Psoriasis is immune-mediated chronic inflammatory disorder related to Th1 pattern, in which, 2 to 3% of white population worldwide have been affected. It is demonstrated that excessive secretion of pro-inflammatory cytokines such as IL-17A, TNF-α, IL-6, IFN-γ, IL-2 and IL-12 are involved in the immunopathogenesis and clinical manifestations of the disease. Common and previous therapeutics strategies have not been beneficial for all patients, yet. So, there is increasing considerations, leading basic medical scientists toward new directions. During last decade, exponential growth of immune based methods with easy accessibility, less morbidity and operatively yields in clinical trials, has opened a new window to novel clinical applications. Recently, approaches with immunological perspectives such as special immunobiomarkers recruitment, stem cells and vectors have been appropriated to psoriasis immunotherapy purposes. Various evidences suggest that interleukin-35 (IL-35) has important roles in immune system regulation as a promising anti-inflammatory agent. Also, it is demonstrated that Mesenchymal Stem Cells (MSCs) are able to hold anti-inflammatory and immunosuppressive properties, too. Here, we suggest a hypothetical cell and gene-based immunotherapy method that it could be advantageous for pro-inflammatory agents diminution in psoriatic patients. We hope that anti-inflammatory effects of IL-35 gene transfer via Adenoassociated virus as a vector by Bone Marrow derived-MSCs (BM-MSCs) in an Imiquimod-induced psoriasis-like mouse model, will probably be efficient in psoriasis global dilemma domination.

Keywords: Psoriasis; IL-35, Mesenchymal stem cell; Regenerative medicine; Clinical applications

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Introduction

Psoriasis is a chronic T-cell mediated inflammatory disorder characterized by excessive turnover of skin immune cells, infiltration of Dendritic Cells (DCs), monocytes and macrophages accompanied by pro-inflammatory cytokines and chemokines production, also uncontrolled keratinocyte proliferation in psoriasis lesions. As a skin autoimmune disorder with white scaled red plaques, 2-3% of the white population worldwide have been affected. With respect to severity of the clinical manifestations, they are divided into three degrees: mild (<2%), moderate (2–10%) and severe
IL-15, IL-6 and IL-20, which are dependent on the Th1 and Th17. However, pro-inflammatory cytokines secretion cannot be the main cause of psoriasis [4, 10]. Most recently, related regulatory cytokine, inhibiting vascular reaction in acute inflammation [18, 19], suppressing the activity of Th1 and cytokines, recent several studies by murine models of.

In psoriasis, the role of immune cells and inflammatory cytokines have been cleared. In the skin lesions of psoriasis, production and secretion of inflammatory cytokines can be noted Tumor Necrosis Factor-α (TNF-α), Interferon-γ (IFN-γ), Interleukin-1 (IL-1), IL-15, IL-6 and IL-20, which are dependent on the Th1 and Th17. However, Pro-inflammatory cytokines secretion cannot be the main cause of psoriasis. [4, 10]

Most recently, with the discovery of IL-23/Th17 axis, cytokine pattern of psoriasis has been shifted from T helper 1 (Th1) to Th17. IL-17A receptors expressed on keratinocytes, DCs, dermal fibroblasts and endothelial cells. Although the molecular mechanisms in psoriasis pathogenesis is still ambiguous, some studies have indicated that Th17 cells can play an effective role in the immunopathogenesis of psoriasis [2, 4, 11-13]. On the other hand, Methotrexate, Cyclosporine, Oral retinoid and three IL-17A inhibitors such as Secukinumab, Ixekizumab and Brodalumab are available to control psoriasis that have not been successful enough in psoriasis treatment [1, 4]. So, in order to focusing on immunopathogenesis of psoriasis, using cytokine activity antagonists can be an interesting method for the management of psoriasis [2]. With the discovery of effective immunological factors in the immunopathology of psoriasis and better optimistic understanding on the immunogenetics aspects of disease, there will be promising progresses for psoriasis solution Treg cells can suppress the proliferation of CD4 + and CD8 + T effector cells, also inhibit Th17 and Th1 activation. Th17 has an important pro-inflammatory activity in autoimmune disease exactly in psoriasis [14-16]. Other elements like B lymphocytes, as part of the adaptive immune system, regulate the immunity by negative and positive effects on it. B cell derived IL-10 and IL-35 are the cytokines that can protect against autoimmune disease [17]. Previous researches have shown that IL-35 is a novel immunosuppressor and anti-inflammatory cytokine (T cell related regulatory cytokine), inhibiting vascular reaction in acute inflammation [18, 19], suppressing the activity of Th1 and Th17, also making Treg improvement more vigorous [20, 21]. So we can comprehend that IL-35 can be the choice for controlling the autoimmune and inflammatory disease [15]. While IL-10 and TGF-β are the common immunosuppressive cytokines, recent several studies by murine models of

autoimmunity suggest that IL-35 may have potent effects in regulating immune reactivity via IL-10-dependent mechanisms [16, 22].

