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IL-25 Gene Delivery; Immunotherapeutic Approach for Cutaneous Squamous Cell Carcinoma

Mohammadzadeh A[1]; Bahmaie N[2,3,4]; Esmaeilzadeh A[5,6,7]*

[1]School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.

[2]Department of Allergy and Immunology, Faculty of Medicine, Graduate School of Health Science, Near East University (NEU), Nicosia, Northern Cyprus, Cyprus.

[3]Clinical Diagnosis Laboratory Expert, Private Baskent Hospital, Nicosia, Northern Cyprus, Cyprus.

[4]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran.

[5]Department of Immunology, Associate professor of Immunology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.

[6]Cancer Gene Therapy Research Center (CGRC), Zanjan University of Medical Sciences, Zanjan, Iran.

[7]Immunotherapy Research & Technology Group, Zanjan University of Medical Sciences, Zanjan, Iran.

***Corresponding Author(s): Abdolreza Esmaeilzadeh**

Department of Immunology, Associate professor of Immunology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.

Mail: a46reza@zums.ac.ir & a46reza@yahoo.com

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Abstract

Squamous Cell Carcinoma (SCC) is a type of cancer, in which, mainly, skin, mouth and esophagus are pronto being affected. As a specified type of this carcinoma, Cutaneous Squamous Cell Carcinoma (CSCC) is regarded as the second most common non-melanoma skin cancer. About 250,000 cases of CSCC, are diagnosed annually, meanwhile, statistics depict a dramatic upsurge that culminated to 5 million in 2011. Classical risk factors of CSCC comprising age, ethnicity, skin phototype, Ultraviolet (UV) exposure, and immunocompromised. In such a complex disease, what turn out to be controversial, are uncompleted recovery and remained side-effects by common and previous therapeutic methods. Resistance to the apoptosis process and oscillations in cytokine profile (TNF-α, IL-24, NF-κβ) occurred at the tumor microenvironment, which is emerging hallmarks in the immunopathogenesis of CSCC. T cell immunity interferes with programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) in tumor progression. Targeting cytokine profile and immune cascades seem to be an appropriate therapeutic and diagnostic modality for CSCC. These have been led to encourage basic clinical scientists to new horizons of clinical applications with immunological perspectives such as special immune biomarkers, stem cells, and vectors, which sound to be easily-accessible with diminished toxic effects in clinical trials. Numerous pieces of evidence propose that Interleukin-25 (IL-25) has important roles in immune system regulation and cell apoptosis.

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Likewise, it has been proved that Adeno-Associated Viruses (AAVs) as vector and Mesenchymal Stem Cells (MSCs) that work in a coordinated manner to handle anti-tumoral effects. Overall, here we suggest a hypothetical gene and cell-based immunotherapy approach for the pro-apoptotic effect of IL-25 gene delivery via AAV by MSCs in a syngeneic dimethylbenz [α]anthracene/12-o-tetradecanoylphorol-13-acetatete (DMBA/TPA) mouse model of CSCC. Studies have shed light on the importance of convincing implication, which could be a reliance for oncologists to tackle their obstacles in treatment and for patients to qualify their lifestyle.

