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Mesenchymal Stem Cells in Asthma

Tunc Akkoc

Abstract

Asthma is one of the worldwide respiratory health problem that affect children and adult. Current treatment strategies such as conventional and allergen immunotherapy still fall behind. Mesenchymal stem cells (MSCs) have wide regenerative capacity and immunoregulatory activity with their wide range of secretions and contact dependent manner. In this review, we focus on the current treatment strategies for asthma and MSCs as a new therapeutic tool.

Keywords

Asthma · İmmunoregulation · İmmunotherapy · Mesenchymal stem cells

Abbreviations

MSCs	Mesenchymal Stem Cells
AIT	Allergen immunotherapy
GVHD	Graft versus host disease
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy
TGF-β	Transforming growth factor beta
SARSs	Systemic adverse reactions
HLA	Human leukocyte antigen
MHC	Major histocompatibility complex
IDO	Indoleamine 2,3-dioxygenase
NO	Nitric oxide
EAMG	Experimental autoimmune myasthenia gravis

T. Akkoc (✉)
Faculty of Medicine, Department of Pediatric Allergy and Immunology, Marmara University, Istanbul, Turkey
e-mail: tuncakkoc@gmail.com

1 Introduction

Stem cells have special concern due to their capability to help in regenerative medicine. Broadly they are classified due to their potency as pluripotent (embryonic and inducible) and multipotent (mesenchymal). Among these, mesenchymal stem cells gain much attention because of their postnatal origin, differentiation capacity, lack of immune activity, and safety for the host. Stem cells have important immunomodulatory effect on autoimmune and allergic diseases.

Asthma is a chronic inflammatory disease and its prevalence has significantly increased with the western life style. Th2 dominant immune response is mainly responsible for pathogenesis. Besides conventional therapies with short- and long-acting beta agonists, inhaled low dose corticosteroids and other anti-IgE/anti-leukotriene therapies, there is an immunotherapy approach with sensitized allergens. Recent studies obviously showed the immunoregulatory effects of Mesenchymal Stem Cells (MSCs) in various autoimmune and atopic disorders.

This review outlines the mechanism of the immunotherapy and immunomodulatory effect of MSCs in allergic disease. Also, the implications of recent studies on immunoregulatory aspects of MSC and dysregulated immune systems are discussed.

2 Asthma and the Immune System

2.1 Overview

Asthma is a major chronic, non-communicable health problem affecting children and adults (Asamoah et al. 2017). Its prevalence has increased in urbanized regions particularly with westernized lifestyle and it affects more than 300 million people around the world (Papi et al. 2018). It is characterized by dense airway inflammation leading to reversible airflow limitation and lung tissue remodeling (Papadopoulos et al. 2012). Its basic diagnostic symptoms include dyspnea, cough, wheezing and chest tightness (Becker and Abrams 2017).

Asthma is a Th2 skewed disease with increased number of $CD4^{+}$T cells which produce IL-4 and IL-5 that lead to production of allergen specific IgE and eosinophils, respectively (Brightling et al. 2002). Eosinophilic inflammation is credited to be a substantial contributor to the histopathological inflammatory changes in asthmatic patients (Brightling et al. 2002; Tan et al. 2016). Chronic airway inflammation leads to airway remodeling characterized by basement membrane thickening, goblet cell hyperplasia, smooth muscle proliferation, peribronchial and perivascular inflammatory cell infiltration and mucus plug formation (Akkoc et al. 2001).

Currently there is no radical cure for asthma, but conventional therapeutic approaches control the disease symptomatically. Stepwise pharmacological treatment involves short-acting beta-2 agonist, long acting beta-2 agonists and inhaled low dose corticosteroids alone or with combination depending on the severity of asthma (Parsons et al. 2013; Cates and Karner 2013). Besides these, theophylline, anti-leukotrienes, anticholinergics, and anti-IgE antibodies (Omalizumab) can be used to control severe asthma (Asamoah et al. 2017; Mirra et al. 2018). All of these are symptom relief treatment approaches and do not educate the immune system. Allergen immunotherapy (AIT) is an alternative to regulate the immune response and an effective treatment strategy for allergic diseases (Berings et al. 2017).

