

Review

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Review

Trogocytosis and Allergy

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Abstract

Trogocytosis is the process of engulfment of a portion of a cell's membrane by another cell. This process is characterized by the transfer of membrane fragments and proteins between adjacent cells without their complete fusion or phagocytosis, which distinguishes it from classical cellular uptake pathways. In the immune system, the initiating signal for trogocytosis is antigen presentation or the interaction of the Fc receptor with an antibody bound to the cell. During trogocytosis, T cells transfer not only the MHC molecule with the antigenic peptide, but also the costimulatory molecules CD80, CD86, OX-40 and others. As a result of trogocytosis, cells can transfer various surface molecules, acquire new immunological properties, and modulate each other's activity. This review examines the basic mechanisms of trogocytosis, the involvement of T2-mediated immunity components in trogocytosis, and its possible role in allergies.

Keywords: trogocytosis; allergy; type2-mediated immunity; antigen presentation

1. Introduction

In the mid-20th century, scientists noticed a process they described as the “stealing” of surface molecules [1]. This phenomenon was first described in amoebae, and later between cells of the immune system [2–5]. The observed process became known as partial phagocytosis, cannibalistic gnawing, extraction, biting off, acquisition, since in translation from the Greek (trogo-) means “nibble” or “to bite off”, and the transfer of membrane proteins was observed between cells [2]. The concept of “trogocytosis” was first introduced into scientific circulation by T. Brown. He discovered that *Naegleria fowleri*, known as the “brain-eating amoeba”, engulfs mouse embryo cells piece by piece [3]. The main difference between amoebas and immune cells is that in the latter case, both cells usually remain alive [3].

Currently, a growing body of research demonstrates the important role of trogocytosis in the immune system. Trogocytosis is an active process in which one cell engulfs a fragment of another, resulting in the transfer of cell surface molecules along with membrane fragments. It is generally distinguished from phagocytosis, which engulfs the entire cell (1). Trogocytosis is involved in antigen presentation, T-lymphocyte differentiation, nervous system remodeling, and embryonic development, and plays a role in anti-infective and anti-tumor immunity (2). Trogocytosis transports not only major histocompatibility complex (MHC) class II molecules, but also costimulatory molecules, tumor antigens, and various pathogens. According to the literature, the following cells can participate in this process: T cells ($\gamma\delta$ T cells and CD4⁺ and CD8⁺ $\alpha\beta$ T cells), B cells, NK cells, dendritic cells, monocytes/macrophages, neutrophils, endothelial cells, fibroblasts, eosinophils, basophils), tumor cells and various pathogens. However, it is still not entirely clear what role trogocytosis plays both under physiological conditions and in pathology. Currently, researchers are focused on studying the trogocytosis of immune cells in the development of infectious diseases,

oncopathology, and, partially, in autoimmune processes. Most of the works by foreign authors are devoted to the role of trogocytosis of CD8⁺ T-lymphocytes in the progression of tumor growth [6], the evasion of the immune response by tumor cells through trogocytosis [6], a decrease in the effectiveness of targeted antitumor therapy and specific CAR-T cells as a result of trogocytosis of tumor antigens and the MHC-TCR complex, respectively [7–9]. However, the role of trogocytosis in allergic diseases is rather poorly covered in the literature.

2. The Main Mechanisms of Trogocytosis by Immune Cells

Trogocytosis in immune cells has been shown to be mediated by two main pathways: the formation of an immunological synapse between MHC and the T-cell receptor (MHC-TCR) and the interaction of the immunoglobulin receptor with its ligand (FcR-Ig) [10–12]. The first pathway has a far greater impact on the immune response, as it can involve CD4⁺ and CD8⁺ T lymphocytes, antigen-presenting cells, natural killer cells, and basophils. The second pathway can be used by B lymphocytes, NK cells, macrophages and neutrophils. According to the literature, several mechanisms of trogocytosis are distinguished: trogocytosis caused by the interaction of TCR–MHC signaling mechanism, cross-dressing as a mechanism of trogocytosis, the mechanism of trogocytosis in neutrophils, leading cells to apoptosis.

