



Role of mesenchymal stem cells and short chain fatty acids in allergy: A prophylactic therapy for future

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ABSTRACT

Allergic diseases are broadly classified as IgE-mediated type-I hypersensitivity immune reactions due to exposure to typically harmless substances known as allergens. These allergenic substances activate antigen presenting cells, which further triggers T-helper 2 cells immune response and class switch B-cells for synthesis of allergen-specific IgE, followed by classical activation of inflammatory mast cells and eosinophils, which releases pre-formed mediators involved in the cascade of allergic symptoms. However, the role of Mesenchymal stem cells (MSCs) in tissue repair ability and immunomodulation, makes them as an appropriate tool for treatment of various allergic diseases. Several clinical and preclinical studies show that MSCs could be a promising alternative therapy to allergic diseases. Further, short chain fatty acids, produced from gut microbes by breaking down complex fibre-rich foods, acts through G-coupled receptor mediated activation of MSCs, and their role as key players involved in amelioration of allergic inflammation needs further investigation. Therefore, there is a need for understating the role of SCFAs on the activation of MSCs, which might shed light on the development of new therapeutic regime in allergy treatment. In summary, this review focuses on the underlying of therapeutic role of MSCs in different allergic diseases and the prospects of SCFA and MSC therapy.

1. Introduction

Immunoglobulin E (IgE) mediated hypersensitivity reaction develops in atopic individual, who are sensitised to typically harmless food or environmental allergens, which is termed as allergic disorder or Allergy. Allergic diseases include food allergy (FA), allergic asthma (AA), allergic rhinitis (AR) and atopic dermatitis (AD or atopic eczema), which shares some of the common inflammatory cascades caused by dynamic interaction of structural tissue cells and inflammatory cells namely basophils, mast cells, dendritic cells, lymphocytes, neutrophils and eosinophils[1]. The prevalence of allergy affects 20% worldwide amongst the sensitised individuals to various predominant allergens. Nearly one of every four children in high-income countries shows relative symptoms of AR, AA, or AD in the last three to four decades. Importantly, the global incidence of allergic rhinitis and allergic asthma are substantially increased among children and adult[2]. The treatment for allergic disorders with anti-histamines, corticosteroids, β_2 adrenergic receptor agonists and anti-leukotrienes block inflammatory mediators and immune cells

temporarily, which acts as stop gaps[3]. However, the long-term relief from allergic diseases is one of the major concerns worldwide as it burdens quality of life and treatment cost.

Mesenchymal stem cells (MSCs) serve as a new treatment strategy for several diseases including allergic diseases. MSCs are non-hematopoietic, multipotent adult stromal progenitor cells that can self-renew and differentiate into several lineages and cell types. Peripheral blood (PB), bone marrow (BM), amniotic fluid, umbilical cord blood (UCB), placenta, dental pulp, and adipose tissue (AT) are different sources of MSCs. These tissues are the source for isolation of MSCs (Fig. 1)[4]. MSCs from different sources have similar characteristics such as trilineage differentiation ability, *in vitro* fibroblast-like appearance, express specific cell surface markers such as CD44, CD73, CD90, CD105, CD271, and STRO-1, and lack of others markers like CD11b, CD14, CD19, CD34, CD45, CD78, and HLA-DR (Table 1)[5–7].

Various reports published in recent years on the therapeutic effects of MSCs in different diseases. For instance, a study on the application of BM-MSC formulation administered in patients suffering from Diabetic Foot Ulcers (DFU) was conducted by Asko Andersen J et al. for

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Abbreviations/Acronyms

MSC-	mesenchymal stem cells
HSC-	hematopoietic stem cells
AR-	allergic rhinitis
AD-	atopic dermatitis
PB-	peripheral blood
BM-	bone marrow
UCB-	umbilical cord blood
AT-	adipose tissue
AMMSC-	MSCs derived from the amniotic membrane
ADMSC-	adipose-derived mesenchymal stem cells
CLP-	caecal ligation and puncture
ALI-	acute lung injury
IBD-	inflammatory bowel disease
TNBS-	2,4,6-trinitrobenzene sulfonic acid
Th2-	CD4+ T helper type 2 cells
APC-	antigen presenting cells
DC-	dendritic cells
IL-	interleukin
AHR-	airway hyperresponsiveness
Tregs-	regulatory T cells
Foxp3-	forkhead box P3 transcription factor

Teff-	T effector cells
TGF- β -	transforming Growth Factor- β
NK-	natural killer cells
ICAM-1-	intercellular adhesion molecule 1
VCAM-1-	vascular cell adhesion molecule-1
PD-L1-	programmed death ligand 1
MAPK-	mitogen-activated protein kinase
VEGF-	vascular endothelial growth factor
TNF-	tumour necrosis factor
PGE2-	prostaglandin E ₂
IFN- γ -	interferon- γ
HGF -	hepatocyte growth factor
FGF-	fibroblast growth factor
IDO-	indoleamine-pyrrole 2,3-dioxygenase
T-MSCs-	tonsil-derived MSCs
BALF-	bronchoalveolar lavage fluid
MC-	mast cells
COX2-	cyclooxygenase-2
EASI-	eczema area and severity index
SCORAD-	Severity scoring for atopic dermatitis
IGA-	investigator's global assessment
SCFA-	short chain fatty acids
GPCR-	G-protein coupled receptors.