2.2 Allergic Disease and the Immune System

The immune system easily differentiates self and non-self and screens harmful pathogens with immune cells in a complex interactive network. Immune tolerance is a well-organized immune mechanism that protects individuals from cancer, autoimmunity, viable pregnancy, graft-versus-host disease (GVHD), rejection of transplanted organs asthma and allergies (Fuchs et al. 2017; Werfel et al. 2016; Chinthrajah et al. 2016). Allergic disease can be classified as allergic rhinitis, allergic asthma, atopic eczema, food allergy and anaphylaxis (Akdis and Akdis 2009; Galli and Tsai 2012; Akdis 2012).

Allergic asthma is basically defined as a type 2 immune response-associated disease. The type 2 dominant immune response is characterized by increased number of CD4 + Th2 cells, IL-4-high and IL-5-high immune activity with enhanced allergen specific IgE, eosinophil and mast cells. This leads to airway hyperresponsiveness with increased airway eosinophilia. Consequently, eosinophilic inflammation responsible for pathophysiological changes causes remodeling seen in asthmatics (Eiwegger and Akdis 2011) (Fig. 1).

2.3 Allergen Immunotherapy

Allergen immunotherapy seems like the only therapeutic approach for allergic conditions and respiratory allergies. This kind of therapy involves delivery of sensitized allergens to patients with gradually increasing amounts of dose for subcutaneous immunotherapy (SCIT),

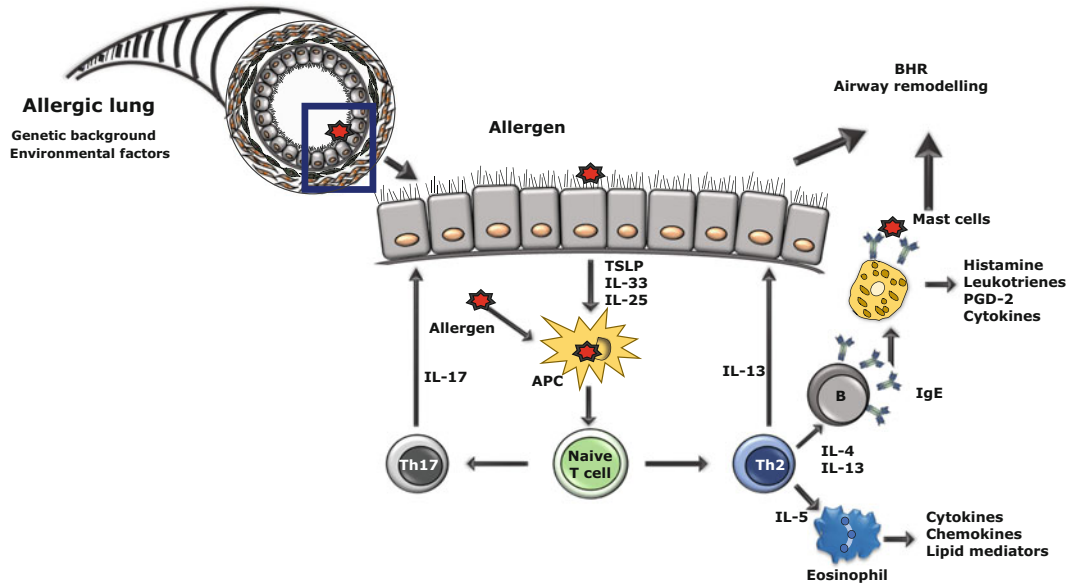

Fig. 1 Pathogenesis of asthma. BHR: Bronchial Hyperreactivity, PDG-2: Prostaglandin E-2, APC: Antigen Presenting Cells, TSLP: Thymic stromal lymphopoietin

