International Immunopharmacology 74 (2019) 105718

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Combined allergic rhinitis and asthma syndrome (CARAS)

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ARTICLE INFO

Keywords:
Asthma
Rhinitis
Allergic syndrome
Allergic inflammation
Disease of the airway

ABSTRACT

Combined allergic rhinitis and asthma syndrome (CARAS) is a concept of "one airway – one disease" or "unified airway disease ". The upper and lower airway inflammation characterizes allergic rhinitis and asthma, respectively and both diseases have shown an intimate connection in their genesis, coexistence and similarities as triggered by the same etiological agents; the same inflammatory cell profile and share therapeutic treatment. This review highlights the concept of CARAS by its phenotype, endotype and biomarker classification. Indeed, rhinitis is divided into four major phenotypes: allergic rhinitis; infectious rhinitis; non-infective/non-allergic rhinitis and mixed rhinitis. On the other hand, asthma has no common consensus yet; however, the most accepted classification is based on the stage of life (early- or late- onset asthma) in which the clinical symptoms are presented. Experimental researches where animals develop a syndrome similar to CARAS have been contributed to better understand the pathogenesis of the syndrome. Therefore, the aim of this review is to clarify current terms related to CARAS as definition, phenotypes, endotypes/biomarkers, physiopathology and treatments.

1. Introduction

The upper and lower airways are classified as unified morphological and functional units. The nose, located at the entrance of the upper airway plays a fundamental role of protection for the lungs, acting in the selection of particles inhaled by the inspired air. The heating, filtration and humidification of the air promotes a cleaning of the air for its entrance to the lungs. In the breathing process most particles with an equivalent aerodynamic diameter (AED) > 15 μm are deposited in the upper respiratory tract. Particles with AED > 2.5 μm are deposited mainly in the trachea and bronchi, whereas those with lower AED penetrate the gas exchange region of the lungs. In this context the size and nature of the allergens directly interfere in promoting the immune response at the site of their deposition, promoting the clinical manifestation of the disease [1].

Combined allergic rhinitis and asthma syndrome (CARAS) is characterized, nowadays, as a single disease related with upper and lower airway inflammation. Allergic rhinitis and asthma have shown an intimate connection in their genesis, the concept of coexistence and similarities such as a. triggered by the same etiological agents; b. have the same inflammatory cell profile; c. present in the respiratory system and d. share therapeutic treatment. Experimental researches where animals develop a syndrome similar to CARAS have been contributed to better understand the pathogenesis of the syndrome as well as to develop new pharmacological drugs to added to the arsenal therapeutic for the treatment of this allergic syndrome due to some patients have not respond to the conventional therapeutic strategy [2–5]. Therefore, the aim of this review is to clarify current terms related to CARAS as definition, phenotypes, endotypes and biomarkers, physiopathology and treatments.

2. Characterization and epidemiology of CARAS

Rhinitis is a general term that describes the appearance of nasal symptoms as nasal congestion, rhinorrhea, sneezing and pruritus (itching/nasal rubbing), resulting from an inflammatory process and/or dysfunction of the nasal mucosa. In addition, it causes sleep deficiency, behavioral and psychological changes, leading to compromise patient's quality of life and being considered a risk factor for traffic safety. This illness presents significant morbidity by interfering with social life, school and intellectual performance as well as work productivity [2,3,6]. Rhinitis is one of the most common diseases worldwide and it is estimated about 25% of the total world population suffer from allergic rhinitis (AR) [4,5] and, more important, is a risk factor for the

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https://doi.org/10.1016/j.intimp.2019.105718
Received 18 February 2019; Received in revised form 30 May 2019; Accepted 21 June 2019
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development of asthma and others chronic respiratory diseases such as rhinosinusitis [7,8].

Asthma is defined as a heterogeneous disease, characterized by a chronic inflammatory pulmonary process which is associated with airway hyperreactivity to direct and indirect stimuli [7,9]. In hypersensitive individuals, this inflammation induces recurrent episodes of wheezing, suffocation, chest tightness and cough, particularly during the night and/or early in the morning and these symptoms may vary over time and intensity. Some of these symptoms are triggered by several factors, such as exercise, exposure to allergens or irritants, climate change and viral respiratory infections [8,10]. Asthma affects > 300 million people worldwide regardless of the country development. Many studies report the highest incidence of asthma in children [11]. The mortality, directly or indirectly caused by asthma, is accounting for 1 in 250 deaths worldwide. In addition, and in global terms, the costs of asthma outweigh those of tuberculosis and HIV/AIDS combined [12].

Numerous contemporary studies, guided by the concept "one airway – one disease", have revealed that the comorbidity between rhinitis and asthma is intima [13] conferring a single pattern of disease in the airways [14,15]. Untreated or incorrectly managed rhinitis increases, by up to three times, the risk of asthmatic exacerbation [13]. In addition, bronchial hyperreactivity is frequent in patients with rhinitis [13]. Indeed, it is common to observe an inflammatory nasal condition in asthmatic patients without no rhinitis symptoms and bronchial inflammation in individuals with rhinitis without asthma symptoms, as well as bronchial inflammation due to nasal provocation with allergens and nasal inflammation due to bronchial provocation [13,14].