2.1. TCR–MHC-Mediated Trogocytosis

Trogocytosis involves interaction between a ligand and a receptor, such as the T cell receptor (TCR) of T lymphocytes with the pMHC (peptide-associated major histocompatibility complex) complex located on the surface of antigen-presenting cells (APCs). Upon contact between APCs and T cells, an immunological synapse is formed, which then activates T cells and the peptide-MHC (pMHC) complexes, along with fragments of APC membranes, are translocated to the surface of T cells [1]. According to literature data, trogocytosis of pMHC-II complexes prolongs the association between TCRs and pMHC-II complexes, maintains TCR signals, and promotes the survival of CD4⁺ T cells even after APC removal. This mechanism leads to full activation and stimulation of T lymphocytes by antigen. In contrast to other processes, such as phagocytosis, trogocytosis prolongs the interaction time between the T cell and the pMHC complex [13]. CD4⁺ T cells take up peptide-MHC class II (pMHC-II) complexes from APCs, while CD8⁺ T cells nibble off peptide-MHC class I (pMHC-I) complexes from APCs. CD4⁺ T cells can also acquire both cognate pMHC-II complexes and bystander pMHC-I complexes, possibly due to the localization of the bystander pMHC-I complex near cognate pMHC-II complexes. Similarly, CD8⁺ T cells can acquire both cognate pMHC-I complexes and bystander pMHC-II complexes [1]. Other molecules have been shown to be transferred along with pMHC, including costimulatory molecules (CD80, CD86, and OX-40) and integrin ligands (e.g., ICAM-1) [14]. Thus, after acquiring the MHC-TCR complex and associated costimulatory molecules, the trogocytized cell (trogocyte) acquires new properties.

It has been shown that CD4⁺CD80⁺CD86⁺ cells are capable of performing an antigen-presenting role in relation to other, non-activated CD4⁺ T-lymphocytes [15–17]. Zhou et al. showed that the transfer of pMHC and CD80 from APCs to T cells can alter T cell proliferation and maintain their activation in the absence of APCs. The number of activated CD4⁺ T cells that trogocytose and capture MHC-peptide complexes then significantly exceeds that of APCs [18]. This can ultimately lead to interactions between new T cells and trogocytized T cells (TT interactions), but this leads to increased apoptosis and induction of anergy [18,19].

It has been shown that CD4⁺ T cells can trogocytose as T-regulatory cells and a subset of Th2 cells. Trogocytosed CD4⁺ T cells react with naive and memory CD4⁺ T cells, leading to anergy of naive CD4⁺ T cells and Th17 activation of memory CD4⁺ T cells [1].

Tregs are capable of depleting CD80/CD86 molecules on APCs by nibbling them through CTLA-4-dependent trogocytosis [20]. It has been shown that CTLA-4-positive cells can nip CD80/CD86 from opposing cells, destroying them and leading to impaired costimulation via the CD28 molecule [21]. Depletion or blockade of CD80 through CTLA-4-dependent trogocytosis leads to an increase in free

PD-L1. Thus, Tregs may exert dual suppressive effects by limiting CD80/CD86 and upregulating free PD-L1 on APCs [22]. Compared with naïve and effector T cells, T regulatory cells have increased trogocytosis activity in order to remove MHC class II and costimulatory molecules from APCs, resulting in the induction of tolerance.

Thus, TCR-pMHC-mediated trogocytosis, on the one hand, can lead to an increase in antigen-presenting cells, and as a consequence, an increase in antigen presentation and an enhancement of the immune response, but, on the other hand, can lead to a weakening of T-lymphocyte activation and the loss of MHC and costimulatory molecules by antigen-presenting cells.

2.2. Cross-Dressing

Cross-dressing is an additional trogocytosis mechanism used by APCs to present antigen to CD8⁺ T cells [20]. This mechanism involves the translocation of peptide-MHC class I complexes from the surface of infected, dead, or tumor cells to APCs, particularly DCs (1,6). As a result, “dressed DCs” (cross-dressed) activate CD8⁺ T cells without prior antigen treatment [23]. Cross-dressed DCs play a major role in the activation of CD8⁺ T cells in viral infection models and during allograft rejection [1].

The conventional DCs are further subdivided into DC type 1 cells (DC1s) and DC type 2 cells (DC2s) [24,25]. DC2s present extracellular antigens on MHCII through the conventional antigen presentation pathway whereas cDC1s are able to present extracellular antigens not only on MHCII, but also on MHCI, called cross-presentation [25]. According to the literature, cross-dressing has been shown to occur by both DC1 and DC2, but DC2s exhibit a higher ability to cross-dress neighboring DC-derived MHCI. This difference may be related to the donor cells from which DCs acquire MHCI.