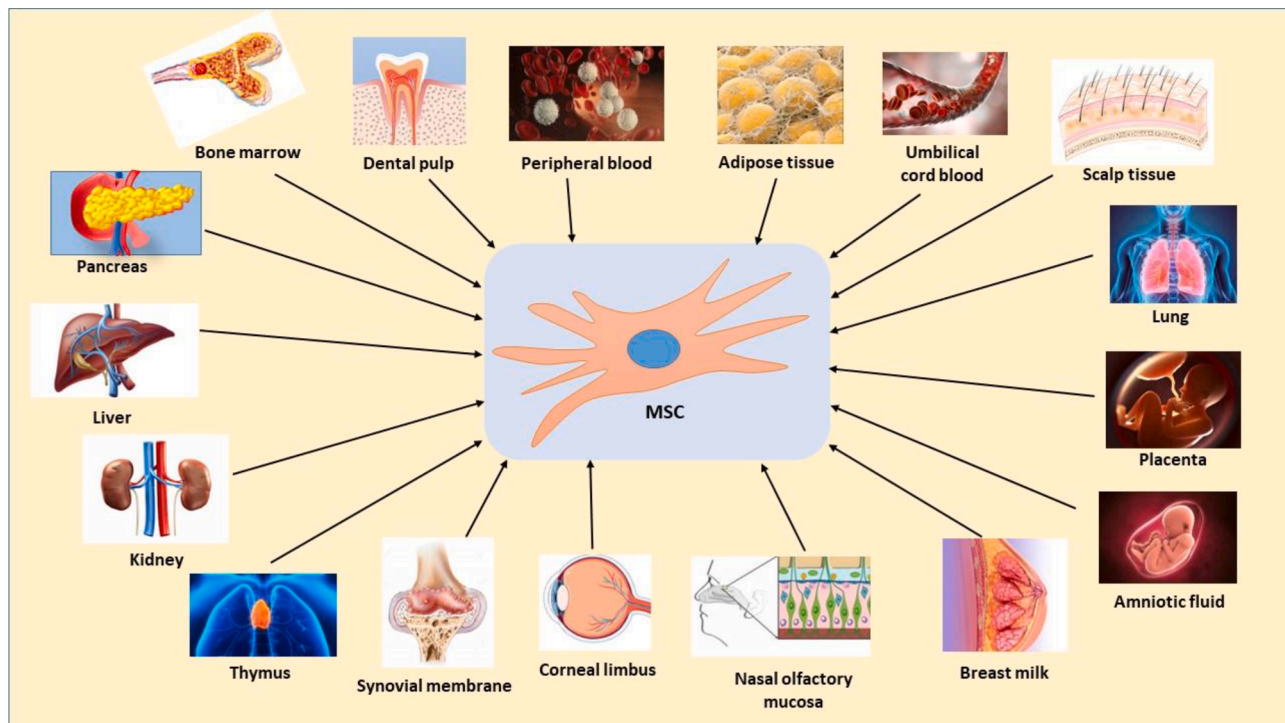


Fig. 1. Different sources of MSCs. The isolation of MSCs can be done from different body parts/ organs and body fluids.

evaluation of the safety profiles of the treatment. Interestingly, one-time treatment with BM-MSC formulation followed-up by six months of observation in patients confirmed improvement in the clinical outcome and that, offers safe and effective treatment approach [21]. A comparative study of the clinical effects of MSCs derived from the amniotic membrane (AMMSC) and umbilical cord (UCMSC) on type 2 diabetes mouse model shows significant improvement of glycolipid metabolism, reduction of hyperglycaemia and improvement from insulin resistance conditions [22]. The administration of a therapeutic dose of

Adipose-derived mesenchymal stem cells (ADMSC) in a septic rat model, reduced 'caecal ligation and puncture' (CLP)-induced acute lung injury (ALI), and enhanced gut microbiota. Here, the preclinical application of ADMSCs offers a potential therapeutic approach to treat sepsis [23]. Further, clinical trial in progressive multiple sclerosis (MS) patients using repeated MSC treatments shows safe and clinical benefits lasted for up to four years [24]. Yet another study by Pan X et al. reported that the therapeutic effects of UCMSCs in alleviating inflammatory bowel disease (IBD) symptoms in an animal model by promoting the expression

Table 1
Biomarkers of MSCs from different sources.

Source of MSCs	Cell Surface Biomarkers Positive	Negative	References
Bone marrow	STRO-1, CD73, CD90, CD105	CD11 b, CD34, CD45	[5]
Dental tissue	CD29, CD44, CD73, CD90, CD166	CD14, CD34, CD45, HLA-DR	[8,9]
Peripheral blood	CD29, CD44, CD73, CD90, CD105, CD106, CD140α	CD11b, CD19, CD34, CD45	[10]
Adipose tissue	CD90, CD44, CD29, CD105, CD13, CD34, CD73, CD166, CD10, CD49e, CD59, HLA-ABC, STRO-1	CD31, CD45, CD14, CD11b, CD34, CD19, CD56, CD146, HLA-DR	[11]
Placenta and umbilical cord	CD44, CD73, CD90, CD105	CD11b, CD14, CD19, CD34, CD45, HLA-DR	[12,13]
Amniotic fluid and membrane	HLA-ABC, STRO-1, CD13, CD29, CD44, CD49e, CD54, CD58, CD73, CD90, CD105, and CD166	HLA-DR, CD31, CD34, CD45	[14]
Foreskin	HLA-ABC, CD29, CD44, CD49e, CD54, CD73, CD90, CD105, CD166	HLA-DR, CD14, CD19, CD31, CD34, CD45, CD62e, CD102, CD106	[15,16]
Endometrium	CD29, CD44, CD73, CD90, CD105, CD140b, CD146	HLA-DR, CD31, CD34, CD45	[17]
Human milk	SCA-1, CD29, CD44, CD90, CD106, CD271	CD33, CD34, CD45, CD73, CD105, CD123, CD133	[18,19]
Menstrual blood	CD29, CD73, CD90, CD105,	HLA-DR, CD34 CD45	[20]

Table 2
Important Th2 cytokines and their roles.