**IL-35 signaling pathway**

IL-35 is a heterodimer cytokine of α and β chain with two subunits (p35 and Epstein-Barr virus-induced gene 3 (EBI3) proteins) [9, 20, 23]. IL-35 is being expressed in non-stimulated murine Tregs and in stimulated human Tregs [16, 22]. It binds to it’s IL-12Rβ2 and IL-27Rα receptors, activating STAT3 and STAT1 transcription factors, respectively [15, 21, 23]. IL-27Ra is expressed in most cell types and IL-12Rβ2 is expressed on activated T, NK, B and to a lesser extent DCs [15, 16]. IL-35 function also leads to conversion of human B cells into Breg cells, suppressing CD4+ CD25+ T effector cells proliferation and promoting T regulatory cells expansion. This cytokine may be used to induce autologous Breg cells secreting IL-35 more and more. Healing the autoimmune and inflammatory disease is one of this cytokine’s effects. Since Breg cells and IL-10, suppress functions of immune system and IL-35 is enable to activate the Breg cells, so IL-35 may be subsequently involved in immune system suppressing [15, 16, 21, 23]. IL-35 enhances tumor progression by accumulation of myeloid cells, tumor angiogenesis leading to anti-tumor immune suppression, which is highlighted in pancreatic cancer cell lines by inhibiting apoptosis through rising the Bcl-2 and decreasing TRAILR1 [24, 25].

**The hypothesis**

As mentioned before, growing concerns about side effects and ineffectiveness of current therapeutics methods to improve psoriatic patients, made us to suggest a novel optimistic treatment approach for psoriatic patients.

In this hypothesis, a strategy for immune cell and gene-based therapy is suggested for psoriasis treatment. In last years, IL-35 has been introduced as a novel cytokine having potential to be a target for new therapies in different inflammatory, autoimmune and infectious disease [22]. So, IL-35 can be used as an immunomodulatory agent in the psoriasis gene therapy. Different stem cells such as Hematopoietic Stem Cells (HSCs) [26], MSCs and various vectors can be recruited for this kind of cell and gene-based therapy. One type of stem cells which have been focused, are MSC [27, 28]. MSCs originate from mesoderm, chondrocytes, osteocytes and adipocytes. They can differentiate into ectodermic and endodermic cells [29]. MSCs express CD29, CD44, CD73, CD90, and CD105 surface markers [30]. MSCs, as non-hematopoietic and multipotential stem cells, can be easily eradicated. Recent studies have shown that MSCs
migrate to the damaged tissues, regulating the immune responses by immunomodulatory properties induction and suppressing proinflammatory cytokines production (Th-1 related cytokines) [31-36]. Subsequently, they prevent the conversion of naive T cells to Th17 cells which is majorly involved in immunopathogenesis of psoriasis [19, 31, 32, 34]. There are various vectors for gene therapy that adenovirus, retrovirus, lentivirus, liposome, and Adeno-associated virus vectors are more fundamental [37]. Adeno-associated viruses are more suitable than other types of gene delivery vehicles due to their high transduction efficacy, expected ability and safety to reduce pro-inflammatory agents in psoriasis immunopathogenesis [14].

All in all, we propose to choose special immunoserobiomarkers, appropriate stem cells and vectors achieving immunotherapeutic goals for this disease through a
hypothetical cell and gene-based therapy method. No hesitate that it is needed a suitable animal model for pre-clinical studies of this hypothesis. According to current documents, Imiquimod (IMQ)-induced psoriasis-like mouse model can be served as a most similar model to human ones for inflammation induction capabilities. Given the above, we hope that the IL-35 gene delivery into the psoriasis IMQ mouse model via transduced BM-MSCs along with Adeno-associated virus vectors, can inhibit and deactivate the secretion of pro-inflammatory cytokines by regulating of immune system via possible pathways.