MHC can also be transferred between dendritic cells via cross-dressing [26–28]. Dendritic cells are professional antigen-producing cells (APCs) that play a key role in the primary immune response. These cells can exchange antigen within the MHC-I complex and then present the peptide to T cells. Using this transfer mechanism, dendritic cells accelerate the immune response, as they do not encounter the antigen and do not process it, thus accelerating T cell activation presenting cells.

2.3. FcγR-Mediated Trogocytosis

FcγR-mediated trogocytosis occurs through the recognition of IgG immune complexes on donor cells by FcγR on acceptor cells [10]. The acceptor cells form immunological synapses with the IgG-opsonized cells, thus allowing for transfer of cell-bound IgG and associated antigen and membrane to the effector cells. The FcγR is expressed on a number of cells, such as macrophages, neutrophils, NK cells, and mast cells. [29].

Neutrophils are the most numerous type of leukocyte in circulating blood [30]. Berg et al. were among the first to discover that neutrophils are capable of not only phagocytosis but also trogocytosis. Unlike other cells, neutrophils act as a group to “nibble off” pathogen particles and induce apoptosis. Significant membrane loss can result in trogoptosis, which is also known as trogocytosis-mediated apoptosis [31]. Neutrophils most often use trogocytosis to combat protozoa, such as *Trichomonas vaginalis* [5]. In addition, neutrophils are capable of killing opsonized tumor cells by trogoptosis [32]. FcγR, in combination with CD11b/CD18 integrins, enhances tumor cell activity by blocking CD47-SIRPα interactions. CD47-SIRPα is a transmembrane protein found on red blood cells that prevents their uptake by macrophages. Neutrophils are thus able to enhance ADCC (antibody-dependent cell-mediated cytotoxicity) of tumor cells (68). Neutrophils are one of the most numerous populations of innate cells involved in the pathogenesis of RA. This cell type is predominantly present in synovial fluid and, to a lesser extent, in synovial tissue. Studies have shown that neutrophils in patients with RA are functionally different from those in healthy donors, as neutrophils from patients with RA have the greatest cytotoxic potential and are rapidly activated in response to ROS. Granules contained in the cytoplasm can be released in response to antibodies to anticitrullinated protein (ACPA) and rheumatoid factor (RF) in the joint of patients with RA via the FcγR receptor (97). Trogocytosis has also been detected in the neutrophil population, with CD8 and

additional TCR and CD3 transferred from T cells as a result of Fc γ R-mediated trogocytosis by neutrophils. In line with this model, Masuda et al. studied this process in autoimmune diseases. Neutrophils, by binding antibodies, can trogocytose various molecules, particularly CD8, TCR, and CD3. Using this principle, the study demonstrated that neutrophils can remove excess autoantibodies, which may be a protective mechanism in autoimmune diseases such as RA. (Human anti-mouse IgG antibodies in serum increase Fc γ R-mediated trogocytosis.) Thus, it was concluded that lower endocytic activity by neutrophils may contribute to the development of autoimmune diseases, as antibody utilization is impaired (98).

Also, antibody therapy enhance tumor cell death through macrophage trogocytosis [34]. However, macrophage trogocytosis does not always result in cell death; sometimes, this process is used for regulation. Macrophages are known to trogocytose hematopoietic stem cells, marking them for retention in the bone marrow [35]. Similarly, brain tissue macrophages, microglia, selectively damage neuronal synapses to prune connections in the developing brain[36].

Macrophage trogocytosis in obesity leads to increased inflammation. Obesity is known to induce the production of proinflammatory cytokines, which can further stimulate macrophage infiltration into adipose tissue. Research has shown that macrophages can trogocytose aged adipocytes at the site of adipocyte-macrophage interaction via an “eat me” signal. Subsequently, trogocytized macrophages secrete IL-6 and MCP-1, which increases adipose tissue inflammation (95, 96).

Following administration of monoclonal antibodies (MAbs), Fc γ receptor (Fc γ R)-expressing cells, including monocytes, macrophages, neutrophils, and NK cells, can cleave MAb-associated cell surface molecules from target cells (tumors) via trogocytosis. This ultimately leads to decreased efficacy of MAb-based therapy [33]. Rituximab infusion in CLL patients reduces CD20 expression on tumor cells via trogocytosis, leading to incomplete tumor cell lysis and subsequent resistance to therapy. A study by Michael E et al. suggested low-dose anti-CD20 therapy to reduce the effect of trogocytosis and enhance clearance of circulating CLL cells [37].