Cytokines	Function
IL-4	Differentiation of Th2 cells, induction of IgE secretion from B-cells, mast cell proliferation, and eosinophil accumulation
IL-5	Eosinophilic airway inflammation, and airway remodelling by inducing the accumulation of extracellular matrix proteins under airway epithelial tissues
IL-9	Differentiation, proliferation and activation of mast cells and their accumulation in the airways, enhancement of goblet cell hyperplasia, and mucus production
IL-13	Epithelial eotaxin expression, influx of eosinophils in the airways, goblet cell hyperplasia, mucus hypersecretion and airway hyperresponsiveness (AHR)

of occludin and claudin-1 (intestinal tight junction proteins), down-regulating the expression of the autophagy marker LC3A/B in the colon, and microvascular regeneration of intestinal wall cells[25]. In a study on Leishmania major-infected BALB/c mice model, multiple intravenous (i. v.) injection of AD-MSCs reduced footpad swelling and parasites burden and observed delay on lesion development [26]. Moreover, studies clearly indicate that MSCs could prevent gut dysbiosis and restore normal gut microflora, which summarises involvement dysregulated metabolic pathway. In another study, 2,4,6-trinitrobenzene sulfonic acid (TNBS) induced colitis mouse model was treated with UCMSCs for restoration of the gut microbiota and repairs the intestinal mucosal barrier, which exerts a protective effect[27]. Taken together, MSCs serve as a progressive therapeutic tool for various disease conditions and that more than 950 clinical trials of MSCs in human treatment were registered as therapeutic modality alternative to the main treatment approach[28].

2. Overview of immune reaction in allergy

The involvement of effector CD4⁺ T helper type 2 (Th2) cells and IgE-producing class-switched B cells against specific allergens serves as the key indicator of allergic manifestation, followed by elevation of activated mucosal mast cells and eosinophil infiltration[1]. In the first stage of allergic inflammation, which is termed as ‘sensitization phase’, in which antigen presenting cells (APCs) like macrophages, dendritic cells (DCs), langerhans cell or monocytes process and present the antigen (or allergens) to naive CD4⁺ T cells, which pave the way for differentiation into Th2 cells. During allergic manifestation, these differentiated Th2 type cells secrete proinflammatory cytokines like interleukin (IL)–4, IL-5, IL-9 and IL-13, which directly play a crucial role in the synthesis of IgE by isotype switching of B cells and induce allergic airway inflammation (Table 2). Allergen-specific IgE secreted by B-cells binds to the high-affinity receptor FcεRI present on the surface of mast cells and basophils and aggravates allergic immune response[1,29,30]. Further, upon subsequent re-exposure to the same allergens during the second stage of allergic inflammation, also referred to as the effector phase, readily increases the release of proinflammatory mediators by activated mast cells and basophils. In addition, accumulation and activation of effector cells such as eosinophils and neutrophils promote airway hyperreactivity (Fig. 2)[29].

3. Role of tregs in immune suppression

Tregs (regulatory T cells) are one among the subsets of CD4⁺ T cells that express the IL-2 receptor α chain (CD25) and help to sustain homeostasis and self-tolerance by controlling immune responses. Foxp3 (forkhead box P3 transcription factor), a member of FOX protein family, plays a prominent role in the development and immunosuppressive activity of Tregs. Naturally occurring Tregs (nTregs) derived from the thymus and secondary lymphoid-derived inducible Tregs (iTregs) from peripheral naive T cells are the two types of Foxp3⁺ Tregs. Both play a predominant role in the immune homeostasis maintenance. It has shown in humans that a lower level of Tregs is linked to airway inflammation [30,31]. There are three different types of mechanisms by which Tregs administer their immune suppressive function:

- 1 Treg cells’ suppressive activity may be aided by their direct association with DCs or T effector cells (Teff) cells. CTLA4, a co-stimulatory molecule present on the Treg cell surface interacts with surface ligands such as CD80 and CD86, of DCs and as a result, DC upregulates and secretes indoleamine 2, 3-dioxygenase, which gives a negative signal to Teff cells. Treg cells can modulate immune responses by inhibiting DC maturation, resulting in inefficient activation of Teff cells, by interacting with lymphocyte activation genes on Treg cells and MHC-II molecules on DCs. The interaction between Treg cells and DCs through neuropilin-1 will limit DC-Teff cell interactions. In addition, Treg cells expressing the serine protease granzyme and galectin-1 could cause Teff cell death or trigger a cell cycle arrest via direct interaction[31–34].
- 2 Secretion of immune-regulatory cytokines such as IL-10 and transforming growth factor-β (TGF-β) by Treg cells is another mechanism to induce immune suppression[35,36].
- 3 Treg cells’ suppressive action can also be mediated by destruction of target cell metabolism. The IL-2 receptor α-chain express on the surface of Treg cells facilitates IL-2 binding. Since IL-2 is needed for Teff cell proliferation and activation, IL-2 deficiency can cause Treg cells to suppress Teff cell growth. Furthermore, hydrolysis of ATP or ADP to cAMP followed by suppression of Teff cell function or DC maturation occurs due to the expression of CD39 and CD73 on Treg cell surface[31,37–39].

