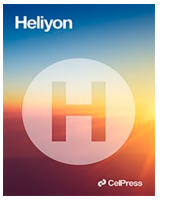
Heliyon 10 (2024) e30553

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Helper T cell subsets: Development, function and clinical role in hypersensitivity reactions in the modern perspective

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ARTICLE INFO

Keywords:
Allergy
CD4
Helper T cell
Hypersensitivity
Lymphocytes

ABSTRACT

Helper T cells are traditionally classified into T helper 1 (T_H1) and T helper 2 (T_H2). The more recent discoveries of T helper 17 (T_H17), follicular helper T cells (T_{FH}) and regulatory T cells (T_{reg}) enhanced our understanding on the mechanisms of immune function and hypersensitivity reactions, which shaped the modern perspective on the function and role of these different subsets of helper T cells in hypersensitivity reactions. Each subset of helper T cells has characteristic roles in different types of hypersensitivity reactions, hence giving rise to the respective characteristic clinical manifestations. The roles of helper T cells in allergic contact dermatitis (T_H1-mediated), drug rash with eosinophilia and systemic symptoms (DRESS) syndrome (T_H2-mediated), and acute generalised exanthematous pustulosis (AGEP) (T_H17-mediated) are summarised in this article, demonstrating the correlation between the type of helper T cell involved and the clinical features. T_{FH} plays crucial roles in antibody class-switch recombination; they may be implicated in antibody-mediated hypersensitivity reactions, but further research is warranted to delineate their exact pathogenic roles. The helper T cell subsets and their specific cytokine profiles implicated in different hypersensitivity reactions could be potential treatment targets by biologics, but more clinical trials are warranted to establish their clinical effectiveness.

1. Introduction

T cells are important components of the adaptive immunity; among them, helper T cells are coordinators of adaptive immunity, which control the activation and regulation of other immune cells upon antigen-specific recognition [1]. Downstream effects of cytokine production by helper T cells coordinate effector mechanisms of both the innate and adaptive immunity [2]. Traditionally, helper T cells are classified into T helper 1 (T_H1), T helper 2 (T_H2); the more recent discoveries of T helper 17 (T_H17), follicular helper T cells (T_{FH}) and regulatory T cells (T_{reg}) enhance our understanding on the mechanisms of immune function and hypersensitivity reactions [3]. Each of them has characteristic roles to play in the defence against different pathogens; correspondingly, each subset of helper T cells has characteristic roles in different types of hypersensitivity reactions [3]. In this article, development and functions of different subsets of helper T cells (T_H1, T_H2, T_H17 and T_{FH}) are illustrated, and their roles in different hypersensitivity reactions are discussed.

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https://doi.org/10.1016/j.heliyon.2024.e30553
Received 14 January 2024; Received in revised form 28 April 2024; Accepted 29 April 2024
Available online 1 May 2024

1.1. Development and activation of helper T cells

After the initial stages of development from haematopoietic stem cells in the bone marrow then in the thymus, naïve T cells leave the thymus and go into the circulation, and eventually reaching the secondary lymphoid organs, where they reside and wait for activation [4]. Antigen-presenting cells, mostly dendritic cells capture antigens from various body sites and are drained to secondary lymphoid organs, where they meet naïve T cells. They load antigens on major histocompatibility complex (MHC) and interact with naïve T cells with matching specificity; MHC-I interacts with naïve $CD8^+$ T cells, whereas MHC-II interacts with naïve $CD4^+$ T cells [5]. With the antigen recognition signal (MHC-T-cell receptor [TCR] interaction) and co-receptor signals, naïve T cells are activated, which proliferate and express interleukin (IL)-2 and IL-2 receptors for positive-feedback self-activation [6].

Differentiation of $CD4^+$ helper T cells into different subsets is determined mainly by the cytokine environment the cells are exposed to [7]. Subsets of helper T cells downstream to naïve T cells are defined by their characteristic cytokine expression profile, and can be broadly classified into T_H1, T_H2, T_H17 and T_{FH} [8]. Interferon-gamma (IFN-γ) and IL-12 promote differentiation of naïve helper T cells to T_H1, IL-4 promotes differentiation of naïve helper T cells to T_H2, while IL-23, IL-6 and transforming growth factor beta (TGF-β) promote differentiation of naïve helper T cells to T_H17; IL-6 plays a role in the differentiation of naïve helper T cells into T_{FH}, and depending on the cytokine environment, differentiating into follicular helper T cell (T_{FH})1, $T_{FH}2$ or $T_{FH}17$ (Fig. 1) [7]. Activated and differentiated helper T cells then migrate to their effector sites to carry out their actions [9].

In general, haptenated proteins are taken up by antigen-presenting cells (APCs) upon exposure to the insulting agent [10]. APCs move to nearby lymph nodes to activate $CD4^+$ helper T cells [10]. Specifically, exogenous antigens captured on MHC-II in APCs (such as dendritic cells) were presented to $CD4^+$ helper T cells. This leads to the activation of $CD4^+$ helper T cells via the TCR and CD3 signalling pathways, subsequently leading to the differentiation of $CD4^+$ helper T cells into more committed lineages, where they have distinct expression profiles and roles in hypersensitivities [9,10]. For example, IL-12 secreted by APCs drives the $CD4^+$ helper T cells to differentiate into the T_H1-like phenotype while exposure to IL-2 and IL-4 leads to the differentiation into the T_H2-like phenotype [9]. Of note, the activation and differentiation of $CD4^+$ helper T cells is dynamically but precisely controlled by environmental cues, such as the presence of cytokines like IL-12, IFN-γ, IL-2 and IL-4 [9]. Additionally, trogocytosis plays an important role in sustaining the immune response mediated by $CD4^+$ helper T cells. Trogocytosis occurs when T cells acquire the antigen-bound MHC-II from APCs directly by 'nibbling' the MHC-II [11]. MHC-dressed $CD4^+$ helper T cells can subsequently present the antigen to nearby immune cells, leading to sustained TCR signalling. The activation of different subsets of $CD4^+$ helper T cells has varying contributions to delayed hypersensitivities. Their precise role will be discussed further.