Introduction

Squamous Cell Carcinoma (SCC) is a type of carcinoma that can be occurred in various organs of the body such as the skin, lips, mouth, esophagus, bladder, prostate, lung, vagina, and cervix. This accounts for a malignant tumor of squamous epithelium, in which, its invasive types can metastasize other organs [1]. Correspondingly, SCC can affect the skin tissue and create Cutaneous Squamous Cell Carcinoma (CSCC). CSCC is the second common Non-Melanoma Skin Carcinoma (NMSC) that includes 20% of all these types of skin cancers with harboring high mutation burdens and high mortality rate in those developing nodal metastasis [2]. About 250,000 cases of CSCC are diagnosed annually and the treated population can exist in. But, a constantly growing rate of progression should be taken into account, too. Its diagnosis trend, depending on frequent pathological biopsies and clinical tests, is complicated and always accompanied by several erroneous and inaccessible laboratories based diagnosis due to the similarity of a wide range of lesions related to this kind of cancer. In such complex disease, what turn out to be more controversial, are uncompleted recovery and remained side-effects by common and previous therapeutic methods as chemo or radiotherapy, bringing about problematic challenges and concerns [3-4]. CSCC is seen in unhealthy skin with chronic lesions such as lung-standing ulcers, sinus tracts, burns, and osteomyelitis. Also, it is observed in the skin of the patients who suffer from chronic inflammatory diseases as Discoid Lupus Erythematosus (DLE), Lichen planus, Lichen sclerosis, Lupus vulgaris, and dystrophic Epidermolysis Bullosa (EB) [5]. Age, UV radiation exposure, ethnicity, skin phototype, and immunocompromised can be known as classical risk factors for CSCC [6]. There are various etiologies considered for CSCC as predisposition determinants including host-derived immunity, environmental, genetic, and viral agents (HPV). From exterior agent's views, there are different factors with a deteriorating role in CSCC pathogenesis such as UV rays, X-rays, arsenic compounds, and other chemical products [7]. The main cause of CSCC is UV rays with a mutagenic impact that is exacerbated by increasing latitudes [2,8]. Seemingly, in the tumor microenvironment, some agents have been discovered, acting as agitator including fluctuation in several cytokine profiles (such as TNF-α, IL-24[9-10], NF-κβ [11]), alterations in apoptosis and cell morphology [12], tumor growth, chemotherapy resistance, immune escape, and tumor metastasis.

T cell immune response probably contributes to cancer cell progression in tumor site interfere with programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) that implicated in the anti-tumor immunity break down [6,13].

Resistance to apoptosis has been known as an important mechanism for tumor progression. Rel/NF-κβ signaling pathway is such an important network in apoptosis and cancer development of the skin [11]. To date, in order to diminish the gravity, many studies have focused on apoptosis in CSCC therapeutic methods: using apoptotic cells in anti-CSCC vaccines [14] and inhibiting anti-apoptotic factors (Flightless I (FLII)) [12]. Focusing on the above, the manipulation of apoptotic mechanisms could be such a helpful category in CSCC control. Mutations in the P53 gene of keratinocytes are caused by UV rays. Also, the inappropriate performance of the RAS gene produces tumoral phenotypes that some of these phenotypes are as follow: tolerance to apoptosis, tolerance to medications, and angiogenesis [15]. On the other hand, SCC produces small amounts of Bcl2, but the clinical results are more aggressive, evolution is faster and metastasis may occur [16]. MMP-9 is highly recognized in invasive and micro-invasive SCC. The progression of AKs to Bowen's disease and invasive SCC results in expression of mib-1 and P53 gene [5]. Inflammation, pro-inflammatory cytokines network, growth, and proliferation of keratinocytes can also be cited as etiologies for CSCC [17,18]. According to available reports, various cytokines constitute IFN-γ, IL-6, GM-CSF, and TGF-β are involved in the proliferation of skin keratinocytes and the pathogenesis of CSCC [19]. In the past, surgery was one of the most common therapeutic methods that have been noticeably used [20]. Also, different cytokines and medications have been used for treatment such as IL-24, later [10]. Fresolimumab is an anti-TGF-β monoclonal antibody, an immune suppressor, as another therapeutic method that is enumerated for CSCC [21]. All in all, identification of cytokine profile in the tumor microenvironment, their fluctuation, and changing is expected to facilitate CSCC diagnosis and treatment. Previous therapeutic methods faced with failure and have not been effective. Whereas optimistic, integrative and comprehensive methods have emerged and proposed cell and gene therapy by stem cells and vectors to revolutionize the existing therapeutic strategies [22-23]. To sum up, according to the mentioned cellular and molecular interactions involved in CSCC immunopathogenesis, authors optimistically offer gene and cell-based immunotherapeutic interventions using MSCs and IL-25 gene for physicians and specialists to accredit their orders for CSCC control and open glistening horizons to patients' lifestyle.