Evaluation of hypothesis

To perform the hypothesis, following experiments are proposed: (Fig.2) (1) In order to design basis of the hypothesis, initially a syngeneic IMQ-induced psoriasis-like mouse model should be made. Also, BM-MSCs and Adeno-associated virus (as a vector) are used for transduction of IL-35 gene into mentioned syngeneic psoriasis-like mice model \[^{10, 36, 38-41}\]. (2) In order to specify control group, they (n=10) contain psoriatic animals, which do not receive any injection. (3) In order to modelling of case
groups, they were characterized and divided into three categories in which 10 mice will be experimented, as below: 3a) Then, first case group receive transduced MSCs by IL-35 gene. 3b) Second case group receive AAV– IL-35 (AAV + IL-35 gene). 3c) Third case group receive MSCs and empty Adeno-associated virus vector. (4) Injection time consideration. (5) Isolation of MSCs from IMQ-induced mice bone marrow and subsequent culture. (6) In order to qualitatively and quantitatively certify the intended goals, several post laboratory actions are needed following: (6a) Enzyme-Linked Immunosorbent Assay (ELISA) for measurement of serum IL-35 secretion levels. (6b) Flowcytometry analysis for measurement the expression levels of some cell surface markers, intracellular molecules and intra cytoplasmic cytokines using fluorescence-conjugated antibodies [42, 43]. (6c) Real-time Polymerase Chain Reaction (Real-time PCR) assay for quantitative measurement expression of IL-35 gene. (6d) Histopathological tests for inflammation on psoriasis-like lesions, following to flowcytometry assessments for circulating levels of T cells and bead-based immunoassay for cytokines [4]. (7) Transfusion of mouse’s modified gene MSC to own blood stream.

Conclusions and discussion

In this hypothesis, given the importance of psoriasis challenge, the authors have tried to offer a specific and cost effective treatment with minimal side effects. Recent data show that imbalance of proinflammatory cytokines and chemokines exactly IL-17, may play a key role in psoriasis immunopathology [2, 11, 13]. Understanding of the immunological and molecular mechanisms of psoriasis microenvironment could be efficient for novel perspectives on cell and gene-based immunotherapies that have been appropriate strategy for psoriasis and various kinds of disorders such as behçet’s disease [34], hodgkin’s lymphoma [17], pancreatic cancer [41] and thyroid cancer [44]. New therapeutic strategies have been suggested for the psoriasis treatment in recent years. Anti-inflammatory effects of IL-35 have been expressed in inflammatory bowel disease models by reduction in Th1/Th17-associated transcription factors, attenuating collagen induced arthritis with IL-17 suppression and IL-10 secreting promotion [45-47]. Also IL-35 producing B cells can have a critical activity in autoimmune encephalomyelitis and autoimmune uveitis by inhibiting Th17, Th1 cells and Treg cells promoting [15]. IL-35, leads to reducing extreme immune system responses by inhibiting pro-inflammatory cytokines secretion and Th17/Th1 inhibition. IL-35 binds to it’s receptor and makes a complex, triggering the activation of STAT1 and STAT3 for regulating the immune system [15, 16, 18, 21, 48]. AAV can be an appropriate vector for transducting MSCs by IL-35 gene to reduce inflammatory responses [14]. Biologic immunotherapy and immunomodulatory therapy can be effective approach for treating psoriasis because of it’s immunopathology mechanisms [49, 50]. Because of multipotent, bystander, and immunomodulatory attributes of MSCs, and their immune reactions regulating activity by Th17 cells differentiation inhibiting, it is hoped that these cells have an effective role in preventing the progression of psoriasis by being injected in psoriasis IMQ-induced mice model [31, 35, 51, 52]. Given the above with focusing on the psoriasis immunopathogenic microenvironment, we can conclude that IL-35 gene delivery into mice genome could be a potentiated choice and suggestion for psoriatic treatment with use of MSCs and Adeno-associated viruses as vector, hope to act as a novel approach for treatment of psoriasis and according to this, also could be a reliance for clinicians concerns diminution.

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Conflicting interests

The authors have declared that no conflict of interests exist.

Author contributions

This study couldn’t be completed unless unsparing efforts and technical guides of Dr. Esmaeilzadeh for conceptualization qualifying, project administration, revision and definitive approval of final manuscript, sincere manner and precious guides of Miss Nazila Bahmaie for useful and comprehensive advices, scientific consultations on laboratory tests and article grammatically peer reviewing, and Azita Mohammadzadeh for main conceptualization and study design, collecting data, conclusive literature review, scientific writing (last original drafts preparation). All authors have approved the final version of the article.

Abbreviations

DCs: Dendritic cells; TNF-α: Tumor necrosis factor alpha; IFN-γ: Interferon gamma; IL-2: Interleukin 2; Th17: T helper 17; Treg: T regulatory; EBV: Epstein-Barr virus-induced gene3; BM-MSC: Bone marrow-mesenchymal stem cell; NKC: Natural killer cell; MSCs: Mesenchymal stem cells; AAV: Adeno-associated virus; IMQ: Imiquimod; ELISA: enzyme linked immunosorbent assay.
References