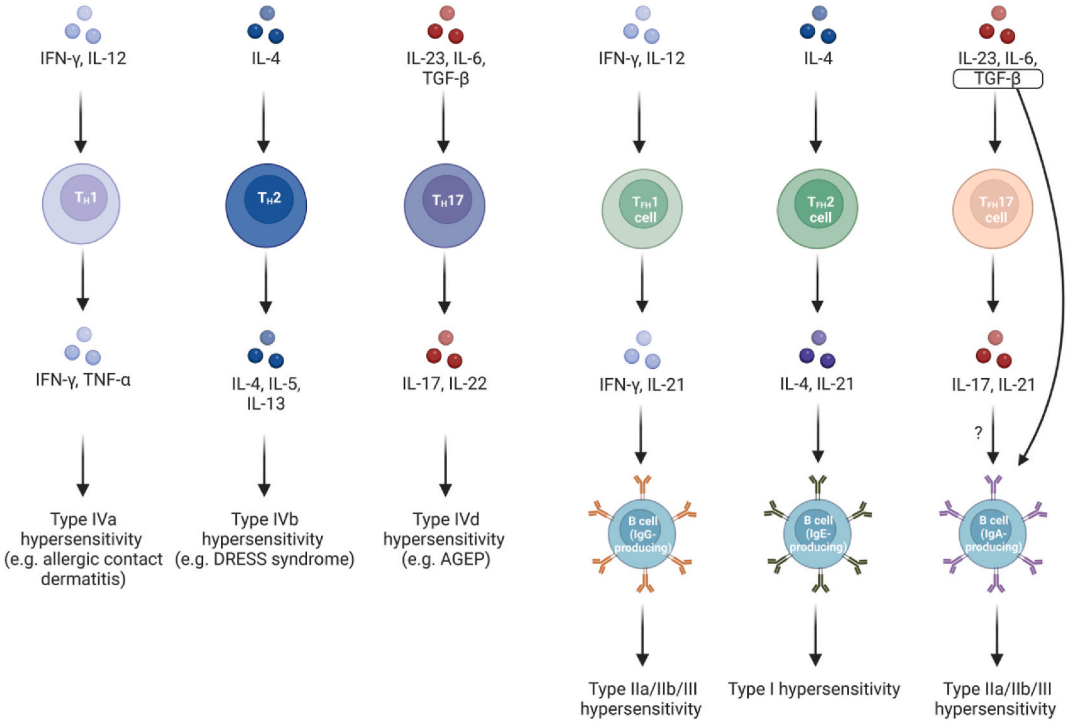

Fig. 1. Summary of helper T cell subsets and their cytokine profile implied in different hypersensitivity reactions.
IFN-γ, interferon-gamma; IL, interleukin; TGF-β, transforming growth factor-beta; TNF-α, tumour necrosis factor-alpha; T_H1, T helper 1; T_H2, T helper 2; T_H17, T helper 17; $T_{FH}1$, T follicular helper 1; $T_{FH}2$, T follicular helper 2; $T_{FH}17$, T follicular helper 17; DRESS, drug rash with eosinophilia and systemic symptoms; AGEP, acute generalised exanthematous pustulosis (Created with BioRender.com).

1.2. Main localisations of helper T cells

Naïve helper T cells enter the circulation after maturation, where they will be redistributed to secondary lymphoid organs and are available for the recognition of the MHC-II antigen [9]. For example, naïve helper T cells enter the lymph nodes via the high endothelial venules, where they can be activated by antigen priming [9]. Helper T cells can subsequently exit the lymph nodes via the lymphatic vessels, allowing them to circulate around the body via the lymph [9]. Secondary lymphoid organs, such as the spleen and lymph nodes, are usually exogenous antigen-rich as they are responsible for trapping exogenous antigens to trigger subsequent immune responses [12]. APCs often exist in the complex architecture of the secondary lymphoid organs, facilitating the activation of naïve helper T cells via the mechanism discussed above [9,12]. For example, dendritic cells responsible for screening exogenous antigens and present the them to naïve helper T cells in the local secondary lymphoid organ with the antigen-bound MHC-II [9]. The activation of naïve helper T cells triggers their differentiation into various effector phenotypes, and they return to the circulation and get recruited to the effector site, where they further interact with other immune cells and exert their immune function [9].

1.3. Recognition of T cells via microscopy

T cells can be identified on optical microscopy by immunocytochemistry (ICC). The conventional method in recognising T cells is by May Grünwald–Giemsa staining [13]. The May Grünwald–Giemsa staining technique allows for the morphological analyses of lymphocytes [13,14]. Lymphocytes are characterised by their condensed chromatin, accumulated stains, and relatively greater nucleus-cytoplasm ratio [13]. Subsequent immunoperoxidase staining of the markers, such as CD4 and CD8 distinguishes T lymphocytes from B lymphocytes [14]. Thus, the T lymphocyte population can be distinguished using optical microscopy.