sublingual immunotherapy (SLIT), or oral immunotherapy. Regarding this approach, the allergen content, administration route, and duration of administration are important for the safety of therapy and immunoregulatory stimulation (Matricardi et al. 2019). The underlying mechanism of AIT involves shifting the T cell immune response from Th2 to regulatory type. T regulatory cells remain at the center of AIT with their anti-inflammatory cytokine production nature like interleukin 10 (IL-10) and transforming growth factor-beta (TGF-β). Among these IL-10 is responsible for downregulation of allergen specific immunoglobulin E (IgE) antibody production and upregulation of immunoglobulin G4 (IgG4) which are called blocking antibodies (Frew 2010). Also, Treg cells act on mast cells, eosinophils and T cells to reduce the release of proinflammatory cytokines. Further AIT prevents localization and functions of mast cells, basophils and eosinophils in the local sensitized tissues, such as bronchial mucosa (Cox et al. 2011a; Moote et al. 2018) (Fig. 2).

Beside AITs safe clinical outcomes due to the nature of the antigen as natural allergens, some systemic adverse reactions (SARs) are monitored during therapy (Cox et al. 2011b).

3 Mesenchymal Stem Cells

3.1 Overview

MSCs are non-specialized multipotent cells that have self-renewal and differentiation capacity into diverse cell types such as adipose, chondrocyte and osteocyte (Al-Nbaheen et al. 2013). The International Society of Cellular Therapy (ISCT) stated the minimum criteria for MSCs as plastic-adherent in standard culture, expressing special cell surface markers such as CD73, CD90 and CD105 while negative for CD14, CD34, CD45, CD19, CD11b, CD79a, and HLA-DR, and differentiation capability into adipocyte, osteocyte, or chondrocytes *in vitro* (Dominici et al. 2006).

Various sources of MSCs are described as including adipose tissue, umbilical cord blood, Wharton's jelly, the placenta, bone marrow and dental tissue (Sueblinvong et al. 2008; Gronthos et al. 2000). Because of minor ethical apprehensions, ease of attaining them in tissue

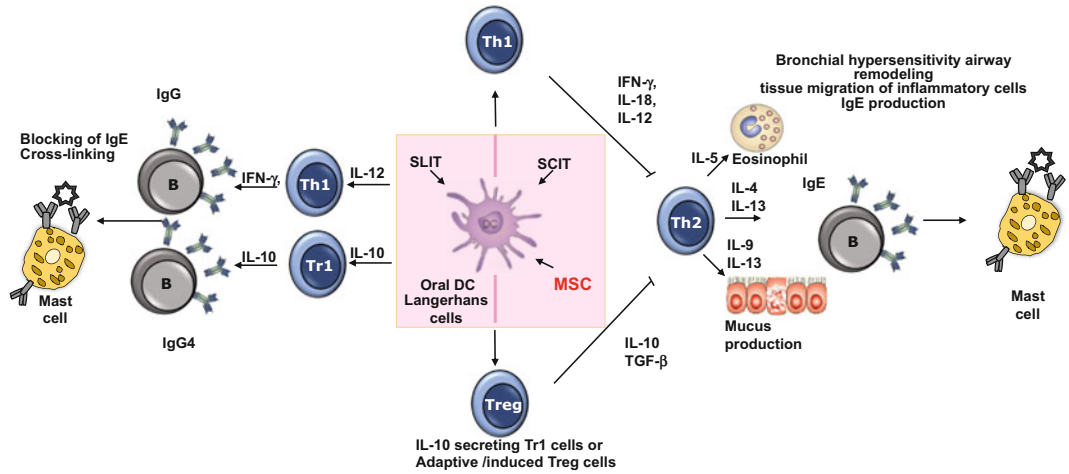

Fig. 2 Mechanism of allergen specific immunotherapy. *SCIT* Subcutaneous Immunotherapy, *SLIT* Sublingual Immunotherapy, *MSC* Mesenchymal Stem Cell, *DC* Dendritic cell

and isolation, suppression of inflammation and role in immunomodulation, they are a promising therapeutic approach for several autoimmune disorders (Ogulur et al. 2014a; Yu et al. 2010).