NK cells also possess the capacity for trogocytosis; their key marker is CD16, a low-affinity receptor for immunoglobulin G (Fc γ RIII) [38]. Consequently, NK cells can also participate in the destruction of cells surrounded by antibodies. However, NK cell trogocytosis does not lead to an enhanced antitumor response [39,40]. For example, when NKG2D and MICA bind, trogocytosis is triggered, resulting in NK cells acquiring MICA from donor or tumor cells. NK cells that have cleaved MICA can interact with NKG2D on NK cells and trigger NK cell fratricide. NK cell fratricide also occurs when NK cells trogocytose the Rae-1 protein, another ligand for NKG2D [41]. Like T cells, NK cells can cleave the non-classical major histocompatibility complex molecule HLA-G through trogocytosis. HLA-G1 on NK cells binds to ILT2 on other NK cells and suppresses NK cell proliferation and cytotoxicity.

Additionally, NK cells can acquire CD9 (a tetraspondin family protein) through trogocytosis and suppress the cytotoxicity of these cells, as studied in high-grade tubo-ovarian serous carcinoma (HGSC). Anti-CD9 antibodies restored the cytotoxic function of NK cells. Similarly, NK cells can cleave PD-1 from C1498 leukemia cells through trogocytosis via the SLAM receptor and suppress their antitumor activity [41–43]. Like CD9, this impairment can be reversed by anti-PD-1, thereby enhancing NK cell cytotoxicity against tumors. NK cells can acquire molecules not only from tumor cells but also during interactions with other cells, such as antigen-producing cells (APCs). By acquiring MHC class II molecules from DCs through trogocytosis, NK cells coated with pMHC can present antigens to CD4 T cells. However, this antigen presentation is inefficient and does not lead to T cell activation, as they lack costimulatory molecules [41,42]. Furthermore, NK cells can cleave the chemokine receptor CCR7 (a receptor involved in lymph node homing) from allogeneic DCs and T cells, promoting NK cell migration to secondary lymphoid organs.

3. T2 (Type 2) Mediated Immunity Involves Key Cells and Trogocytosis

Type 2 immunity underlies allergic diseases such as asthma, allergic rhinitis, chronic rhinosinusitis, food and drug allergies, and atopic dermatitis [44]. Type 2 immunity evolved to

protect against parasitic infections and toxins, plays a role in expelling parasites and larvae from internal tissues into the lumen and beyond the body, maintains microbe-rich epithelial barriers of the skin and mucous membranes, and balances the type 1 immune response and its destructive effects. Type 2 immunity consists of ILC2, TC2 cells, and Th2 cells producing IL-4, IL-5, and IL-13, which induce mast cell, basophil, and eosinophil activation, as well as B cell activation and IgE antibody production [45]. According to literature data, most cells involved in T2 immunity, with the exception of eosinophils, can participate in trogocytosis [46]. However, in the work of S. Andreone it was shown that eosinophils carry out trogocytosis of tumor cells, capturing PD-1 and TIGIT molecules [47]. Presumably, eosinophils can also trogocytose checkpoints during the immune response to an allergen, regulating the immune response.

It is known that basophils can acquire a peptide/MHC class II complex from the surface of dendritic cells during trogocytosis. Due to the ability of basophils to produce IL-4, this allows them to influence the differentiation of CD4⁺ T-naïve cells toward T-helper type 2 cells [48]. Basophils have demonstrated the ability to induce Th2 cell differentiation in an experimental model of allergic immune response [49]. However, basophils are a minor subpopulation of blood granulocytes (less than 1% of blood leukocytes), which may limit the actual role of basophil trogocytosis in the development of allergic reactions.

Mast cells can also trogocytose, whereby mast cells receive MHC-II from DCs and can initiate T cell responses [50]. Furthermore, synapses between mast cells and DCs enhance antigen transfer from mast cells to DCs [51].

In addition to producing effector cytokines, ILC2 have been shown to express MHC class II (MHCII) in combination with the costimulatory ligands CD80, CD86, and OX40 ligand (OX40L), allowing for direct cross-talk between ILC2 and CD4⁺ T cells [52,53]. Interestingly, MHC class II expression on the cell surface of ILC2s is at least partly mediated by trogocytosis [54], likely acquired from other professional APCs. It remains unclear whether costimulatory molecules are acquired through trogocytosis or transcribed by ILC2s. In co-culture experiments, ovalbumin alone, but not ovalbumin-loaded ILC2s, resulted in T cell proliferation and Th2-polarization of the immune response. The authors of this publication suggest that ILC2s do not direct the T cell response by directly presenting antigen, but may do so through surface antigen exchange or trogocytosis [54]. Although ILC2s are capable of activating T cells by presenting antigens to T cells, there is also evidence that T cells can assist ILC2s in the development of the immune response. In vitro, T cells have been shown to enhance ILC2 proliferation in an antigen-dependent manner, which correlates with IL-2 production by T lymphocytes [55].