Apart from ICC, T cells can also be identified on via immunofluorescent (IF) microscopy. For example, T lymphocytes can be recognised by labelling their surface markers by fluorescent conjugated antibodies of different emission maxima to allow for their identification and distinguishment [15]. For example, labelling the lymphocytes with a fluorescent conjugated antibody targeting CD3 reveals the T lymphocyte population among white blood cells [15]. Due to the multiplexing capability of IF microscopy, more biomarkers can be labelled simultaneously to allow for the further distinguishment of T cell populations [15]. Specifically, T lymphocytes can be labelled with anti-CD4/CD8/FOXP3 antibodies to subdivide their population: Helper T cells are $CD4^+$; Cytotoxic T cells are $CD8^+$; regulatory T cells are $FOXP3^+$ [15,16].

Recently, electron microscopy has been utilised in studying the behaviour of T_H17 cells in releasing extracellular traps upon stimulation [17]. However, the challenge to distinguish between B cells and T cells in scanning electron microscopy remains a technical barrier to using microscopy to study populations of helper T cells – cell enrichment is required to ensure the purity of helper T cell populations before studying their behaviour [17,18]. Similarly, scanning electron microscopy (SEM) is used to study how the microvilli structure of T lymphocytes facilitates their target recognition [19]. Interestingly, the strength of T lymphocyte-target cell interaction depends on CD2 expression, which is a small protein enhancing T lymphocytes' adhesive properties [19]. Electron microscopy enables the study of the subtle architecture and behaviour of T lymphocytes, which were otherwise challenging using conventional microscopy such as IF microscopy.

1.4. Immunohistochemical markers of T lymphocytes and helper T cells

T cell biomarkers such as CD3, CD4, and CD8 are commonly labelled for T lymphocyte recognition in the clinical setting. CD3 highlights the total T cell population and allows for the exclusion of the non-T cell population according to their CD3 expression [15]. The CD4/8 expression distinguishes T helper cells ($CD4^+$) from cytotoxic T cells ($CD8^+$) [15,16]. Thus, CD3, CD4 and CD8 are the most fundamental biomarkers in T lymphocytes.

The $CD4^+$ helper T cells can be further subdivided by the expression of biomarkers such as CD45RO, programmed cell death protein 1 (PD-1), and inducible co-stimulator (ICOS) [20,21]. CD45RO is a marker expressed on memory $CD4^+$ T cells but not naïve $CD4^+$ T cells [20]. Therefore, CD45RO highlights the activation status of the $CD4^+$ helper T cells. Similarly, PD-1 is expressed in activated T cells [22]. Thus, PD-1 expression in $CD4^+$ T cells corresponds to the effector-memory phenotype of helper T cells [23]. ICOS is also a biomarker highlighting $CD4^+$ helper T cell activation as they correlate to T cell antigen priming [24]. In general, $CD4^+$ helper T cells express distinct biomarkers with their activation status. This allows for the detection and subdivision of their phenotypes.

1.5. T_H1 – function and role in allergic contact dermatitis

In the context of hypersensitivity, T_H1 cells play an important role in allergic contact dermatitis [25]. Allergic contact dermatitis is a delayed-type hypersensitivity upon contact of the insulting substance with skin; the insulting substance is usually a hapten, which combines with human protein upon contact to become antigenic [26]. It is classified as a type IVa hypersensitivity (i.e. T_H1-monocyte-mediated) according to the modified Gell and Coombs classification of hypersensitivity [25]. In the sensitisation phase, haptenated proteins are taken up by antigen-presenting cells in the skin (e.g. Langerhans cells and dermal dendritic cells), which are drained to nearby lymph nodes and interact with naïve helper T cells; the activated helper T cells polarise to T_H1 cells, which leave the lymph node and reach the site where the haptenated proteins are present and eliminate them; this process takes around 2 weeks [27]. As shown in Fig. 2, upon re-exposure to the insulting agent, haptenated proteins are taken up by antigen-presenting cells and moved to nearby lymph nodes in a similar manner as the sensitisation phase, but this time the memory T cells are activated, which are polarised to T_H1 cells [10]. They are recruited to the site of antigen contact within shorter period (24–72 h), and they activate macrophages to

eliminate the haptenated proteins through the following mechanisms. T_H1 cells induce macrophages to become M1 macrophages through the secretion of IFN-γ and expression of CD40-ligand [28]. They enhance inflammation and tissue damage by mechanisms such as increased inducible nitric oxide synthase expression and increased phago-lysosomal fusion [29]. IFN-γ and CD40-ligand also increase the expression of MHC-II and secretion of IL-12 by macrophages, such that a positive-feedback activation loop is formed [30]. Moreover, IFN-γ and tumour necrosis factor-alpha (TNF-α) from T_H1 cells stimulate keratinocytes to secrete cytokines and chemokines such as IL-1, IL-33, CXCL9 and CXCL10, which mediate and augment cutaneous inflammation [31,32]. Synergistically, T_H1 cells secrete granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 to the circulation to increase the production of monocytes in the bone marrow, and they secrete TNF-α and LT-β to recruit more monocytes (which become macrophages) from the circulation to the effector site [33–35]. On top of activation of macrophages, T_H1 cells provide 'help' to license $CD8^+$ cytotoxic T cells during their activation in secondary lymphoid organs; T_H1 cells also secrete IL-2 to stimulate proliferation and activation of $CD8^+$ cytotoxic T cells [36]. However, the activated macrophages and $CD8^+$ cytotoxic T cells lead to excess tissue damage, giving rise to inflammation of the skin with erythema, blistering, pruritis, scaling and/or swelling at the site of insulting substance contact [37].