3. Phenotypes, endotypes and biomarkers of CARAS

Rhinitis and asthma are characterized as heterogeneous airway inflammatory diseases resulting from various etiologies and the most accepted concept comes from the phenotype classification, where a set of clinical signals, temporal pattern, severity, duration, therapeutically response and/or disease control and presence of comorbidities are standardized [16]. Indeed, rhinitis is divided into four major phenotypes: 1.) allergic rhinitis (AR), in response to aeroallergens in sensitized individuals; 2.) infectious rhinitis, in response to microorganisms present in the nasal cavity; 3.) non-infective and non-allergic rhinitis in response to irritants, medications, hormonal imbalance and neuronal dysfunction; and 4.) mixed rhinitis, presenting more than two concomitant phenotypes [17–20].

On the other hand, asthma has no common consensus yet; however, the most accepted phenotype classification is based on the stage of life (early-onset childhood or late-onset adult) in which the clinical symptoms are presented. Thereby, two major phenotypes have been defined: 1.) T2-type asthma, T_H2 profile and early-onset in childhood, and 2.) non-T2-type asthma, with a low T_H2 profile and late-onset in adulthood. However, within these two major phenotypes, subphenotypes are distinguished. In T2-type asthma, the early-onset subtypes are allergic asthma and exercise-induced asthma; and the late-onset subtypes are eosinophilic asthma and later onset asthma in women. In non-T2 type asthma, the subtypes are: obesity-related asthma, neutrophilic asthma associated with smoking, and smooth muscle-mediated paucigranulocytic asthma [7–9].

In allergic rhinitis and asthma, endotypes and biomarkers are associated with phenotypic classification, aiming to identify molecular targets in the genesis of the disease, allowing a more precise therapeutic treatment [16,20]. Thus, rhinitis is divided into four endotypes: 1.) Type 2 immune response, the biomarkers of this endotype are the classical cytokines of the T_H2 profile, eosinophils and IgE; 2.) Type 1 immune response, its biomarkers are neutrophilia and IFNγ (T_H1 profile); 3.) neurogenic rhinitis, its biomarkers are neurokinins (NK) and substance P (SP) and 4.) epithelial dysfunction, having the alarmines: TSLP (thymic stroma lymphopoetin), IL-33 and IL-25, as their biomarkers. In asthma, the already established and well described endotype is T_H2 immune response that is classified as 1.) exacerbated form (T_H2^{hi} phenotype) and 2.) absent or not observed (T_H2^{lo}) T_H2 phenotype. Biomarkers involve T_H2 profile cytokines (IL-4, IL-5 and IL-13) and tissue eosinophilia and sputum fluids, in addition to levels of IgE, periostin and FeNO. The neutrophil and cytokines of the T_H17 profile are biomarkers of the neutrophilic asthma phenotype and adipokine is involved in asthma in obese individuals [8,10,21,22] (Fig. 1).

4. Physiopathology of CARAS

The combined allergic rhinitis and asthma syndrome (CARAS) is characterized by a predominant T_H2 immune response (T_H2 phenotype) and its physiopathology profile is directly related to atopic individuals, which are genetically predisposing to stimuli (aeroallergens) and develop an immediate hypersensitivity. Aeroallergens are often soluble proteins present in various sites such as: dust mites; cockroach wings; fungi; saliva and urine of domestic animals [23] and are easily dispersed in the air with the ability to enter the respiratory tract promoting an imbalance between innate and adaptive immune responses and consequently triggers the CARAS [24].

The allergen sensitization phase (first phase of the allergic process) of the genetic predisposing individual initiates with the first contact with the allergen which activates epithelial cells, promoting the secretion of alarmines and cytokines, which are important to the inflammatory process of CARAS [25]. The alarmines as IL-33, IL-25 and TSLP act on intra-epithelium cells located below the respiratory epithelium, named innate lymphoid cell type 2 (ILC2), leading to the production of classical type 2 cytokines as IL-13 and IL-5 and also on antigen-presenting cells (APCs), especially on dendritic cells (DC) [24,26–29]. The activated DC recognizes, internalizes and processes the allergen and migrates to the draining lymph node to present it, through major histocompatibility complex class 2 molecules (MHC-II) to naive $CD4^+$T lymphocytes. In an IL-4 microenvironment, these cells polarize to a T_H2 profile by activation of the transcription factors GATA-3 and STAT6. Therefore, these polarized cells produce the classical type 2 cytokines as IL-4, IL-13 and IL-5 [7] that activate B lymphocytes (IL-4 and IL-13) to produce IgE-allergen specific. This immunoglobulin binds to its high affinity receptor (FcεRI) presents on the cytoplasmic membrane of mast cells, basophils and circulating eosinophils characterizing allergic sensitization process [10,22,30] (Fig. 2 a).

