidence confirmed that initiation of ACD is driven by hapten-specific CD8+ T cells [16, 17]. CD8+ T cell-mediated cytotoxicity of hapten-loaded keratinocytes is the major pathogenetic event in ACD, while Th1 and Th17 cells are mostly involved in the amplification of the allergic reaction [18, 19]. Recently, it has been demonstrated that natural killer (NK) lymphocytes, once activated by Th1-derived supernatants, also contribute to the tissue damage in ACD by inducing keratinocyte apoptosis in a hapten-independent manner [20]. Early consequence of the apoptotic process is the cleavage of E-cadherins, that guarantee keratinocyte adhesion through homotypic interactions [21]. This phenomenon is responsible for the typical spongiotic appearance of the eczematous reaction. In this scenario, keratinocytes are not only target cells for T cell and NK mediated cytotoxicity, but significantly participate to

the amplification of inflammation. In particular, once activated by T cell derived cytokines interferon (IFN)- γ , TNF- α and IL-17, keratinocytes release a plethora of cytokines and chemokines, which direct new waves of leukocytes at the site of hapten challenge [18]. Additionally, IFN- γ and IL-17 synergistically upregulate keratinocyte expression of intercellular adhesion molecule (ICAM)-1, the principal molecule that mediate T cell-keratinocyte interactions [19]. Fig. (1) schematizes the whole mechanism of ACD and possible molecular targets for its neutralization. These targets will be discussed in detail in the following paragraphs.

T REGULATORY CELLS AND TOLEROGENTIC MECHANISMS IN ACD

Much of the knowledge on the immune mechanisms regulating contact sensitization has been derived from the murine contact hypersensitivity (CHS) model, which is induced by applying sensitizing doses of the hapten onto the shaved abdomen of the mouse, and is quantified by measuring the ear thickness 24 and 48 hours after the ear challenge with the relevant chemical. Two distinct experimental approaches have clearly proven that CHS is intrinsically regulated through a variety of mechanisms: the ultraviolet (UV)-B induced immune tolerance and oral tolerance. Although the mechanisms involved in the establishment of hapten-specific immune tolerance have not been fully elucidated, convincing data have demonstrated a role of Treg cells and/or the release of suppressive cytokines in the tolerogenic mechanisms. A hapten applied onto UV-B irradiated skin fails to sensitize animals while inducing a long-lasting hapten-specific immune tolerance [22, 23]. UV-B irradiation has multiple effects on the skin immune system, including a direct toxic effect on skin Langerhans cells, and the induction of IL-10 secretion by mast cells and keratinocytes. IL-10, in turn, is responsible of the impaired maturation of skin DCs [24]. In contrast, UV-B induced tolerance appears reverted by IL-12 and IL-18 administration [25]. Thus, upon UV-B irradiation, immature or par-