The role of T_H1 in the pathophysiology of allergic contact dermatitis is supported by studies on murine models as well as patient samples. Murine contact hypersensitivity model is a widely used animal model for allergic contact dermatitis; it is prepared by administering organic haptens with potent sensitising capacity in mice (such as trinitrochlorobenzene, oxazolone and 2,4-dinitrofluorobenzene), thus inducing delayed-type hypersensitivity response [38]. It has been demonstrated that mice with the IFN-γ gene or IFN-γ receptor gene knocked out had reduced contact hypersensitivity response and diminished inflammatory cell infiltration, indicating their pivotal role of the T_H1-IFN-γ axis in the pathogenesis [31,39,40]. Stimulated predominantly by T_H1 cells, $CD8^+$ cytotoxic T cells mediate skin inflammation in murine contact hypersensitivity through induction of keratinocyte apoptosis [36,41]. Other murine studies also showed that full contact hypersensitivity response was generated only in the presence of both $CD4^+$ T cells and $CD8^+$ cytotoxic T cells, and $CD4^+$ T cells alone only resulted in partial response while $CD8^+$ cytotoxic T cells alone could not mediate contact hypersensitivity response; it also revealed impaired migration of $CD8^+$ cytotoxic T cells to skin in the absence of $CD4^+$ T cell [42,43]. These highlighted the interaction between $CD4^+$ cells and $CD8^+$ cytotoxic T cells, as well as the coordinating role of T_H1 in the contact hypersensitivity [43]. Although animal models provide valuable information to the pathophysiological mechanism of allergic contact dermatitis, they are limited by their differences from human allergic contact dermatitis. The culprit agents that are more relevant to the human disease are weak sensitisers (e.g. nickel, fragrance) which cannot elicit contact hypersensitivity response in murine models, in contrast to the potent sensitisers used in murine models which are rarely encountered in daily life. Due to the difference in skin architecture which mice have much fewer layers of keratinocytes in the epidermis than human, murine contact hypersensitivity models do not exhibit intracellular oedema and vesicle formation, which are hallmarks of human allergic contract dermatitis [44]. Murine

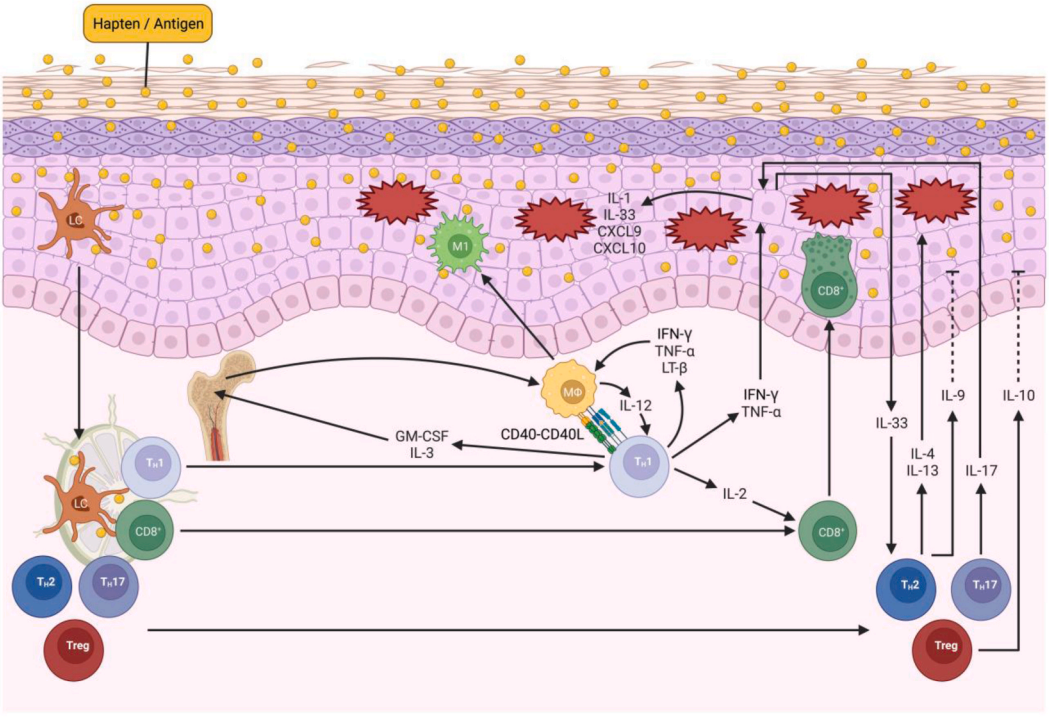

Fig. 2. The role of T_H1 and their interactions with other cell types in allergic contact dermatitis.
$CD8^+$, $CD8^+$ T cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-gamma; IL, interleukin; LC, Langerhans cell; LT-β, lymphotoxin-beta; MΦ, macrophage; M1, M1 macrophage; TGF-β, transforming growth factor-beta; TNF-α, tumour necrosis factor-alpha; T_H1, T helper 1; T_H2, T helper 2; T_H17, T helper 17; Treg, regulatory T cell (Created with BioRender.com).

models are characterised by more neutrophil infiltration instead of the predominant lymphocyte infiltration in the human disease [44]. This can be explained by the substantially lower amount of memory T cells in laboratory mice (which express specific adhesion molecules required for recruitment to the inflamed skin) rendering non-allergen-specific T cell infiltration unlikely to occur in murine models [45,46], as well as the greater mast cell activation and resultant activated neutrophil infiltration in murine models [44,47]. Therefore, studies on human patient samples offer important information. Multiple patient blood analyses demonstrated T_H1 cytokines response upon stimulation of allergen-specific $CD4^+$ T cells by antigen-presenting cells carrying the respective antigen [48–50]. Studies on inflamed skin of the patients upon patch test also showed dominant T_H1 cell infiltration and increased expression of cytokines and chemokines along or downstream of the T_H1-IFN-γ axis [51–53].