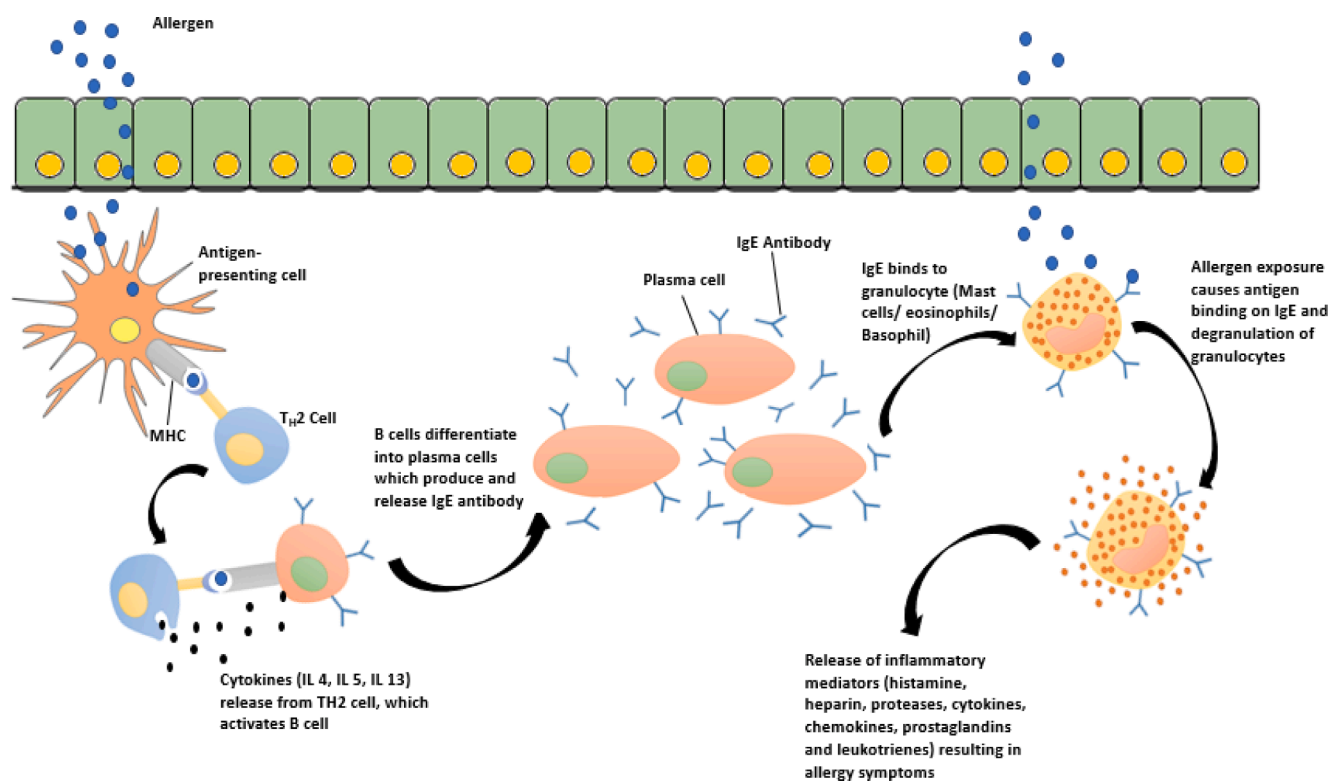


Fig. 2. Immunological mechanism of allergic inflammation. Antigen presenting cells capture allergens entered into the body and present it into CD4+T cells. Differentiation of CD4+T cells into Th2 cells mediate IgE synthesis by isotype switching of B cells and induce allergic airway inflammation.

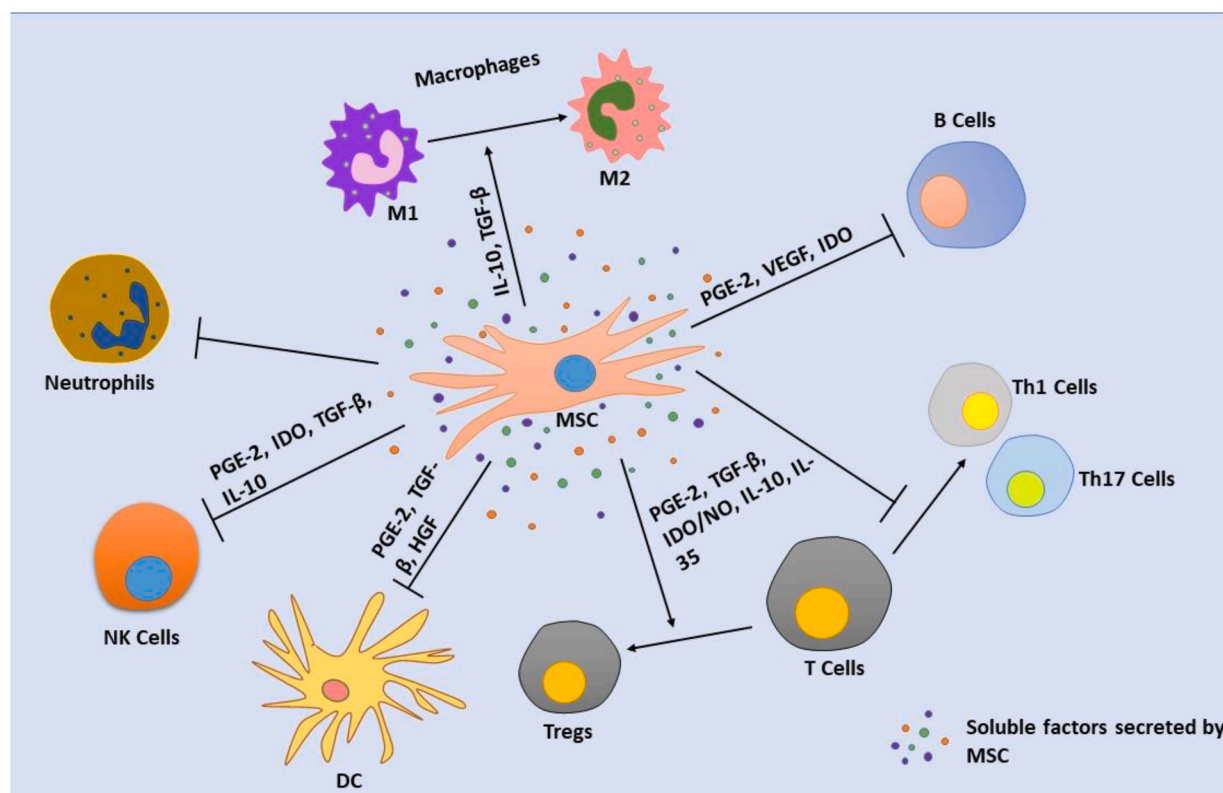


Fig. 3. Immunomodulation by MSCs. Immunomodulatory effects of MSCs, through cell-to-cell contact and soluble factors secretion, on immune cells. PGE2- Prostaglandin E₂; TGF-β- Transforming Growth Factor-β; HGF- Hepatocyte Growth Factor; VEGF- Vascular Endothelial Growth Factor; IDO- Indoleamine-pyrrole 2,3-dioxygenase; NO- Nitric Oxide; IL- Interleukin; DC- Dendritic Cells; NK- Natural Killer cells.

Table 3

Examples of clinical trials on allergic diseases using MSCs from different sources.