IL-25 Signaling Pathway

IL-25 (IL-17E) is one of the IL-17 family members that is secreted by Type 2 helper T cell (TH2) and mast cells [21]. It is worth mentioning that the IL-17E isoform of the IL-17 family is undetectable in non-lesional skin but it is plainly soared in lesional and psoriatic skin [24]. IL-17RB and IL-17RA are functional subunits of the IL-25 receptor that impose and trigger its immunobiological effects by this receptor [25-26]. MBP+ eosinophils, tryptase$^+$ mast cells, and CD31$^+$ endothelial cells are expressional cell sources of IL-25 and its receptor in bronchial submucosa and dermis. Hence, IL-25 can be placed at the central point of pro-inflammatory mediators released by affecting eosinophils [27].Chromosome 14 (14q 11-12) is the genomic position of IL-25. IL-25 binds to its receptors and induces activation of FADD and TRADD complexes, then causes caspase-mediated apoptosis by activation of caspases 8 and 3 and subsequently, induces apoptosis [28]. Also, IL-25 can be effective in different immunological conditions such as parasitic helminths infection [29], asthmatic respiratory disorders [30], atopical dermatitis, [31] and different kinds of tumors [32]. Regarded to recent studies and findings, IL-25 represents caspase-mediated apoptotic effects on pancreatic and breast tumors and devastates tumoral mass without affecting non-tumoral cells [28,33] (Figure 1).

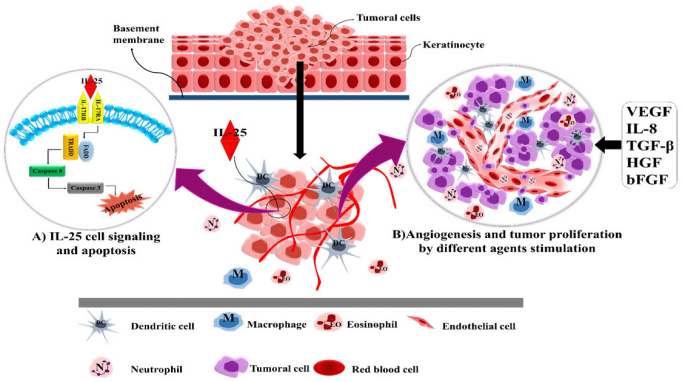

Figure1: Created by Dr. Esmaeilzadeh and et al.

Figure 1: IL-25 signaling pathway in CSCC microenvironment. *A)* IL-25 binding to its receptors, FADD and TRADD complexes activation, caspases 8 and 3 activation, caspase-mediated apoptosis. *B)* Angiogenesis and tumor proliferation by attenuation of apoptosis, metastasis and by stimulation of different agents (such as Basic Fibroblast Growth Factor (bFGF), Hematopoietic Growth Factor (HGF), Transforming Growth Factor beta-1 (TGF-β1), Vascular Endothelial Growth Factor and Interlukine-8 (IL-8)).