The second phase of the allergic process comes from the allergen reexposure that binds directly to, at least two, IgE-FcεRI complex on mast cells and circulating basophils/eosinophils. The cross-link between allergen and IgE activates the cells that release pre-stocked mediator as histamine in a process named cell degranulation, and also formation of other mediators such as prostaglandins and leukotrienes [21,24]. Resident mast cells are located near the mucosa surface and blood vessels. The maturation of these cells occurs by stem cell factors (SCF) and IL-3 [31]. Circulating basophils amplify the allergic response by releasing into the bloodstream, mainly histamine, in addition to the production of IL-4 [32]. Histamine, prostaglandins and leukotrienes play a central role in CARAS by promoting local vasodilation, vascular permeability, edema, and inflammatory cell migration into the airways and consequently bronchoconstriction. In the upper airway, histamine plays a key role in sensory nerve endings, parasympathetic reflex stimulation of glandular secretions and vasodilation, and increases in capillary permeability, promoting the symptoms of immediate reaction of the AR (nasal pruritus, sneezing, rhinorrhea) [33,34].

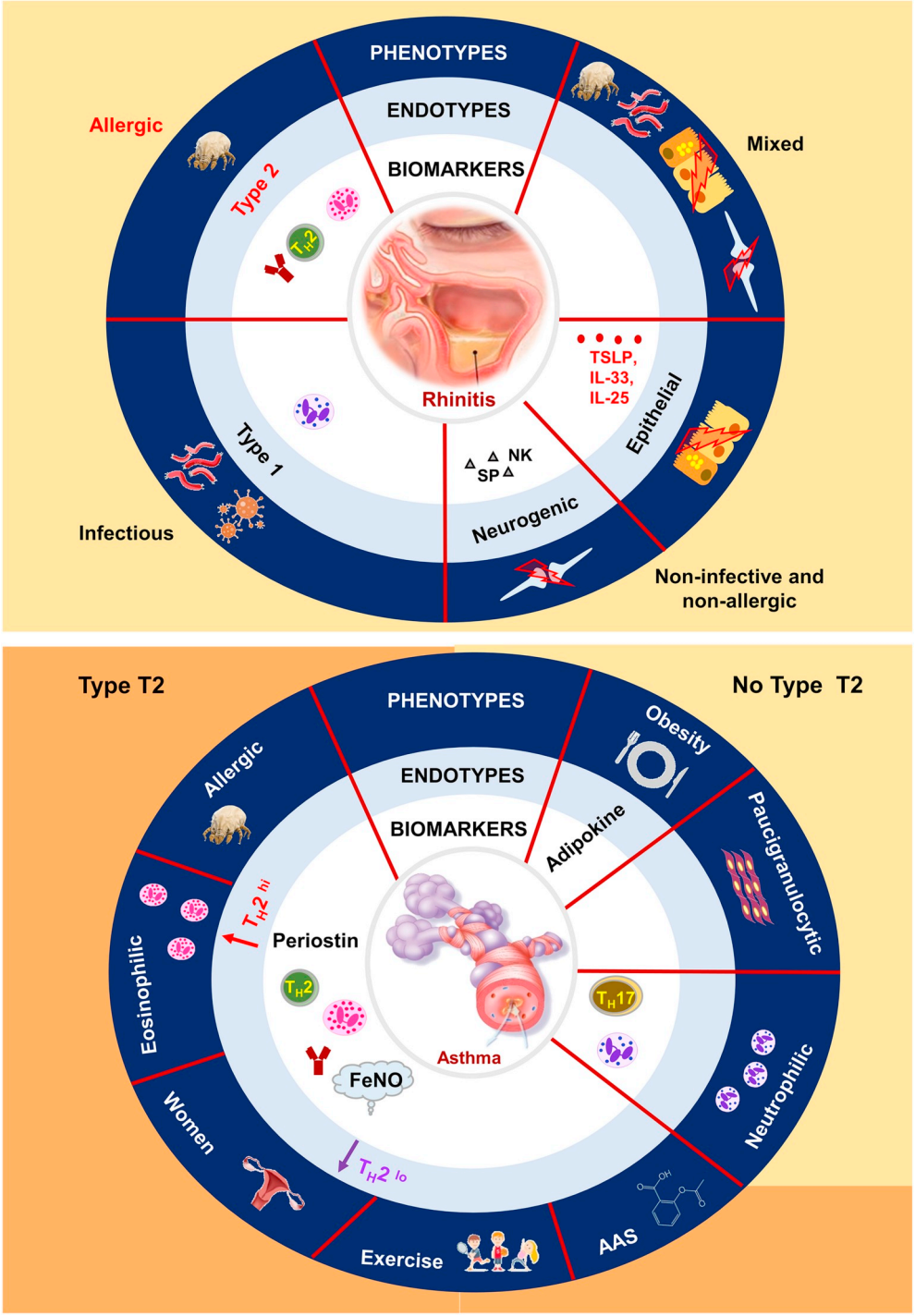

Fig. 1. Phenotypes, endotypes and biomarkers of rhinitis and asthma. Rhinitis and asthma are characterized by phenotypes associated with their endotypes and biomarkers. Rhinitis is classified by the following phenotypes: allergic; infectious; non-infective and non-allergic and mix; endotypes: type2; type1; neurogenic and epithelial and by biomarkers: IgE; Th2 and eosinophilia (type 2); neutrophilia (type 1), substance P (SP) and neurokininis (NK) (neurogenic) and alarmins (TSLP-thimic stroma limphopoetin, IL-33 and IL-25) (epithelial). The rhinitis mixed phenotype involves the interaction of all phenotypes with their respective endotypes and biomarkers. Asthma is classified in two phenotypes: type T2 and no type T2; eight sub-phenotypes: allergic, eosinophilic, in women, exercise, acetylsalicylic acid (AAS)-induced, neutrophilic, paucigranulocytic and obesity. The sub-phenopytes are divided: Type T2 (allergic, eosinophilic, in women, exercise and AAS-induced) and no type T2 (obesity, paucigranulocytic and neutrophilic). In endotypes: type 2 may present either T_H2^{hi} or T_H2^{low}, depending on the level of the biomarker expression as T_H2 cytokines, IgE, eosinophilia, periostin and exhaled nitric oxide fraction (FENO) and no type T2 with its biomarkers: adipokine (obesity); paucigranulocytic (no biomarker defined) and neutrophilic (T_H17 profile and neutrophilia as biomarkers).