3.2 Immunomodulation and MSC

The immune system is a communicating network of cells and molecules with the competency to protect the host from a broad range of pathogens, while distinguishing self and non-self-tolerance. Once the immune system loses its capability to discriminate self-cells and tissues from others, immune-tolerance-related diseases arise such as cancer, autoimmunity and allergy (Fuchs et al. 2017; Palomares et al. 2014).

MSCs are specialized cells that regulate the immune system and control inflammatory disease-related immune reactions. Mainly MSCs express low- to moderate-intensity levels of human leukocyte antigen (HLA) and major histocompatibility complex class I (MHC-I) while they lack MHC-II and costimulatory molecules such as CD80, CD86, CD40 and CD40L (Le Blanc and Ringden 2007; De Miguel et al. 2012).

Conversation and regulation of the immune system is provided by cytokines. T cell subsets are signatures with different tendencies toward cytokine secretions. Regarding their cytokine profile, they control or direct the immune system to autoimmunity or allergic disease. Inflammation is also modulated via cytokines and mainly pro-inflammatory cytokines (TNF-α, IL-1-α, IL-6) increase in that state.

MSCs have a high capacity to modulate immune responses. Basically, they suppress pathologic T cell proliferation and regulate the balance of Th1 (autoimmunity related)/Th2(allergic disease related). In addition to this they modulate the T regulatory cells (Tregs), regulate antibody secretion profile of B cells and antigen presentation of dendritic cells (Le Blanc et al. 2003; Saldanha-Araujo et al. 2011). The innate and adaptive immune system is also regulated by MSCs originating other immunomodulatory molecules such as interleukin-10 (IL-10), TGF-**β**, indoleamine 2,3-dioxygenase (IDO), and nitric oxide (NO) (Del Fattore et al. 2015; Kyurkchiev et al. 2014; Castro-Manrreza 2016).

Our previous studies indicate the immunoregulatory properties of MSCs from different sources on different dysregulated-immune system related diseases (Ulusoy et al. 2015; Duman et al. 2019; Cerman et al. 2016). One of these showed human dental follicle MSC treatment for a MuSK-associated experimental autoimmune myasthenia gravis (EAMG) model led to the outcome of downregulated anti-MUSK IgG1, IgG2 and IgG3 and prevention of IgG3 and Complement

3 (C3) deposition into the neuromuscular junction (NMJ) *in vivo*. This regulation was established by suppression of proinflammatory IL-6 and IL-12. These immunoregulatory outcomes also improved clinical grades in the model (Ulusoy et al. 2015). Recent studies also showed that rat bone marrow derived MSCs suppress inflammation by downregulating TNF-α, fibrosis and enhancing NK cells in rat liver in a rat hepatic fibrosis model. Also, IFN-γ, TNF-α and IL-1α are downregulated and IL-10 levels are upregulated in the periphery (Duman et al. 2019).

4 MSCs and Asthma

4.1 Overview

Asthma is characterized by chronic airway inflammation related to dominant Th2 immune response and infiltration of eosinophils and mast cells within small airways (Lai et al. 2009). Several therapeutic approaches are designed to suppress allergic inflammation in acute and chronic murine models. Among them most promising was an immunotherapy approach with an allergen which upregulates Treg cell and downregulates Th2 type immune response in acute and chronic asthma models (Akkoc et al. 2008a, b, 2010, 2011; Eifan et al. 2010; Keles et al. 2011; Townley et al. 2004; Yazi et al. 2008). Allergen-specific immunotherapy is a basic and approved treatment option for allergic diseases. Also, it was shown previously that adjuvants such as *Mycobacterium vaccae* induce T reg cells while reversing Th2 immune deviation in murine models (Akkoc et al. 2018).