The Hypothesis

Due to uncompleted recovery by previous therapeutic methods, this hypothesis aims to investigate the pro-apoptotic effects of IL-25 gene delivery by MSCs for CSCC immunotherapy. IL-25 has been introduced as a novel cytokine having the potential to be a significant target for novel therapies in different cancers, respiratory airways allergy, lung tissue disorders, parasitic and infectious disease [29-32]. Different stem cells such as Hematopoietic Stem Cells (HSCs), Cancer Stem Cells (CSCs) [11], Chimeric Antigen Receptor (CAR) T cells [34-35], MSCs [36], and various vectors can be recruited for this kind of gene and cell-based immunotherapies. According to current studies [37], cell and gene-based immunotherapies using MSCs and different vehicles are known as a novel approach in cancer treatment. MSCs are responsible for growth, wound healing, and cell replacement during pathological conditions. So they have a major role in repairing tissue damage and degenerative diseases that makes them a perfect vector for keeping antitumor factors [22]. MSCs seem to play an anti-tumoral role via down-regulation of anti-apoptotic factor (Bcl-2) and the PI-3K/AKT pathway inhibition [38]. MSCs have anti-tumoral features and potentially immunosuppressive side effects that help them to regulate the immune system, inflammation and have pathologic and therapeutic role in the tumor microenvironment [39-40]. This type of stem cells is easy to culture, manipulate and isolate in ex vivo culture. Viral and non-viral vectors are recommended in gene and cell-based therapy of cancer [41-42]. Different types of viruses have been modified in gene therapy applications including Retrovirus, Adenovirus, Adeno-Associated Virus (AAV), Lentivirus, and Herpes Simplex Virus (HSV) [43-44]. We need a vector without causing immune or genotoxicity properties. AAV is a DNA virus nonpathogenic vector with respect to safety. It can be used in clinical applications as a suitable vector for gene therapy goals [22,45-47]. AAV can be used for delivering therapeutic transgenes in different categories: cytotoxic or suicide genes, anti-angiogenesis genes, tumor suppression, cytokines for stimulating the immune system, and anti-tumor gene [48]. Interleukins are key mediators for regulating inflammatory and immune responses in the cancer microenvironment and they can be beneficial therapeutic factors by using MSCs as delivery vehicles and AAVs as vectors for targeted immune gene and cell therapy of cancer [37]. According to the principles mentioned, tolerance/resistance to apoptosis is one of the pathogenesis basis in CSCC which can be a progressive pathway to recovery and treatment of the disease. Given that, IL-25 also has pro-apoptotic properties, many lines of evidence show that this cytokine can be valuable and effective in CSCC improvement and helping in the treatment of this kind of tumor. The overall purpose of this study is to provide a therapeutic idea for CSCC healing using IL-25, as the IL-25 gene is injected to a Dimethylbenz[α]Anthracene/12-o-Tetradecanoylphorol-13-Acetatete (DMBA/TPA) [18] CSCC animal model using gene therapy and cell therapy through genetically modified MSCs recruitment. This makes the malignant cells more exposed to IL-25 and induces apoptosis in tumor cells.

Evaluation of hypothesis

According to cases pointed earlier, we propose the following levels to test and assess the hypothesis (Figure 2).

1. Initially induction of syngeneic DMBA/TPA CSCC mouse model, the separation of MSCs from the bone marrow of mice model, and Adeno-Associated Virus (as a vector) for transduction of the IL-25 gene into the mentioned model. It is of high prominence to mention that all of the injections are done subcutaneously.

2. Control group, containing 10 syngeneic DMBA/TPA CSCC animal models (receive no injections).

3. Case groups, characterization of 30 mice into three categories, as below: 3a) Transduction of MSCs by IL-25 gene delivery into the First case group (n=10). 3b) AAV– IL-25 gene delivery into Second case group (n=10).

3c. MSCs and empty AAV vector into Third case group (n=10).

4. Isolation of MSCs: carrying out from DMBA/TPA mouse model bone marrow and subsequent culture [49].

5. Serum IL-25 levels detection by Enzyme-Linked Immunosorbent Assay (ELISA).

5a. Detecting apoptotic DNA fragmentation by Terminal deoxynucleotidyl Transferase UTP Nick End Labeling (TUNEL) assay [33].

5b. Measuring the expression levels of cell surface markers by Flow cytometry, intracellular molecules and intracytoplasmic cytokines using fluorescence-conjugated antibodies.

5c. IL-25 gene expression by Real-time Polymerase Chain Reaction (PCR).

6. Transfusion of mouse's modified gene MSC to own bloodstream.

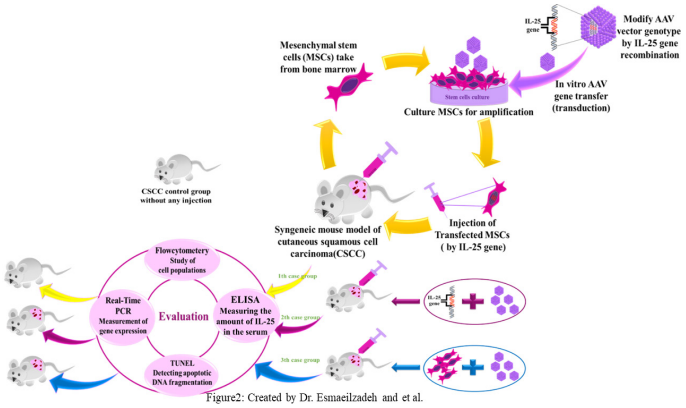

Figure2: Created by Dr. Esmaeilzadeh and et al.

Figure 2: Schematic design of hypothesis procedure. IL-25 as a pro apoptotic cytokine in gene and cell based immunotherapy of CSCC.