S No	Disease	Treatment	Route	Study Phase	Trial Identifier
1	Allergic Rhinitis	Umbilical cord blood MSCs	–	Phase 1	NCT05151133
2	Asthma	Bone marrow MSCs	Peripheral intravenous infusion	Phase 1	NCT03137199
3	Allergic rhinitis Chronic rhinosinusitis	Olfactory mucosa derived MSCs	–	Phase 1 and 2	NCT05167552
4	Atopic dermatitis	ADSTEM (Adult human mesenchymal stem cells)	–	Phase 1 Phase 2	NCT02888704 NCT04137562
5	Asthma	Trophic factors from umbilical cord mesenchymal stem cells	Intranasal	Phase 1 and 2	NCT02192736

4. Role of MSC in allergy treatment

MSCs has emerged as appealing therapeutic resources in transplantation, tissue regeneration, and autoimmune disorders due to their high potential expansion capability *ex vivo*, multilineage differentiation potential, and immune suppression functions[40]. In autoimmune and inflammation-related diseases such as inflammatory bowel disease, collagen-induced arthritis, multiple sclerosis, graft-versus-host disease, sepsis, and type I diabetes, MSCs therapy has shown greater potential in regulation of inflammatory responses. So far, the clinical data from several studies demonstrate the role of MSCs in ameliorating allergic conditions such as AA, AR, AD, and FA as well[41].

Immunomodulatory roles of MSCs through regulation of both innate and adaptive immunity are primarily achieved by interactions with immune cells such as T cells, B cells, natural killer (NK) cells, macrophages, dendritic cells, neutrophils, and monocytes via cell-to-cell contact and/ or paracrine interaction. The naïve T cell and memory T cell response to interact with APCs can be inhibited by MSCs by inducing the production of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which activates T cells and recruit leukocyte into the site of inflammation. The interaction of MSCs with CD4⁺ T cells causes the activation of Notch1/ FOXP3 pathway and results in the increase of CD4⁺CD25⁺FOXP3⁺ cell percentage. Further, high-level expression of cell adhesion molecules programmed death ligand 1 (PD-L1) and PD-L2 by some of the MSCs can suppress T cell proliferation by cell cycle arrest. Furthermore, prevention of B cell proliferation by blocking the cell cycle in G0/G1 phase through the activation of p38 mitogen-activated protein kinase (MAPK) pathways, and suppression of B cell's caspase-3 mediated apoptosis by upregulating vascular endothelial growth factor (VEGF) are also a part of the MSCs cell-to-cell contact to upregulate immunomodulatory mechanism [42,43].

Secretion of multifunctional molecules or soluble factors such as chemokines, cytokines and growth factors through different paracrine activities serves as another method to achieve immunomodulatory effect by MSCs. TGF- β 1, tumor necrosis factor- α (TNF- α), prostaglandin E₂ (PGE₂), interferon- γ (IFN- γ), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), indoleamine-pyrrole 2,3-dioxygenase (IDO), and nitric oxide are some of the examples of these soluble factors. Fig. 3 represents immune regulatory cells and the soluble factors involved in the immunomodulation mechanism by MSCs[42,43].

4.1. Clinical trials with MSCs on allergic diseases

Only few of the completed or ongoing clinical trials on AR therapy by

UC-MSCs and olfactory mucosa derived MSCs, asthma therapy by BM-MSCs and trophic factors from UC-MSCs, AD therapy by ADSTEM (Adult human mesenchymal stem cells) were reported (Table 3) (data obtained from ClinicalTrials.gov database). The details of clinical trials MSCs therapy are provided in detail as follows.

4.2. MSCs therapy in allergic airway diseases

MSCs has the potential to alleviate allergic airway inflammation and improve lung function. Administration of AT-MSCs in asthmatic mouse model significantly reduces levels of serum IgE and IgG, as well as Th2 cytokines (IL-4, IL-5, and IL-13), whereas the levels of IFN- γ , regulatory cytokines such as IL-10 and TGF- β and Treg cell ratio were significantly increased compared to untreated asthmatic mice[44]. Tonsil-derived MSCs (T-MSCs) administered on mouse model of AR significantly reduced allergic symptoms and inflammatory parameters such as eosinophil infiltration, serum IgE levels, Th2 cytokines, innate cytokines such as IL-25 and IL-33 and chemokines such as CCL11 and CCL24 [45].

A comparative study conducted by Ebrahim et al., in 2019 compared the immunomodulatory effects of AT-MSCs versus antileukotriene drug Montelukast. Substantial decrease in allergic symptoms, OVA-specific IgE, IgG1 and IgG2a, proinflammatory cytokines such as IL-4 and TNF- α , chemokine CCL11, VCAM-1 and enhanced PGE₂ production were observed in both AT-MSC and Montelukast treated rat models. Moreover, the AT-MSC treatment shows direct restoring effect on nasal mucosa structure [46].

The effect of ectomesenchymal stem cells (ECTO-MSCs) obtained from mice nasal mucosa on mice model of nasal mucosa inflammation were assessed in terms of inflammatory cells, immunoglobulins and cytokine production. ECTO-MSCs improved Th-1 immune response and suppressed Th-2 immune response to nasal inflammation by down-regulating IgE, IL-4, IL-5 and IL-10 and upregulating IgG2 and IFN- γ [47]. In another study, treatment with bone marrow-derived MSCs (BM-MSC) on asthma mouse model shows significant reduction of IgE levels, and cytokines such as IL-4, IL-5, IL-13, and IL-17 and increase in IL-10 and TGF- β levels in both serum and bronchoalveolar lavage fluid (BALF)[48].

These collective evidence from preclinical studies suggests the role of MSC based therapy in the allergic airway disease-animal models may offer an alternative, highly promising approach with more reliability and productivity to benefit patients with allergic airway disease who are unable to be cured with conventional therapies. However, there is still a long way from the current allergic airway disease-animal model trials to the final therapeutic implementation in human allergic airway disease therapy for a safer, efficient, and routine manner. In conclusion, whether MSC therapy would be a standalone treatment for human allergic airway diseases needs further investigation [23].