Cysteinyl leukotrienes (CysLTs) produced by lipoxygenase (LOX) are involved in bronchoconstriction, airway hyperresponsiveness, eosinophil and neutrophil airway influx, edema, goblet cell metaplasia, decreased of mucociliary clearance, epithelial hypertrophy, subepithelial collagen deposition, smooth muscle proliferation and vascular permeability all of these parameters are characteristics of asthma. In addition, vascular permeability, production and secretion of mucus and influx of inflammatory cells are also present in rhinitis [35]. The prostaglandin-forming cyclooxygenase (COX), when inhibited by gene deletion or pharmacotherapy, increases the allergic inflammatory process present in several experimental protocols due to LOX pathway. Prostaglandins are released in large amount by mast cells after their activation by IgE/allergen, therefore, PGE2, in the airways, inhibits the cystenyl leukotriene pathway and PGE2 inhibition promotes an exacerbation of the airway inflammatory process. In asthma, thromboxane A2 acts as inflammatory mediator and bronchoconstrictor [36] (Fig. 2 b).

The T_H2 profile maintenance, in CARAS, is mediated by an intense network among cells and inflammatory mediators and is characterized as late phase reaction. Indeed, IL-4 plays an essential role as a positive feedback of the process [21,22,37]. IL-4 and IL-13 promote amplification of inflammatory tissue process by activating type 2 macrophages (M2) with TGF-β release, fibroblasts and inducing IgE-allergen specific production [21]. In smooth muscle cells, these two cytokines actively participate in the process of muscular hypertrophy/hyperplasia, leading to the lung hyperreactivity [21,37], also hyperplasia/hypertrophy of

goblet cells with hypersecretion of mucus and metaplasia of epithelial into mucus-producing cells [37,38].

Another classical cytokine of the T_H2 profile is IL-5 responsible for eosinophil maturation into the bone marrow and eosinophil migration to the airways [12,39]. Recruitment of eosinophils into the airways results from chemokines such as eotaxin 1, 2 and 3 (CCL11, CCL24 and CCL26, respectively). Activated eosinophils into the airways release enzymes as eosinophilic cationic protein (ECP) and main basic protein (MBP), which cause rupture of the integrity of the epithelium directly causing airway hyperreactivity [39–41] and remodeling [42–45]. The remodeling process is related to deposition of extracellular matrix, increased of subepithelial mesenchymal cell number and, mainly, increased of smooth muscle mass with airflow obstruction [42,43,46]. In addition, eosinophils have an important role of allergen presentation to memory T lymphocytes [44,45,47] (Fig. 2 c).