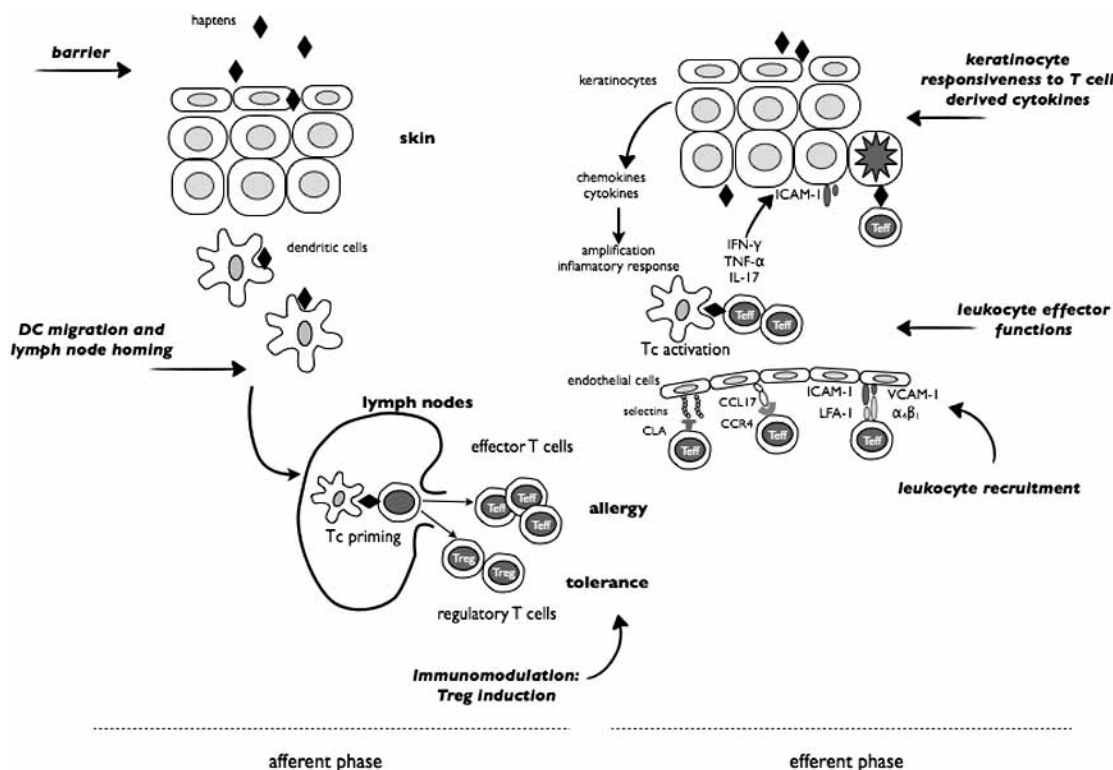


Fig. (1). Allergic contact dermatitis pathogenesis and potential targets.

Allergic contact dermatitis develops in two distinct phases: sensitization (or afferent) and efferent phase. Therapeutic targets include: i) barrier creams, ii) dendritic cell migration and maturation, iii) immunomodulatory therapies aimed to increase the expansion of Treg; iv) the leukocyte recruitment into the skin; v) the activation of T cells; vi) the keratinocyte responsiveness to T cell derived cytokines.

tially mature DCs, expressing low levels of costimulatory molecules, reach the secondary lymphoid organs where they may predominantly expand IL-10-producing Treg [26]. Importantly, UV-B induced Treg can prevent induction of CHS when transferred into naïve animals, but they fail to prevent CHS expression when transferred into already sensitized mice. This observation possibly indicates that attempts to induce hapten-specific UV-B-mediated immune suppression may have preventive but not therapeutic effect in already sensitized individuals. The second experimental approach for tolerance induction in animals is the oral tolerance induced by feeding the animals with the skin sensitizer. Following this route, the hapten challenges the gut immune system, which is primarily involved in the development of immune tolerance toward dietary antigens, and expands CD4⁺CD25⁺ Treg cells, which could prevent subsequent sensitization through skin application of the chemical [27, 28].

In aggregate, these observations demonstrated that murine immune system have the intrinsic capacity to regulate hapten-responsiveness and that the equilibrium between allergy and tolerance can be affected by multiple factors, including the route of administration, the functional properties of antigen presenting cells and the antigen dose.

Many data also support the role of Treg cells in human ACD. An increased number of Treg1 lymphocytes releasing high amount of nickel-specific IL-10 have been described in individuals exposed to the metal without nickel hypersensitivity [29, 30]. Additionally, non-allergic individuals have enhanced nickel-specific suppressor CD4⁺CD25⁺ Treg in peripheral blood compared to nickel-allergic donors [31]. These findings indirectly demonstrated that nickel-allergy is regulated by specific Treg subpopulations and suggest that ACD to the metal develops when one or more of these regulatory mechanisms are impaired.

CURRENT AND FUTURE APPROACH FOR MANAGEMENT OF ACD

Current view is that once established, ACD is a lifelong disease. Thus, prevention and avoidance of the causative contact sensitizer is critical in the management of the patient affected by ACD. However, in patients with polysensitizations or sensitized to extremely diffuse sensitizers, such as nickel, both prevention and avoidance may be a challenge.

Procedures to limit hapten penetration may help to reduce the amount of immunogenic hapten-peptide complexes generated upon exposure. Similarly, the use of chelants for metal allergy has been proposed, but efficacy may be limited. Indeed, most of the therapeutic approaches are directed to dampen the effector mechanisms of ACD, including attempts to block T cell transmigration into the skin, leukocyte activation, or keratinocyte-dependent amplification of the inflammatory response.

Thanks to the abundant information on the mechanisms governing T cell recruitment into inflamed skin, many compounds with antagonistic properties on leukocyte-endothelial cell interactions have been developed and entered clinical trials in the last few years. This approach has advantages compared to immunosuppressive therapy, since it targets selective T cell subpopulation while maintaining immunoprotection in other districts. On the other hand, effectiveness may be limited by the redundancy of the mechanisms involved in T cell extravasation and positioning into the skin. Proposed targets include selectins, which mediate initial rolling of leukocytes over the endothelium, adhesion molecules, as well as chemokine-chemokine receptor pairs [32-34]. Strategies aimed to interfere either with selectin functions through the administration of blocking antibodies, or the modulation of the post-transcriptional glycosylation of selectin ligands, such as the administration of fluorinated antagonists, have revealed some efficacy in murine CHS. However, their use in human disease was disappointing [35]. On the opposite, the promiscuity of the selectin system and the