4.3. MSCs therapy in atopic dermatitis (AD)

Kim et al., in 2015 reported that the nucleotide binding oligomerization domain 2 (NOD2) activation in human umbilical cord blood-derived MSCs (hUCB-MSCs) shows an increased protective effect against AD in a mouse model and reduced infiltration and degranulation of mast cells (MCs). The regulation of disease manifestation reported due to increase in PGE₂ production through NOD2- cyclooxygenase-2 signalling pathway, which leads to suppression of MC degranulation. Furthermore IL-4 treatment on hUCB-MSCs upregulated the TGF- β 1 production, which shows to reduce MC degranulation by repressing high-affinity Fc ϵ R1 receptor expression (39). In the same mouse model, the therapeutic effect of administering human adipose tissue-derived MSCs (hAT-MSCs) shows cyclooxygenase-2 (COX-2) signalling mediated inhibition of B cell proliferation and maturation by significant downregulation of the serum IgE level[49]. The effective therapy of hUCB-MSCs pre-exposed to MC granules by suppressing the allergic immune response and stimulating the mechanism of the tissue

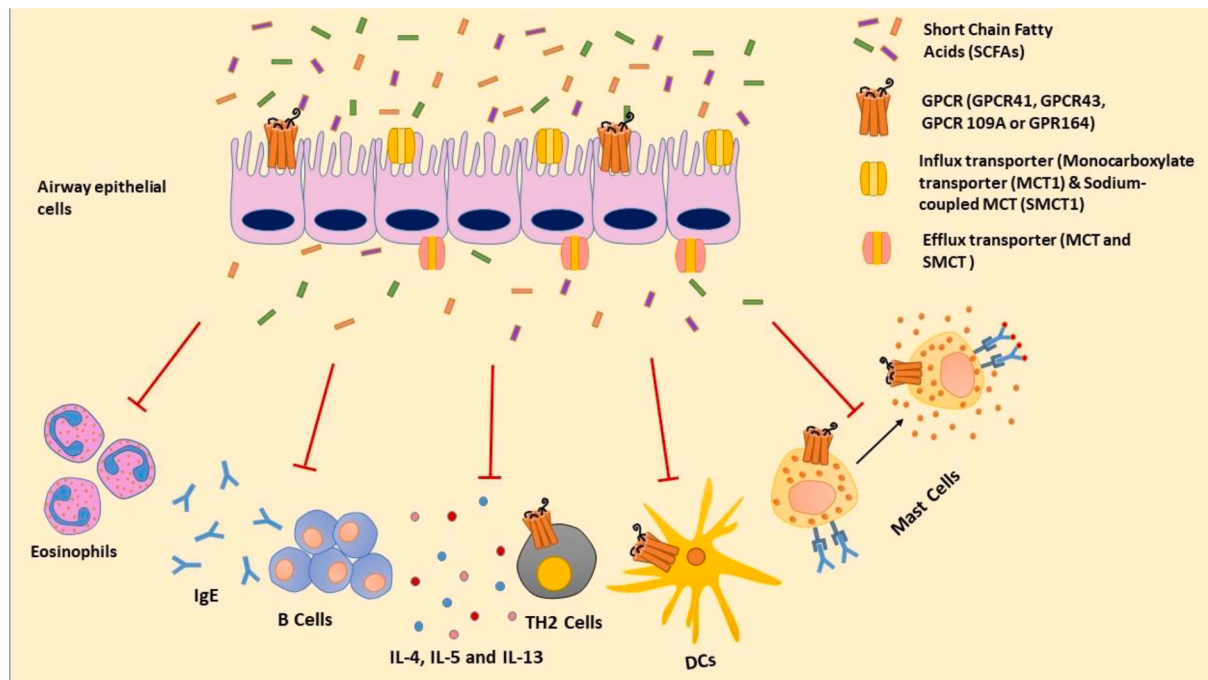


Fig. 4. Immune mechanisms by SCFAs in allergic airway diseases. SCFAs enters to the airway through GPCRs (G protein-coupled receptors) or monocarboxylate transporters (MCT1 and SMCT1). SCFAs inhibits DCs, Th2 cytokines mediated IgE synthesis by B cells, and activation of mast cells and eosinophils [65].

regeneration more effectively than naive cells have been observed in experimental AD, which suggests a potential improvement strategy for stem cell therapy[50].

To determine the safety and efficacy of hUCB-MSCs in AD treatment, a two phase clinical trial has been conducted by Kim et al., (2017) in moderate to severe AD patients. A marked improvement of AD symptoms such as downregulation of serum IgE levels, and blood eosinophils, 50% reduction in Eczema Area and Severity Index (EASI) and Severity Scoring for Atopic Dermatitis (SCORAD) scores, and 33% reduction in Investigator's Global assessment (IGA) score were resulted from the study without any serious adverse events. These findings indicate that infusing UCB-MSCs into patients with moderate-to-severe AD may be a potential treatment option[51].

4.4. MSCs therapy in food allergy

Food allergy incidence has risen gradually over the last few decades, and it makes immunotherapeutic treatment options more popular. Variable treatment efficacies, adverse allergic reactions, and clinical safety deficiencies make the clinical trials of immunotherapeutic treatment methods more difficult[52]. However, the use of MSCs in food allergy treatments are very limited. In one of the studies conducted by Yan et al., in 2018, human umbilical cord-derived MSCs (hUC-MSCs) considerably reduced the clinical indications of food allergy in an OVA-induced mouse model. Along with immunosuppressive activity such as decrease in the serum IgE levels, Th2 cell count, and Th2 cytokine level, hUC-MSCs have re-established the gut flora in the mice model [40]. To fully understand the effectiveness and underlying mechanisms of MSC therapy in food allergy, a variety of additional studies are required.