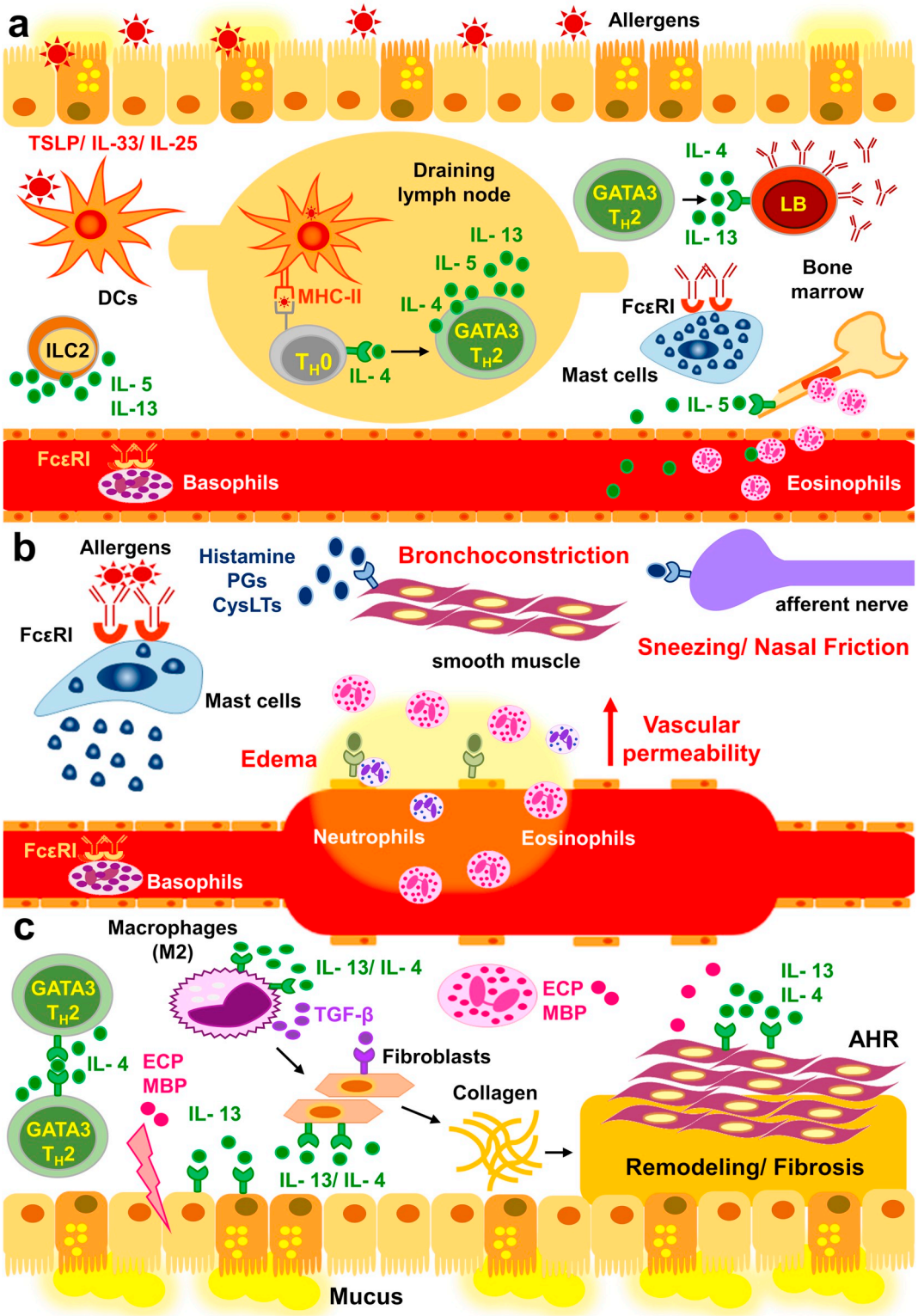

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Fig. 2. Phases of the physiopathology of CARAS. a) First phase of the allergen reaction (sensitization phase). Allergens stimulate epithelial cells to release the alarmines as TSLP, IL-33 and IL-25 that stimulate ILCs 2 to produce IL-13 and IL-5. The alarmines stimulate the APCs (DCs) to dive to the draining lymph node to activate T_H0 via MHC-II and polarize to T_H2 profile with the production of IL-4, IL-5 and IL-13. IL-5 is an important inducer of eosinophilia by acting in the bone marrow and provoking the production, maturation and migration of eosinophils to the inflame site. IL-4 and IL-13 stimulate the production of IgE by B cells that binds to FcεRI receptors in the membrane of mast cells and circulating basophils and eosinophils conferring the first stage of allergen sensitization. b) Second phase of the allergic reaction (challenge phase). Allergen re-exposure results in allergen-IgE-cell crosslink in mast cells that activates the degranulation process with releases of pre-stocked mediators as vasoactive amines - histamine and neo-formed mediators as prostaglandins (PGs) and cystenyl leukotrienes (CysLTs). These mediators will be responsible for the immediate phase reaction acting on the afferent nerves causing the clinical signs of sneezing and nasal friction (rhinitis), on the endothelial cells promoting increased vascular permeability with fluid extravasation to the tissues and formation of edema as well as on the smooth muscles promoting bronchoconstriction (asthma). c) Third late phase of the allergic reaction (T_H2 profile maintenance). The polarization of the T_H2 profile is maintained by the constant IL-4 and IL-13production. These cytokines act on goblet cells promoting mucus hyper-production, smooth muscle cell hyperplasia and hypertrophy and airway hyperresponsiveness (AHR). In addition, they activate macrophages (M2), which produce transforming growth factor β (TGF-β), associated with fibroblast hyper-production of collagen fibers with tissue remodeling and fibrosis. Eosinophils are the effector cells of the chronic inflammatory process by releasing mediators such as eosinophilic cationic protein (ECP) and main basic protein (MBP), which act directly on epithelial destruction, tissue remodeling and AHR. TSLP (thymic stroma lymphopoietin), IL (interleukins), ILC (cell lymphoid innate), APC (antigen presenting cell), DC (dendritic cells), MHC-II (major histocompatibility complex of class 2), IgE (immunoglobulin E), FcεRI (high affinity IgE receptor).