overlapping functions of E- and P-selectins in governing leukocyte recruitment into peripheral tissues may require molecules with a broader spectrum of activity. Among agents regulating leukocyte-endothelial cell interactions, efomycines are a family of small molecules obtained from *Streptomyces BS1261* that structurally mimics the selecting binding site of selectin ligands [36]. Efomycines, by preventing leukocyte interaction with endothelial cell selectins, have displayed promising anti-inflammatory effects both *in vitro* and in animal models of skin inflammation. Additionally, their action may not be limited to the control of T cell recruitment into the skin, but may also affect T lymphocyte viability and cytokine release.

Another attractive strategy is to target chemokine receptors on selective leukocyte subpopulations. Chemokines not only promote T cell recruitment into peripheral tissues, but play a critical role in T cell adhesion to endothelial cells and in modulating T cell functions. Among chemokine receptors, three major molecules appear involved in skin positioning of pathogenetic T cells during ACD: CCR4, which mediates T cell-endothelial cell binding in the initial phase of leukocyte migration into inflamed tissue [37]; CCR10, the receptor for CCL27, which is specifically released by keratinocytes [38, 39]; and CCR6, expressed by the majority of Th17 cells [40]. Attempts to block chemokine-receptor axes have provided inconsistent results, although there are clear *in vitro* as well as *in vivo* evidence for future applications.

Finally, approaches aimed at targeting integrins appear so far the most promising, albeit their use has been until now limited to severe autoimmune disorders. Natalizumab (anti-VLA4) is being used in the treatment of non responsive patients affected by multiple sclerosis [41]; Alicaforfen, an antisense inhibitor of ICAM-1, is being used in the treatment of Crohn disease [42]. Given the critical role of ICAM-1 in the pathogenesis of ACD, this drug may be also effective in the treatment of severe ACD.

Most of the therapeutic approaches for ACD are based on drugs targeting lymphocyte activation, either systemically or locally administered. Local immunosuppression is usually achieved with topical application of corticosteroids, which remain the mainstay of treatment of ACD. The macrolactam immunomodulators Tacrolimus and Pimecrolimus have been recently introduced in the therapy of several immune-mediated skin diseases, including atopic dermatitis and ACD [43, 44]. They both inhibit the transcription of proinflammatory cytokine genes, such as interleukin 2, which are dependent on the nuclear factor of activated T cell (NF-AT), by binding to the FK-binding protein or macrophilin 12, and blocking the catalytic function of calcineurin, leading to the inhibition of the transport of the cytoplasmic component of NF-AT to the cell nucleus [45]. Although functionally similar, Pimecrolimus has a three-fold lower binding affinity for macrophilin 12, when compared to Tacrolimus [46].

More severe ACD reactions often require a systemic immunosuppressive treatment, mostly based on systemic corticosteroids regimen and/or cyclosporine administration. Cyclosporine acts primarily as a systemic immune moderator by binding cyclophilin and blocking calcineurin, similarly to Tacrolimus and Pimecrolimus. Therapeutic effectiveness of cyclosporine in ACD results from its dramatic effects on T cell functions, as well as on cytokine release [47]. Mycophenolate Mofetil (MMF) is a morpholino-ethyl ester of mycophenolic acid (MPA), converted intracellularly to MPA, an anti-metabolite drug which blocks T cell proliferation and antibody production by B cells interfering with DNA and RNA synthesis. The drug is highly efficient in preventing hapten sensitization in animal models, but does not affect the expression of the allergic reaction in already sensitized animals, thus suggesting that the magnitude of the inflammatory response is independent from local T cell expansion [48]. Similar results were obtained with the angiogenesis inhibitor AE-941 (Neovastat), which dampened the

immune reaction only when administered in the sensitization phase of CHS [49].

Given the role of skin DCs in the development of ACD, novel approaches aimed to limit their functional maturation and migration to secondary lymphoid organs have been investigated. Fingolimid (FTY720) is a synthetic structural analog of mytiocin that affect the sphingosine-1-phosphate (S1P) signalling by binding S1P receptors. Topical administration of FTY720 and S1P in the mouse impaired the secretion of IL-12 [50], IFN- γ and IL-6 [51] induced by hapten administration. This effect is paralleled by a reduced migration of DCs towards regional lymph nodes and impaired expansion of T cells upon hapten encounter. Systemic administration of FTY720 effectively impairs afferent but not efferent phase of murine CHS [52] and may thus be not effective in reducing skin inflammation in already sensitized individuals.