Although T_H1 cells play a crucial role in the pathophysiology of allergic contact dermatitis, other T cell subsets (e.g. T_H2, T_H17 and Treg) were also found to be involved, and they may also engage in intricate cross-talk, thus contributing to the hypersensitivity reaction [39,49–51,53–56]. IL-33 secreted by keratinocytes under the induction of IFN-γ and TNF-α can promote type 2 immune response orchestrated by T_H2 cells [32]. Although IFN-γ can suppress T_H2 proliferation and hence type 2 immune response, recent evidence showed the possibility of coexistence of type 1 and type 2 immune response, especially in the chronic phase of allergic contact dermatitis [32,57]. IL-17 from T_H17 licenses T_H1 cells to execute intercellular adhesion molecule (ICAM)-1-dependent non-allergen-specific killing of keratinocytes with IFN-γ, thus amplifying skin inflammation in allergic contact dermatitis [58]. Allergen-specific Treg cells are found in peripheral blood of non-allergic individuals [59], and they may play a regulatory role in allergic contact dermatitis through secretion of IL-10 and production of adenosine by CD39 [60,61]. IL-9, a T_H2 cytokine also regulates the T_H1 immune response in allergic contact dermatitis [62]. The relative contribution of different T helper cell subsets is likely related to the type of culprit allergen; for example, allergic contact dermatitis to nickel demonstrates highly polarised T_H1/T_H17 immune response and minimal T_H2 immune response, while allergic contact dermatitis to poison ivy and fragrance exhibits relatively more T_H2 immune response [55,63]. Comorbidity of atopic dermatitis is also associated with higher relative contribution by T_H2 cells [64].

1.6. T_H2 – function and role in drug rash with eosinophilia and systemic symptoms (DRESS) syndrome

In the context of hypersensitivity, T_H2 cells play an important role in drug rash with eosinophilia and systemic symptoms (DRESS) syndrome [25]. DRESS syndrome is a severe cutaneous adverse drug reaction with systemic involvement, characterised by cutaneous eruption and eosinophilia; other manifestations may include fever, lymphadenopathy, atypical lymphocytosis, hepatitis, nephritis, pneumonitis and carditis [65]. It is classified as a type IVb hypersensitivity (i.e. T_H2-eosinophil-mediated) according to the modified Gell and Coombs classification of hypersensitivity [25]. As shown in Fig. 3, during the sensitisation phase, antigen-presenting cells take up the drug antigens (haptenated to human proteins) and present them to T cells after loading on MHC; the cytokine environment

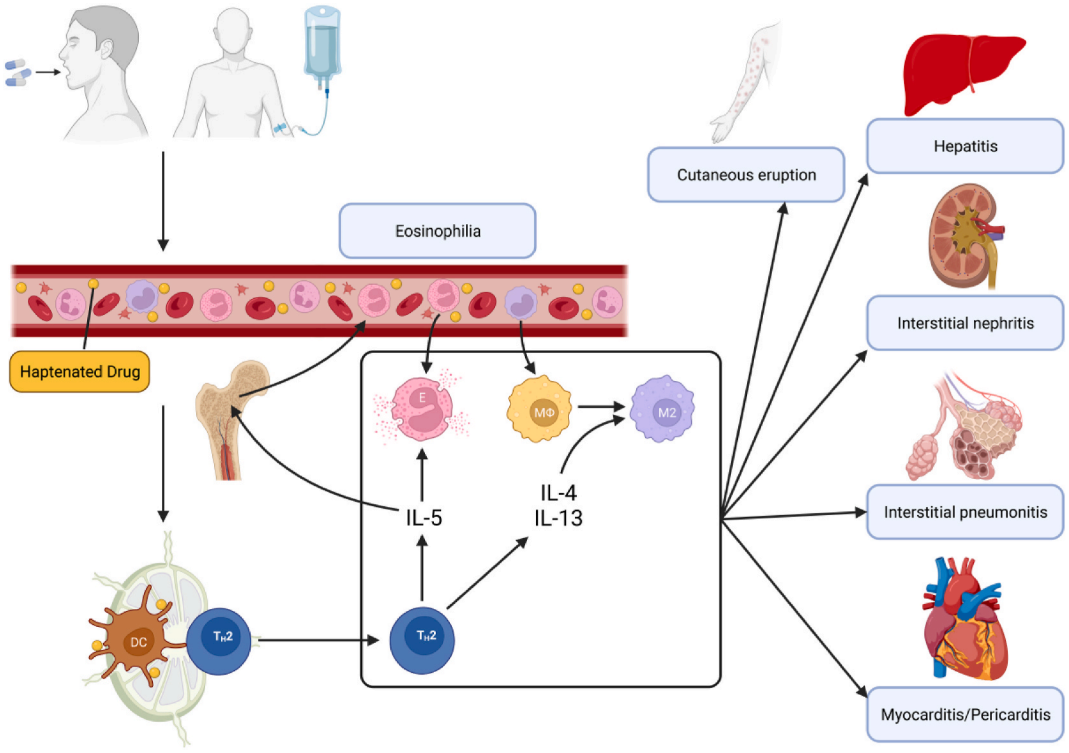

Fig. 3. The role of T_H2 and their interactions with other cell types in DRESS syndrome.
DC, dendritic cell; E, eosinophil, IL, interleukin; MΦ, macrophage; M2, M2 macrophage; T_H2, T helper 2 (Created with BioRender.com).