5. Immunoregulation of CARAS

One of the mechanisms of immunoregulation of type 2 immune response, in CARAS, is the presence and performance of T regulatory cells (Tregs). These cells act through cellular contact and secreting cytokines. There are four main suppressive mechanisms driven by Tregs: a) suppressor cytokines (IL-10, TGF-β and IL-35); b) metabolic inactivation (CD25, cAMP, adenosine 2 receptor, histamine 2 receptor, CD39 and CD73); c) suppression of DC activation (CTLA-4, PD-1) and d) cytolysis (granzyme A and B) [8,48–50]. Tregs adoptive transference studies, in mice, demonstrated that these cells are able to suppress the pathological processes of experimental asthma through the production and action of IL-10 and TGF-β, cytokines capable of suppressing the pulmonary dendritic cells (DC) activation and, through direct interaction with endothelial cells, preventing angiogenesis [10]. Tregs directly inhibit mast cell degranulation through the OX40-OX40L interaction by decreasing FcεRI expression and reduction of IgE anchored in their membranes [50]. In addition, Tregs induce IgG4 production on B cell instead of IgE production [50].

Another immunoregulatory cell, in CARAS, is the $CD8^+$T cells that inhibit the allergen sensitization phase by IFN-γ production which drives to T_H1 phenotype [10,25,51]. Depletion of $CD8^+$T cells is involved with IgE allergen-specific serum levels, airway hyperreactivity and remodeling [21,52]. In addition, IFN-γ antagonizes the transcription factor GATA 3 formation responsible for the T_H2 cell generation. Indeed, T_H1 cell adoptive transference or IL-12 administration, in mice, are responsible for the transcription factor T bet activation that drives to T_H1 profile into the airways of experimental model of CARAS [8,10,53] (Fig. 3 a).

6. CARAS treatment

The treatment of the syndrome is based on two different strategies: non-pharmacological and pharmacological therapies. The non-pharmacological therapeutic strategy requires the removal of the allergen from the individual environment and the intended clinical improvement will be detected in at least 3 months. The impact of the non-pharmacological treatment is therefore directly related to the number of time that the sensitized individual is exposed to allergen [54,55].

On the other hand, the pharmacological therapeutic strategy is based on two phases of CARAS physiopathology: 1.) the immediate phase process or allergic reaction and 2.) the late phase process or the chronic inflammatory process of the upper and lower airways [56]. The main medications used to control the allergic reaction in rhinitis are antihistamine [14,54,57] and nasal decongestants that promote a rapid vasoconstriction and relief of the nasal air blockade [58]. For the rapid control of the asthmatic crisis is used the bronchodilators classified as β-adrenergic agonists, M3 muscarinic receptor antagonists, or/and phosphodiesterase [59]. Antagonists of leukotriene receptor (CysLts) are used to control the symptoms of both diseases [9,34,60,61].

The treatment for the chronic inflammatory process of CARAS is mainly by corticosteroids, which immunosuppress the T_H2 profile [13,14,56,62]. The cromoglycate, which stabilizes mast cell membrane, prevents mast cell degranulation on allergens cross-contact and, in combination with corticosteroids, is used in CARAS as therapeutic strategy [14,63]. However, side and adverse effects related with these drugs are reported as sedation, decreasing of attention and cognition, urinary retention, intestinal constipation and hypotension for antihistamine drugs [33,34]. Headache and decongestant tolerance [64], muscle tremor, tachycardia and hypopotassemia for β-adrenergic agonist drugs [59]. Glaucoma for muscarinic antagonista drugs [59]; abdominal pain, headache and somnolence for CysLTs antagonist drugs [65]; nausea and vomiting, diuresis and epileptic seizures for theophylline [59] and local irritation, bleeding, interference in the hypothalamic-pituitary-adrenal axis (HPA), bone resorption, cataract and glaucoma for corticosteroid drugs. Therefore, these adverse effects have been driven the studies to discovery new molecules to treat both diseases based on their endotypes/biomarkers. In this context, the immunobiological therapy is current therapy of choice as monoclonal antibody anti-IgE (Omalizumab®) [66] and monoclonal antibody anti-IL-5 (Mepolizumab®) [8,67]. In addition, promising monoclonal antibodies anti-IL-13 and anti-IL-4 are on pre-clinical trial [8] (Fig. 3 b).