5. Interplay of microbial metabolites and MSCs in allergy: future outcomes

Gut microbiome has a beneficial impact on the biological processes of host by conversion of complex fibre-rich food to highly relevant metabolites. However, modern diet and lifestyle has led to dysbiosis of

the gut microbiome environment, which play a prominent role in the emergence of immune-mediated disorders including allergic diseases [53]. The primary metabolites generated by the gut microbiota are short-chain fatty acids (SCFAs), specifically acetate (C2), propionate (C3), and butyrate (C4) (respectively in a 60:20:20 ratio). SCFAs, produced by gut microbes by anaerobic fermentation of fibre-rich foods, have a multifaceted role in human metabolism, for instance regulation of hunger, lipid metabolism, and glucose homeostasis[54–56]. Further, G protein-coupled receptors (GPCRs) such as GPCR41 (also known as free fatty acid receptor-3 or FFAR3), GPCR43 (free fatty acid receptor-2 or FFAR2), GPCR109A and OR51E2 plays pivotal role in the SCFA-mediated signalling pathways of various cells and involved in the epigenetic modifications such as inhibition of histone deacetylase (HDAC) activity [54]. The binding of SCFAs on GPCRs are selective based on their length. GPCR43 prefers to bind with the shorter SCFAs such as acetate and propionate, whereas GPCR41 binds propionate, butyrate, and valerate preferentially with a lesser affinity for acetate. GPCRs signals through heterotrimeric G-proteins such as G_s , G_i/o , $G_q/11$, or $G_{12/13}$, however, the signalling mechanism occur upon the binding of SCFAs to GPCRs are poorly understood and needed more research attention in this specific area [57].

5.1. Short chain fatty acids in immunomodulation

Preclinical studies have reported that SCFAs activates DCs, which suppresses Th2 activation and ameliorate allergic inflammation[58,59]. A recent study reported that, acetate produced from a high-fibre diet by gut microbiome enhanced Treg cell mediated protection from asthma development in pregnant mice. Further, acetate induces FoxP3 promoter acetylation by inhibition of HDAC and enhance the number of Tregs and its function[60]. The effects of butyrate on allergic airway constriction were studied by Folkerts et Al. on allergen induced guinea pigs. The butyrate treatment shows prevention of histamine release and airway tightness in precision-cut lung slices (PCLS) of guinea pigs. Further, concentration-dependent inhibition of IgE- and non-IgE-mediated human and mouse mast cell degranulation were observed in the treatment with propionate and butyrate, but not with acetate. Interestingly,

Table 4
Short chain fatty acids and their effects in different preclinical studies.

S No	Short Chain Fatty Acid	Study Model	Result	Refs.
1	Acetate	Allergic airway disease	- Reduction in total inflammatory cells in BALF, Th2 cytokines (IL-4, IL-5, IL-13), IFN-γ and IgE - Enhanced T-regulatory cells and acetylation of Foxp3 promoter	[60]
2	a) Butyrate b) Butyrate and Propionate	ex vivo model of mast cell-mediated pathology	- Inhibition of allergen-induced histamine release and airway contraction - Downregulation of BTK, SYK and LAT (transducers of FcϵRI-mediated signals essential for mast cell activation) - Inhibition of mast cell degranulation (both human and mouse)	[61]
3	a) Butyrate, acetate, and propionate (BAP) b) Butyrate	Allergic lung inflammation	- Reduction in inflammatory cell's infiltration, IgE and IL-4 production - Attenuation of OVA-induced airway inflammation - Decreased DC function (ability to activate lymphocytes, trafficking mechanisms)	[63]
4	Butyrate	Allergic airway inflammation	- Reduction in allergen-induced airway and lung eosinophilia and type 2 cytokine levels - Improved airway hyperresponsiveness	[64]
5	Butyrate	Atopic dermatitis like skin inflammation	- Reduction in epidermal thickness, and IgE level - Enhanced terminal differentiation of epidermal keratinocytes - Strengthens skin barrier - Induction of mitochondria-dependent epidermal differentiation	[68]

this study reports inhibition of histone deacetylase by propionate and butyrate, and further shows that the mechanism occurs independent of GPR41, GPR43 and peroxisome proliferator-activated receptors (PPAR) [61,62]. Another study shows SCFA dietary intake leads to reduction in severe asthma symptoms, which was associated with the T cells and DCs in a vancomycin-treated mice. Vancomycin treatment depletes the level of SCFA level in mice [63]. Further, a study conducted by Theiler et al. (2019), shows that SCFAs deplete human eosinophils, and that interestingly butyrate ameliorates allergen-induced lung and airway eosinophilia, and Th2 cytokines [64]. Fig. 4 represents the mechanism of SCFAs on alleviation of allergic airway diseases.

Roduit C et al. (2019) provides evidence for significant correlations between infant's diet and SCFA levels. The analysis of fecal butyrate and propionate levels shows $\geq$ 95th percentile in one year old infants, and in a followed-up study of these children at the age of 3 and 6 years respectively showed no signs in the development of atopic sensitization and asthma symptoms. Further, food allergies and allergic rhinitis diagnosis were less common in children with the highest butyrate levels. In addition, mice administered with SCFAs orally experienced a marked reduction in the intensity of allergic airway inflammation [66]. A cohort

study of infants (6–24 months) shows lower levels of butyrate and valerate in transient AD subjects compared to healthy and persistent AD subjects [67]. Further, the direct role of butyrate in the regulation of mitochondrial metabolism of epidermal keratinocytes and the changes in the synthesis of essential structural elements has improved the function of skin barrier. Moreover, dietary fibres and SCFAs strengthen the epidermal barrier, which eventually prevents early allergic sensitivity and disease progression [68]. Different SCFAs and their role in the amelioration of allergic conditions are listed in Table 4.

In addition, studies confirm the role of SCFAs on alleviating food allergy. Tan J et al., in 2016 reported that, treatment of SCFAs such as acetate and butyrate reduce food-induced allergy in a mouse model by enhancing retinal dehydrogenase activity in CD103(+) dendritic cells. Mucosal CD103(+) DC has reported to induce tolerance to food antigens and promote differentiation of Treg cells [69].