favours type 2 immune responses, thus, T_H2 cells are sensitised [66]. Upon re-exposure to the drug, haptenated drug antigens are taken up by antigen-presenting cells, which load them on MHC and present the antigen-MHC complex to memory T cells, which are polarised to T_H2 cells [66]. T_H2 cells secrete IL-5 to activate eosinophils, which can release granules containing toxins that can mediate inflammation and tissue damage [67,68]. Through the actions of IL-4 and IL-13 produced by T_H2 cells, macrophages are activated and polarised to become M2 macrophages, which facilitate tissue repair and remodelling through stimulation of collagen synthesis and TGF-β production [69]. In their severe form, these effector mechanisms of eosinophil activation and promotion of inflammation as the result of T_H2 activation manifest as DRESS syndrome, which eosinophilic inflammation can occur in the various organs such as the skin (skin rash), liver (deranged liver function, hepatitis or liver failure), kidneys (interstitial nephritis), lungs (pneumonitis) and heart (myocarditis or pericarditis) [66].

There have not been animal models for DRESS syndrome, and hence the evidence on its pathophysiology mainly comes from studies on patient samples. Skin-homing T_H2 cells that produce IL-13 were markedly enriched in peripheral blood of DRESS syndrome patients during the active stage [70]. IL-5 is significantly elevated in DRESS syndrome patients' serum, and it is enriched in skin affected by eosinophilic drug eruptions [71,72]. In human, IL-5, chiefly produced by T_H2 cells, is a key cytokine in type 2 immune response; it acts on IL-5 receptors which are composed of an IL-5-specific α chain and a common β-chain (shared with IL-3 and GM-CSF) on eosinophils or their precursors to trigger downstream signalling, eventually leading to enhanced eosinophil proliferation, maturation, survival, chemotaxis and effector site infiltration [73–75]. Hence, the T_H2-IL-5-IL-5 receptor axis plays a crucial role in eosinophilic inflammation. Apart from DRESS syndrome, the T_H2-IL-5 eosinophilic inflammatory pathway is also implicated in a number of diseases including asthma, eosinophilic granulomatosis with polyangiitis and chronic rhinosinusitis with nasal polyps, which can respond well to treatment that blocks IL-5 or IL-5 receptors [76–78]. Hence, blockage of the IL-5/IL-5 receptor pathway may also be effective in DRESS syndrome [79].

1.7. T_H17 – function and role in acute generalised exanthematous pustulosis (AGEP)

In the context of hypersensitivity, T_H17 cells play an important role in acute generalised exanthematous pustulosis (AGEP) [25]. AGEP is a severe cutaneous adverse drug reaction featuring formation of pustules over the skin, usually accompanied by fever and neutrophilic leucocytosis [80]. Although being named 'acute', AGEP is also a delayed-type hypersensitivity, only that its onset can be as short as a few hours (most are fewer than 10 days), in contrast to other delayed-type hypersensitivities [81]. It is classified as a type

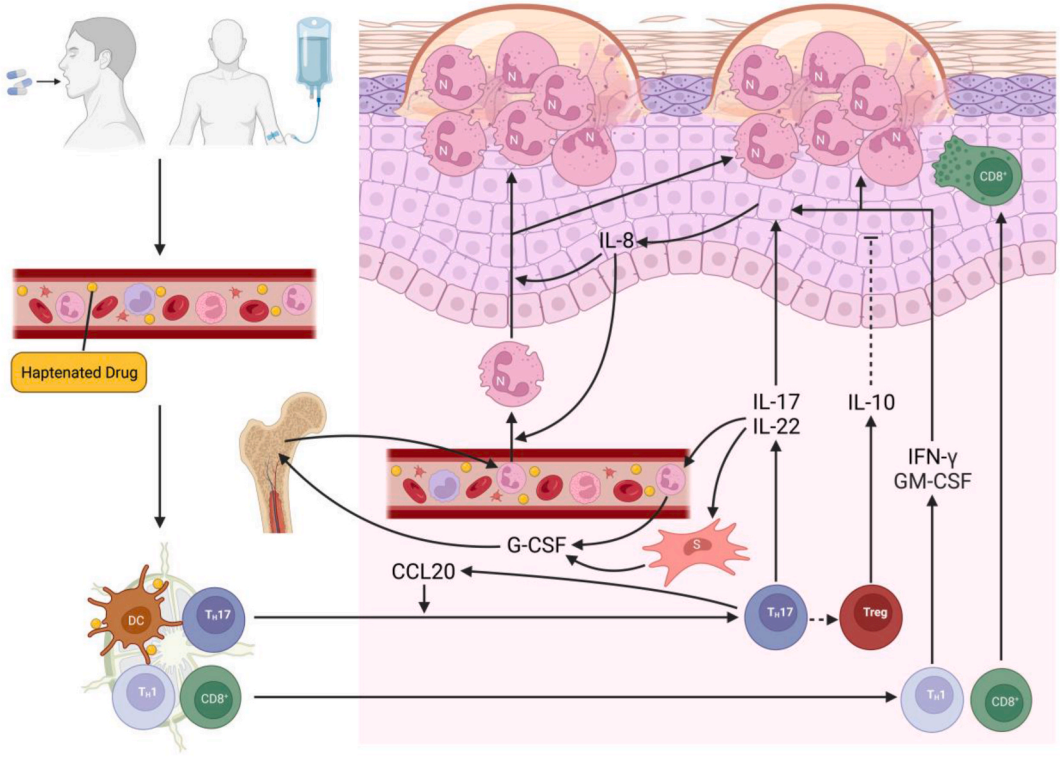

Fig. 4. The role of T_H17 and their interactions with other cell types in AGEP.
$CD8^+$, $CD8^+$ T cell; DC, dendritic cell; G-CSF, granulocyte-colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-gamma; IL, interleukin; N, neutrophil; S, stromal cell; T_H1, T helper 1; T_H17, T helper 17; Treg, regulatory T cell (Created with BioRender.com).