7. Experimental models of CARAS

Experimental models of human diseases are important tool for a better understanding and elucidation of physiopathology mechanisms of diseases and, consequently, evaluation of safety and efficacy of new therapies before they are introduced in human clinical trials [68]. However, requirements for the use of animal care, emphasizing the fulfillment of ethical precepts, were established for the use of experimental animals. The result of it was the Guide to Care and Use of Laboratory Animals - National Institutes of Health (NIH), 8th edition, 2011. In addition, there are limitations of animal models and among them is the difficulty to mimic the phenotype and endotype characteristics of asthma and rhinitis. Nevertheless, animal models have been fundamental for the amplification and better elucidation and knowledge of the inflammatory, structural and physiological parameters present in the respiratory tract diseases, observed in separate experimental models [69–73]. However, the identification of biomarkers, which differentiate them, will achieve a new baseline of treatment [74–76].

Animal models to investigate allergic respiratory diseases induced by ovalbumin (OVA) or aeroallergens have been widely used to elucidate immunological and non-immunological mechanisms involved in the pathogenesis of asthma and rhinitis. In addition, they are useful for identifying and investigating new molecular targets to control allergic inflammation [77,78], however physiological and morphological

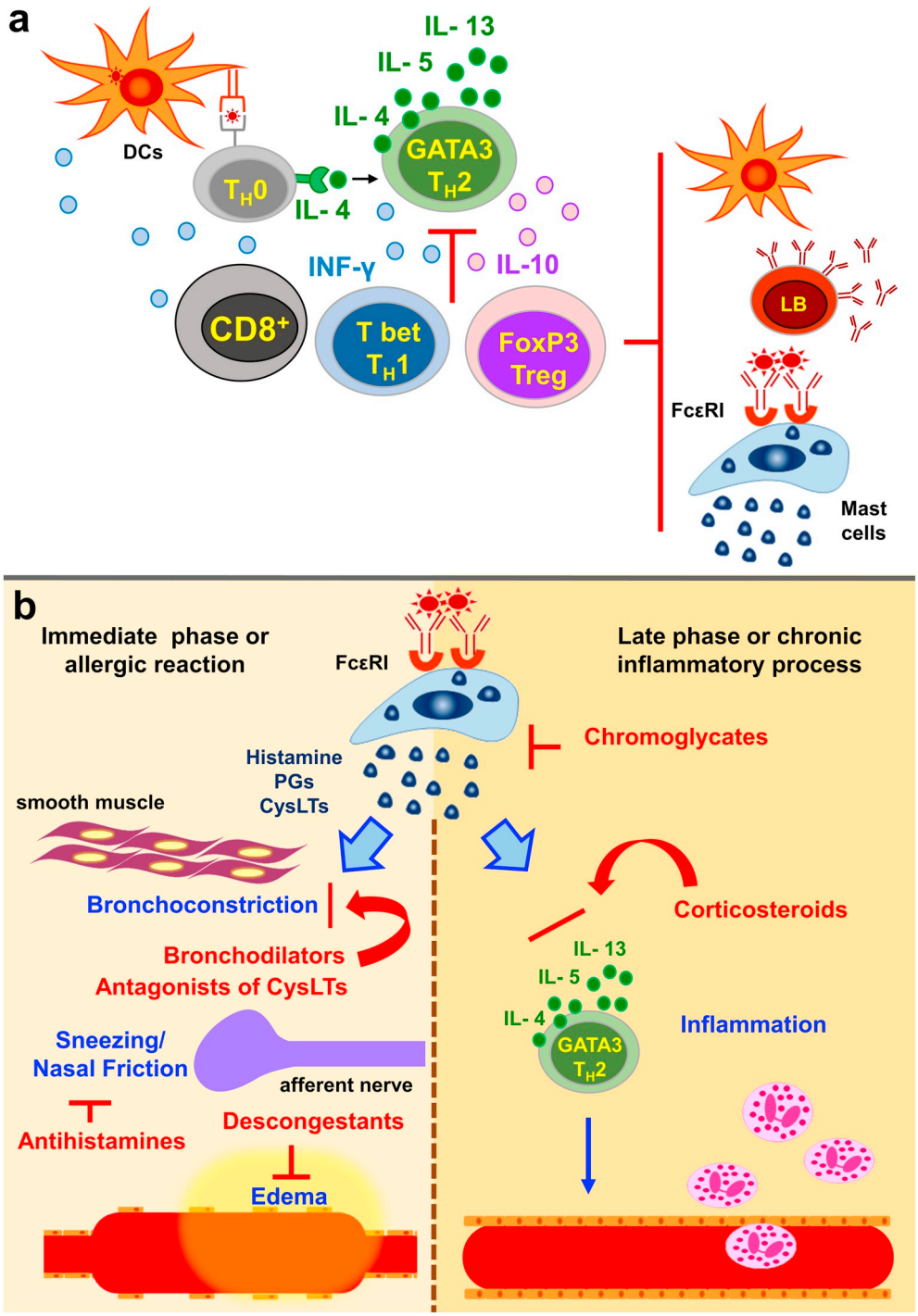

Fig. 3. Immunoregulation mechanisms and pharmacological treatment of CARAS. a) Treg cells produce IL-10 that inhibits T_H2 profile polarization, suppresses the dendritic cells (DCs) activation and prevents mast cell degranulation and IgE production. The T_H1 profile as well as the $CD8^+$T cells produce inferteron gamma (IFN-γ) that antagonizes the T_H2 cytokine profile. b) The pharmacological tools used in the immediate phase or allergic reactions are bronchodilators, cystic leukotrienes (CysLTs) antagonists, antihistamines and nasal decongestants. All these therapeutic classes have quick action, providing a rapid relief of the immediate reaction of CARAS. In addition, the therapeutic classes chosen in the late phase or in the chronic phase of the allergic process of the upper and lower airways are the corticosteroids, direct acting in inflammatory process. The chromoglycates act as mast cell stabilizers, preventing cell degranulation and diminishing the allergic process.

differences between animal and human should be considered. Indeed, non-clinical studies should be preceded of clinical studies of phases I, II and III/IV. In the literature, until 2018, only six papers used the CARAS experimental model [79–84] that represents a favorable scenario to understand the physiopathology of this syndrome, besides being fundamental for the new drug test [69,85].

Mice, similarly to most animals, do not naturally develop a chronic allergic inflammatory disease, thus animal models require protocols of allergic sensitization and subsequent allergen re-exposure (challenge) to induce an allergic inflammatory response [70]. Studies have been demonstrated that both asthma and rhinitis are chronic diseases resulting from intermittent or continuous aeroallergen exposure responsible for developing the inflammatory process and, consequently, an exacerbated immune response in the airways. This aeroallergen exposure occurs mainly through the airway, by inhalation route, during the respiratory process [86–88].