Recent studies address MSC's as an encouraging therapeutic approach for curing allergic and autoimmune disorders. Studies were carried out on murine models and in-vitro human studies.

4.2 Murine Models

Close models for type-I allergic disease are important to reflect bronchial asthma that resembles the main features of the human allergic disorder. Depending the severity of disease, acute and chronic models were developed. The acute asthma model is characterized by high levels of allergen-specific IgE production, bronchial hypersensitive reactions to allergens and methacholine provocation test, and cellular infiltrate in proximal airways (Herz et al. 2004). Changes are more dramatic in chronic asthma models. Airway remodeling is mostly seen in chronic models with goblet cell hyperplasia, thickening of smooth, muscle and basement membrane. These dramatic changes also reach the distal small airways (Akkoc et al. 2001). Recent meta-analyses of MSC transplantation in asthmatic models have collected studies (Zhang and He 2019). Really various ways of administrating (intravenous and intratracheal) MSC's successfully downregulates airway inflammation and airway remodeling in acute and chronic asthma models. Our results demonstrated that allogeneic pluripotent stem cells also control allergic acute inflammation, reverse airway cell infiltration in proximal airways, downregulate eosinophil accumulation in Broncho alveolar lavage and allergen specific IgE levels in serum. Further while IL-10 levels increased, IL-4 levels were downregulated in lung cell suspensions (Ogulur et al. 2014b). These results successfully reveal the therapeutic ability of stem cells in acute and chronic asthma models.

4.3 Experimental Human Studies

Stem cell application to patients needs time regarding ethical issues and some unknown side effects that may be seen during long term follow up. Allogeneic MSC's were successfully used without serious adverse reactions. Also encouraging results are seen in those studies.

Importantly the immunomodulatory properties of MSCs are accredited for allergic disease and autoimmune disorders. The most expected results for MSC in allergic disease are downregulation of Th2 type cytokines, allergen specific T cell proliferation and detrimental memory T cells, and upregulation of Treg cells and naive T cells. Genç et al. compared the *in vitro*

immunomodulatory effect of dental follicle MSC (DF-MSC) on mononuclear cells of asthmatic patients and patients that completed 3 years of allergen specific immunotherapy (Genc et al. 2018). DF-MSCs properly suppressed proliferative responses of CD4+ T cells, IL-4 and GATA-3 expression. The outstanding results of this study are downregulation of effector and effector memory CD4+ T cells, and downregulation of IDO and costimulatory pathway in antigen presentation as in immunotherapy group. Another study revealed that IFN-γ pre-treated DF-MSCs enhanced Treg cells andIL10 levels (Genc et al. 2019). Both studies showed the immunomodulatory effect of DF-MSCs on Derp-1^{+} allergic polymorphonuclear cell of patients *in vitro*.

5 Conclusion and Perspective

Recent studies of MSC administration in murine models of asthma provide valuable information concerning the safe application *in vivo* with lack of immunogenicity and adverse effects. MSC applications may be intravenous, intranasal or intratracheal. The source of MSCs is an important manner. In murine models of asthma, MSCs are derived from bone marrow, adipose tissue or umbilical cord. All sources provided safe results with *in vivo* experiments.

In humans, recent developments in relation to the clinical and cellular/molecular mechanisms of AIT aim at enhancing clinical and immunologic tolerance, decreasing side effects, and increasing efficacy. Hypoallergenic recombinant allergen and allergoid vaccines and use of probiotics, vitamins and biological agent supplements to support AIT are expected to enhance efficacy. Many novel developments in molecular mechanisms that affect early desensitization, T- and B- cell tolerance, specific antibody regulation, and induction of IgG4 and several key molecules that can act as biomarkers are continuously being developed. As new technologies and novel strategies emerge, we are in need of more research into the mechanisms, biomarker discovery, and disease phenotyping for AIT. There will always be take-home messages for other immune tolerance-related conditions, such as autoimmunity, organ transplantation, chronic infections, cancer, and recurrent abortion.

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