4. The Role of Trogocytosis in Allergy

The development of an allergic reaction begins with the presentation of an allergen to naïve T-helpers [56]. Trogocytosis can lead to an increase in APC numbers due to DC cross-dressing and the production of pMHC and costimulatory molecules by T lymphocytes [1]. Furthermore, ILC and basophils can perform antigen-presenting functions in the T2 immunity [48,54]. On the other hand, there is reason to believe that the enhancement may not be sufficient to significantly contribute to the development of allergy. Allergen-stimulated basophils exhibit low levels of MHCII on their cell surface, significantly lower than the levels observed on B cells and DCs [57]. Furthermore, basophils did not activate antigen-specific T cell proliferation, and basophil deficiency did not reduce T cell proliferation or T2 cytokine production.

As mentioned above, CD4⁺ T cells after trogocytosis can become T-regulatory cells and Th2 cells [1]. CD4 T cells, during in vitro co-culture with APCs and trogocytosis, demonstrated a decrease in IFN- γ expression from 13.4% to 1.5%, while expression of the Th2 cytokine IL-4 shifted to 77.4% [41]. Moreover, Th2-polarized CD4 T cells demonstrated increased trogocytosis compared to T helper type 1 (Th1) or non-polarized CD4 T cells. However, in another study, CD4⁺ T lymphocytes carrying MHC II molecules on their surface, on the contrary, are able to exert negative regulation on the Th2 immune

response, suppressing the development of CD4⁺ T lymphocytes and promoting their apoptosis [18,19].

Tregs are key cells capable of suppressing the immune response to an allergen and promoting the development of tolerance in allergies. It is known that CD4⁺ T lymphocytes that perform trogocytosis are subsequently capable of differentiating into Tregs, limiting the excessive immune response [58]. Tregs themselves are also capable of trogocytosis [59,60]. Compared to naive and effector T cells, Tregs have increased trogocytotic activity [25], aimed at removing MHC class II molecules and the costimulatory molecules CD80 and CD86 from antigen-presenting cells, which leads to a decrease in antigen-presenting function and the induction of tolerance.

Among T cells, TCR $\alpha\beta$ +CD3+CD4[−]CD8[−] T cells—double-negative T cells (DNTs)—are also implicated in the pathogenesis of allergic asthma. For example, in a mouse model of OVA-induced allergic asthma, adoptive transfer of DNTs reduced lung inflammation, mucus production, and OVA-specific IgG/IgE. Murine DNTs were shown to acquire MHCII molecules from DCs via Lag3/CD223 (a CD4 homolog that binds to MHCII). DNTs may suppress the antigen-presenting activity of DCs, similar to Tregs, by capturing MHCII from the DC surface and impairing antigen presentation (24, 61).

Consequently, data on the role of trogocytosis in allergies are contradictory. However, given the fact that Treg cells trogocytize more actively than conventional T cells, the process of trogocytosis is likely to contribute more to the development of tolerance to the antigen.

5. Conclusions

Trogocytosis, as a form of cell interaction, is observed in both health and disease. Cells involved in the development of allergies are capable of trogocytosis. Through trogocytosis, cells can acquire new functions, participating in immune regulation. Thus, trogocytosis plays a crucial role in the immune system. The “nibbling” of various molecules by immune cells, tumor cells, and others, can lead to both beneficial and detrimental effects. In the case of immune cells, trogocytosis alters the direction of the immune response, either activating or suppressing cell activity. The possible role of trogocytosis in various immunopathological processes, in particular in allergies, has not been fully studied. On the one hand, trogocytosis promotes the polarization of the immune response towards T_H2, on the other hand, it suppresses the immune response through the generation of Tregs and their “biting off” molecules from the surface of APCs, which prevents the development of the immune response. However, given the fact that Treg cells trogocytize more actively than conventional T cells, the process of trogocytosis is likely to contribute more to the development of tolerance to the antigen. The exact mechanisms and role of trogocytosis in allergies remain unclear. Further research into trogocytosis may contribute to a better understanding of pathological processes and the discovery of new targets for therapy.

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