To mimic human asthma and rhinitis, the allergen -sensitization and -challenged phases should be considered in the experimental models [89] thus, the first contact with allergen can be systemic (i.e. intraperitoneal injection), dermal, or local to the airways (inhalation or intranasal administration) characterizing sensitization phase and repeated allergen inhaled or intrasanal drops procedure characterized the challenged phase [77,90]. One of the experimental protocol that mimic human rhinitis and asthma is the one that uses isogenic mice sensitized, via ip., with OVA associated with an adjuvant (aluminum hydroxide) as an allergen. The sensitization phase occurs twice spaced by 7 to 14 days

and the allergen challenged, via aerosol, occurs after one week of the last sensitization injection [91–94]. Most researches prefer to use allergen aerosol for challenges because is less invasive and do not require animal sedations, but the disadvantage is that uses a greater amount of allergen. Even though the intra nasal route used for allergen challenge requires sedation and is more invasive, the advantage of it is that allergens are instilled locally and directly into the airways, which leads to more intense allergic inflammation [89]. Therefore, chronic exposure to the allergen that occurs in several days, mimics the most significant form of human asthma and rhinitis, which makes possible the study of new drugs and immunotherapeutic strategies [89,94].

Despite the OVA is the most common allergen used in the experimental model of allergic rhinitis and asthma, several other allergens can be used as Der p (*Dermatophagoides pteronvssinus*) or Der f (*D. farinae*) from house dust mites (HDM); fungi (*Aspergillus fumigatus*, *Alternaria alternata*); extracts of cockroach; *Ascaris* antigens; cotton powder; ragweed and latex (*Hevea brasiliensis*). The choice of the allergen depends on the condition to be replicated and can be used alone or in combination [95].

Several species of animals can be used in experimental model of CARAS including mice, guinea pig, cat, dog, pig, cattle, sheep, horse and primates to understand the mechanisms involved in the pathogenesis of this syndrome. However the most commonly used is the mice model [72,73,96–98] due to the gestation time is shorter than others animals, around 20 days, and also they can have a higher number at once [89,99]. Another vantage is that mice are technically easy to create, maintain and manipulate. In addition, they present a wide variety of specific reagents available for analysis on cellular and humoral immune responses. They also present a greater facility for genetic mutation, the so-called transgenic mice or knockout mice, which are genetically modified for the modeling of diseases of the airways [100,101].

The isogenic mouse line most commonly used in the experimental models of asthma and rhinitis is the isogenic BALB/c mice, which is characterized by developing a polarized immune response to Th2 profile, similar of the human disease. However, the C57BL/6 and A/J isogenic lineages are also used in experimental models of allergic respiratory diseases and have shown a satisfactory response [77].

8. Conclusion and perspectives

Taking into account the information described above where the concept of “one airway – one disease” for allergic rhinitis and asthma characterizing as combined allergic rhinitis and asthma syndrome (CARAS), where the physiopathology of both diseases is related with their phenotypes, endotypes and biomarkers, this review adds knowledge which has made it possible to direct and personalize treatment. In addition, the recognition of animal models that portray the syndrome has brought insights in mechanisms of action that can be target for studies of new drugs to treat both diseases as one.

Acknowledgments

This study was partly funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001, and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico - Brasil).

Declaration of Competing Interest

The authors report no declarations of interest.

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