Phospholipase A2 (PLA2), a membrane enzyme which hydrolyzes phospholipids and releases arachidonic acid and lysophospholipids, is certainly involved in the amplification of skin inflammation during ACD. Topical application of PLA2 inhibitors regulated the expression of ACD, by reducing the magnitude of skin inflammation in allergic patients, as compared to placebo treated individuals [53].

Although TNF- α has revealed a critical cytokine in ACD, strategies aimed to block this cytokine were not effective in the control of hapten hypersensitivity. Indeed, cases of hapten-sensitization occurring during anti-TNF therapy have been reported [54, 55].

Current research in the field of immune-mediated skin diseases is delineating the molecular mechanisms involved in keratinocyte responses to T cell derived cytokines, in particular IFN- γ , TNF- α and IL-17, which are mostly involved in the expression of ACD. Given the critical role of keratinocytes in the amplification process of the allergic reaction, attempts to decrease their responsiveness to pro-inflammatory cytokines may succeed in dampening allergic reactions. Of particular interest appear the suppressor of cytokine signaling (SOCS) molecules, a family of endogenous suppressor molecules which are induced by cytokines and that act in a regulatory negative feedback thus regulating cytokine-induced pro-inflammatory genes in keratinocytes [56, 57]. Peptides mimicking SOCS1, a critical controller of IFN- γ -induced keratinocyte activation, are currently under investigation as a potential innovative anti-inflammatory therapy.

TOWARDS THE DEVELOPMENT OF HAPTEN-SPECIFIC DESENSITIZATION THERAPIES IN ACD

Current view is that chances to develop hypersensitivity reaction towards chemicals depends upon a balance between hapten-specific effector T cells and Treg lymphocytes. Similarly, equilibrium between the two subsets affects the magnitude of the immune response in already sensitized individuals [58, 59]. Recent observations indicate that, other than natural thymic-derived CD4+CD25+ Treg lymphocytes, specific Treg subpopulations are induced upon antigen encounter at peripheral sites [60]. This finding opens new perspectives in the development of hyposensitizing approaches aimed to expand antigen-specific T cells with regulatory function.

Indirect evidence of induction of specific immunotolerance towards nickel, the most common skin sensitizer in western countries, has been provided by the observation that children exposed to nickel released by orthodontic braces were partially protected from development of nickel allergy during their life [6]. Another study demonstrated that the frequency of nickel allergy was significantly lower in Russian women drinking nickel-contaminated water, compared to unexposed control [61]. Indeed, oral administration of nickel sulphate has been demonstrated to improve the severity of nickel allergy and to decrease nickel sensitivity in allergic individuals, as measured with patch test reactivity [62]. However, effective-

ness was strictly dependent on the dosage, and restricted to patients receiving 3.5 to 5 mg nickel sulphate on a daily basis. Similar results were obtained with sublingual administration of the metal [63]. However, in all these studies immunologic functions of nickel-treated versus untreated patients have not been investigated, and the studies did not include adequate follow up. Thus, although the approach is highly promising, more detailed investigations are required to define both the doses and duration of treatment, and to disclose the mechanisms of tolerance induction.

CONCLUSIONS

Understanding of the mechanisms involved in the expression of ACD allowed the development of multiple strategies aimed to prevent or limit tissue inflammation in hapten-sensitized individuals. Although the golden standard of ACD treatment remains the local and/or system immunosuppressive therapy, new approaches targeting either leukocyte recruitment into peripheral tissues or keratinocyte responsiveness to pro-inflammatory stimuli are being investigated, and may represent in the next future valid alternatives in the treatment of ACD. Moreover, recognition of the mechanisms regulating ACD reaction and identification of subsets of Treg which specifically control immune responses to skin applied haptens, are opening new possibilities in the development of vaccines for ACD patients.

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ABBREVIATIONS

ACD	=	Allergic contact dermatitis
APC	=	Antigen presenting cells
CCL	=	CC chemokine ligand
CCR	=	CC chemokine receptor
CLA	=	Cutaneous lymphocyte associated antigen
CHS	=	Contact hypersensitivity
DCs	=	Dendritic cells
ICAM	=	Intercellular adhesion molecule
IFN	=	Interferon
IL	=	Interleukin
MHC	=	Major histocompatibility complex
MMF	=	Mycophenolate mofetil
MPA	=	Mycophenolic acid
NF-AT	=	Nuclear factor of activated T cell
NK	=	Natural killer
PLA2	=	Phospholipase 2
S1P	=	Sphingosine-1-phosphate
SOCS	=	Suppressor of cytokine signaling
TCR	=	T Cell Receptor
TNF	=	Tumor necrosis factor
Treg	=	T regulatory (cells)

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