IVd hypersensitivity (i.e. T_H17-neutrophil-mediated) according to the modified Gell and Coombs classification of hypersensitivity [25]. Sensitisation phase upon initial encounter of the insulting drug is polarised to type 3 immune response as a result of the cytokine environment, favouring T_H17 cell development; upon re-exposure to the insulting drug, memory T cells are activated, which are polarised to T_H17 cells. As shown in Fig. 4, T_H17 cells secrete IL-17 and IL-22 [82]. IL-17 induces stromal cells and leucocytes of myeloid lineage to secrete granulocyte-colony-stimulating factor (G-CSF), which promotes neutrophil production in the bone marrow; IL-17 and IL-22 also stimulates epithelial cells and stromal cells to secrete chemokines (e.g. IL-8) to increase the recruitment of neutrophils to the effector site [83]. On top of that, T_H17 cells produce chemokine CCL20 to attract more T_H17 cells to the effector site, forming a positive-feedback loop [84]. Collectively, T_H17 cells carry out their effector functions to induce neutrophil-predominant inflammation, leading to manifestations similar to pyogenic bacterial infections, that is, pustule formation and neutrophilic leucocytosis; thus, resulting in the manifestations of AGEP [81,85].

Animal models for AGEP do not exist yet. T_H17 cells, IL-17 and IL-22, as well as the neutrophilic chemokine IL-8 were found to be markedly elevated in the peripheral blood of patients with active AGEP [85–87]. Studies on skin biopsies of patients also showed similar findings, supporting the T_H17-mediated pathophysiology in AGEP [88,89]. T_H17 cells exhibit plasticity potential and can transdifferentiate into Treg cells expressing IL-10 and FOXP3, which may contribute to the resolution of inflammation [90]. Driven by the cytokine environment, T_H17 cells also demonstrated plasticity potential to T_H1 and T_H2 with co-expression of IL-17/IFN-γ and IL-17/IL-4 in other conditions; however, their roles in AGEP are currently unknown [91–93]. $CD8^+$ T cells are involved in keratinocyte apoptosis and vesicle formation, which are then enriched by neutrophils to become pustules [94]. T_H1 are also involved by secreting IFN-γ and GM-CSF, which enhance neutrophil survival, release of IL-8, and hence pustule formation [89,95].

1.8. T_{FH} – function and role in types I, IIa, IIb and III hypersensitivity reactions

T_{FH} cells are important in humoral immune response; more precisely, the T-dependent B-cell activation, which is crucial to germinal centre reaction, antibody affinity maturation and antibody class-switch recombination [96]. Naïve B cells capture humoral antigens in the follicular region (B-cell area) of secondary lymphoid organs (where they originally rest and reside) and present them to naïve T cells at the junction between B-cell area and T-cell area of secondary lymphoid organs [97]. After interaction, the activated B cells and T cells migrate to lymphoid follicles together, with the T cells becoming T_{FH} cells, followed by formation of germinal centre [98]. Depending on the nature of the pathogen/antigen, thus the overall cytokine environment created by innate immune sensing cells and innate lymphoid cells, T_{FH} cells are sub-polarised to T follicular helper 1 ($T_{FH}1$), T follicular helper 2 ($T_{FH}2$) and T follicular helper 17 ($T_{FH}17$) cells, corresponding to type 1, type 2 and type 3 immune responses respectively [99]. IL-21 from T_{FH} cells are important to B-cell proliferation and differentiation into plasma cells [100]. T_{FH} cells mediate affinity maturation by providing survival signals to high-affinity B cells which successfully capture antigens from follicular dendritic cells [101]. T_{FH} cells also provide signals and secrete cytokines to guide class-switch recombination; IFN-γ from $T_{FH}1$ cells promotes antibody class-switching to IgG, IL-4 from $T_{FH}2$ cells promotes antibody class-switching to IgE; TGF-β, produced as part of type 3 immune response promotes antibody class-switching to IgA, but the direct effect of IL-17 from $T_{FH}17$ cells on antibody class-switching remains unclear (Fig. 1) [102,103].

Due to their crucial role in antibody class-switch recombination, T_{FH} cells may be implicated in antibody-mediated hypersensitivity reactions, namely type I, type IIa, type IIb and type III hypersensitivity reactions according to the modified Gell and Coombs classification of hypersensitivity [25]. Type I hypersensitivity is an immediate-type hypersensitivity mediated by IgE, and is the result of Fcε receptor cross-linking and mast cell degranulation; examples include allergic urticaria, allergic rhinitis, acute asthma and anaphylaxis [25,104]. Type IIa hypersensitivity is characterised by antibody-mediated cytotoxicity, which IgM and/or IgG (or uncommonly, IgA) antibodies leading to lysis of body cells upon antigen binding; examples include immune-mediated haemolysis and idiopathic thrombocytopenia [25]. Type IIb hypersensitivity is characterised by antibody-mediated (IgM and/or IgG, or uncommonly, IgA) cell stimulation; a subtype of chronic spontaneous urticaria is a type IIb hypersensitivity [25,105]. Type III hypersensitivity are mediated by immune complexes (antigen bound to IgM and/or IgG, or less commonly, IgA), resulting in complement activation and inflammation; examples include serum sickness and drug-induced lupus [25]. However, there is still a knowledge gap in the pathogenic roles of T_{FH} cells in these hypersensitivity reactions.