Recently, studies have reported that SCFAs could regulate the regeneration and differentiation of MSCs. Moreover, effect of SCFAs on differentiation of dental MSCs into odontoblasts, and dentinogenic differentiation of dental MSCs by treatment in a dentinogenesis-delayed mice were reported by Ren et al., in 2020 [70]. The role of SCFAs in stimulating mitosis and differentiation of human neural progenitor cells and their influence on the expression of proliferation, apoptosis, and neurogenesis-related genes were showed by Yang L et al., in 2020 [71]. These recent reports hypothesize that SCFAs might be potentially interact with MSCs through GPCRs and alter its differentiation potential through either epigenetic modifications or regulation of other signalling mechanisms, which requires to be addressed in the future. The combination of SCFAs and MSCs in the treatment of allergy might be a better therapeutic option in alleviating incidences of allergic diseases (Fig. 5). The effects SCFAs on regeneration, cell survival and proliferation of MSCs and their utilization in therapeutic level has to be addressed in detail. In conclusion, the interplay between SCFAs and development and proliferation of MSCs might shed a new light on the treatment of various allergic disorders.

6. Conclusion

In the recent past, allergic disorders such as allergic-asthma, -rhinitis, -skin diseases and food allergies have gained global public health interest. MSCs acts in tissue repair mechanism due to their ability to self-renew and differentiate. Further, multilineage differentiation potential and immune suppression functions of MSCs shows therapeutic potential in transplantation, tissue regeneration, and autoimmune disorders. Based on numerous studies, the emergence of MSC as a viable therapeutic option over the current treatment approaches might lead to substantial improvement in the various allergic disorders. In addition, human gut microbial metabolites like SCFAs play significant role in the maintenance of human metabolism and homeostasis, which might influence the proliferation and differentiation potential of MSCs. Furthermore, G protein coupled receptor play prominent role in the SCFA-mediated signalling pathways and regulate cellular metabolisms through epigenetic modification by inhibiting histone deacetylase activity. Therefore, the combinatorial treatment of SCFA and MSCs might be a promising area of research for the development of better therapeutic option to allergic disordered. However, studies on therapeutic effectiveness of SCFAs and MSCs are limited. To conclude, evidence-based study for understanding the role of SCFAs and MSCs requires further investigation, followed by pharmacodynamic studies and subsequent clinical trials.

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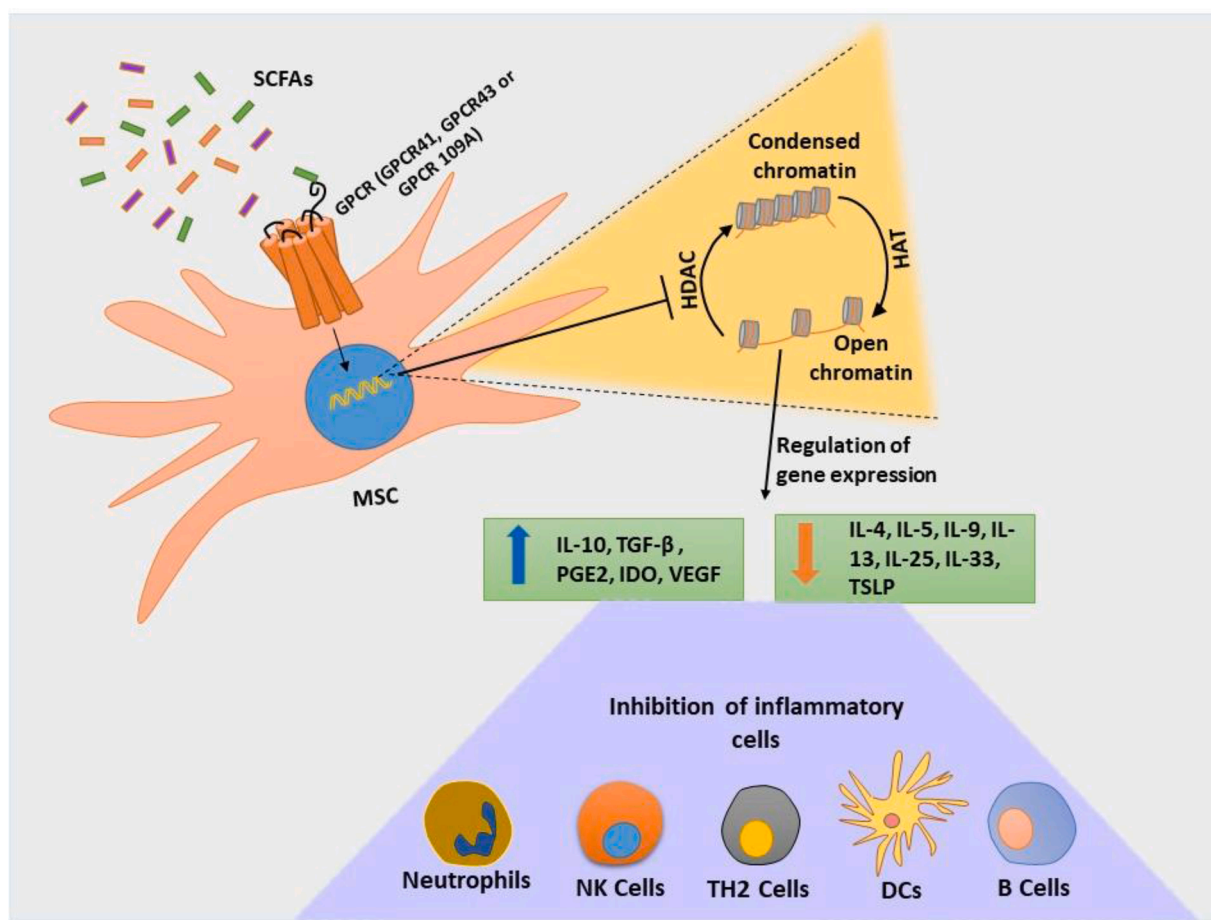


Fig. 5. SCFAs signalling in MSCs. SCFAs signals through GPCR in MSCs, which may cause epigenetic modifications and results in the synthesis of anti-inflammatory mediators and inhibition of allergic responses. GPCR- G protein-coupled receptors, HDAC- Histone deacetylase, HAT- Histone acetyl transferase.

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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