1.9. Implications on treatment of hypersensitivity reactions and future directions

There has been evidence demonstrating the possibility of helper T cell subset function modulation by monoclonal antibodies. *Anti*-IL-5 and *anti*-IL-5 receptor monoclonal antibodies could suppress T_H2-mediated immune response by blocking the T_H2-IL-5-IL-5 receptor axis, hence reducing eosinophilic activation and inflammation [106]. *Anti*-IL-5 receptor monoclonal antibodies (e.g. benralizumab) could also induce eosinophil apoptosis at the effector site [107]. *Anti*-IL-17 monoclonal antibodies bind to IL-17A and/or IL-17F, and reduce neutrophil recruitment to effector sites through IL-17 signalling blockade, counteracting T_H17 function [108–110]. *Anti*-DNAM-1 monoclonal antibody, which interferes with DNAM-1 binding to CD155, could suppress T_H1 and T_H17 function of cytokine production (IFN-γ, TNF-α, IL-6, and IL-17) [111]. Anti-CD6D1 monoclonal antibody was found to reduce differentiation of naïve T cells to T_H17 and thus decreasing IL-17 production [112].

Knowledge of the crucial roles of helper T cell subsets and their cytokine profile in the pathogenic mechanism of the aforementioned hypersensitivity reactions has helped the development of new treatments by inspiring clinical attempts of using cytokine-specific biologics to treat these hypersensitivity reactions. *Anti*-IL-5 or IL-5 receptor monoclonal antibodies such as mepolizumab, benralizumab and reslizumab have been successfully used to treat DRESS syndrome patients in a number of case reports, including cases which responded suboptimally to systemic corticosteroids [79,113]. There have also been case reports of successful treatment of

refractory and severe AGEP using *anti*-IL-17 monoclonal antibodies such as secukinumab and ixekizumab [114–116]. On top of benefiting the corticosteroid-refractory patients, the use of cytokine-specific biologics may also achieve steroid-sparing effect, thus reducing the side effects from corticosteroids [113]. However, the use of cytokine-specific biologics for DRESS syndrome and AGEP is limited by the lack of high-level evidence of effectiveness from randomised controlled trials. Currently, their clinical use are only based on expert opinion and case series/reports. More evidence is needed to support their routine clinical use. Hence, clinical trials on cytokine-specific biologics for the treatment of these hypersensitivity reactions are warranted.

The signalling crosstalk between other immune cells and T helper cells highlights the significance in studying immunomodulation in hypersensitivities. For example, Treg is responsible for modulating inflammatory responses in delayed-type hypersensitivities [117]. They possess immunosuppressive properties, such as suppressing the production of proinflammatory cytokines by interacting with helper T cells [117,118]. Specifically, Treg was found to be the key regulator of $CD4^+$ helper T cells as they suppress the production of proinflammatory cytokines such as IL-1β, IL-6 and IL-12, potentially via the CD25 signalling axis [119,120]. Additionally, the early production of IL-2 by T_H2 cells activates Treg, which in turn suppresses helper T cells' IL-4 and IL-5 production [118]. This indicates that Treg contributes to the modulation of T_H1/T_H2 responses. Treg is a potential therapeutic target against delayed-type hypersensitivities considering its immunomodulating role. More studies investigating the role of Treg in the microenvironment of hypersensitivity would benefit the understanding of the crosstalk between T cells of different phenotypes, and possibly deriving new treatments for delayed-type hypersensitivities.

On the other hand, DCs also contribute to activating T cells in delayed-type hypersensitivities by eliciting their immunomodulatory functions. For example, their ability to mediate the immune response in allergic contact dermatitis and delayed-type drug hypersensitivity highlights their pivotal role as an immunomodulator in hypersensitivities [121,122]. Interestingly, the DCs in drug-induced delayed-type hypersensitivity displayed a semimature phenotype; semimature DCs activate Treg and they do not produce proinflammatory cytokines, as opposed to the classical role of DCs in activating T lymphocytes [122]. Semimature DCs' role in immunosuppression and its potential role in the management delayed-type hypersensitivities warrant further investigation.

2. Conclusion

Different subsets of helper T cells play important roles in various types of hypersensitivity reactions such as allergic contact dermatitis, DRESS syndrome and AGEP. They have a common origin from naïve T cells and differentiated into different subsets depending on the cytokine environment. They carry out specialised effector functions to orchestrate the respective pathomechanisms. Hypersensitivities with different phenotypes reflect the differences in the underlying mechanisms, in which different subsets of helper T cells are involved. The specific helper T cell subset and cytokine profile in different hypersensitivity reactions could be potential treatment targets by biologics. More clinical trials are warranted to investigate the clinical effectiveness of cytokine-specific biologics in the treatment of different hypersensitivity reactions.

CRediT authorship contribution statement

Andy Ka Chun Kan: Writing – original draft, Conceptualization. **Wang Tik Tang:** Writing – review & editing. **Philip H. Li:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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