Discussion & conclusions

In this hypothesis, given the importance of CSCC, the authors have attempted to provide a better, more effective and comprehensive treatment with the least complications and side effects. Previous treatments such as chemotherapy, radiotherapy, monoclonal antibody and other methods did not have enough constructive effects on CSCC improvement. According to the molecular aspects related to the tumor microenvironment, defects in apoptosis mechanisms play important and deleterious roles in tumor pathogenesis, so induction of apoptosis processes can be a reasonable method for treatment of this malignancy [5]. IL-25 (IL-17E), via binding to its receptor, can induce apoptosis in cancerous cells without affecting nonmalignant cells. Also, IL-25/IL-25R signaling can induce a pro-inflammatory response in lung fibroblastic tissues. Pro-apoptotic impacts of IL-25 have been expressed in breast and pancreatic cancer by triggering activation of FADD and TRADD complex, then caspases 8 and 3 activations have occurred [28,33].Understanding of the immunological and molecular mechanisms of cancer microenvironment could be efficient for novel perspectives on gene and cell-based immunotherapies that have been an appropriate strategy for cancer and various kinds of disorders such as Psoriasis [47,50-52], Behcet's disease [53], Hodgkin's lymphoma [54], Pancreatic cancer [33], Prostate cancer [55] and Thyroid cancer [56]. There are different kinds of studies that have investigated cytokines effects on cancerous cells. IL-24 is one of the cytokines that has a pro-apoptotic effect on solid cancer cells specially CSCC. Its intra-tumoral injection with adenovirus vector was effective in previous studies [9-10]. IL-25 (IL-17E) had a pro-apoptotic role in the breast cancer microenvironment and affected tumoral cells without affecting nonmalignant cells [28] also it is an agent that has antitumor efficacy in melanoma, colon, lung, and pancreatic cancer [57]. Biologic immunotherapy and immunomodulatory therapy can be an effective approach for treating CSCC because of it's immunopathology mechanisms. Viruses commonly used in cancer gene therapies, AAVs have high transduction efficiency and Low immunogenicity [48]. They can be an appropriate and nonpathogenic vector for transducing MSCs by the IL-25 gene. Because of the multipotent, bystander and immunomodulatory properties of MSCs and their ability to repairing tissue damages and degenerative disease [22,58]. Recently the application of stem cell therapy and particularly MSCs transplantation for cancer therapy has become the center of focus among the investigations [37,59], it is hoped that these cells have an effective role in preventing the progression of CSCC by being injected in the CSCC mice model. The absence of apoptosis is one of the important mechanisms of cancerous cells. This challenge encourages basic clinical scientists to new directions as the appropriate generation of immunotherapeutic approaches. It seems that further investigations on IL-25 with its pro-apoptotic effects and IL-25/IL-25R signaling, may provide novel and promising therapeutic opportunities for the treatment of CSCC, be a reliance for oncologist's concerns diminution and also impose less expenditure for patients.

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Authorship Contributions

This hypothetic study couldn't be completed unless unsparing efforts and technical guides of Abdolreza Esmaeilzadeh for conceptualization qualifying, project administration, study design, scientific writing, theoretical and academic peer reviewing, definitive approval of the final manuscript, precious guides of Nazila Bahmaie for comprehensive advice on manuscript grammatically and Azita Mohammadzadeh for main conceptualization and collecting data, conclusive literature review, images designation, normative writing (last original drafts preparation). All authors have approved the final version of the article.

Ethical Consideration

Ethical issues (including plagiarism, double publication) have been completely observed by the authors.

References

1. Sakagami H. Apoptosis-inducing activity and tumor-specificity of antitumor agents against oral squamous cell carcinoma. Japanese Dental Science Review. 2010; 46: 173-187.
2. Li YY, Hanna GJ, Laga AC, Hadded RI, Lorch JH, et al. Genomic analysis of metastatic cutaneous squamous cell carcinoma. Clinical Cancer Research. 2015; 21: 1447-1456.
3. Su A, Ra S, Li X, Zhou J, Binder S. Differentiating cutaneous squamous cell carcinoma and pseudoepitheliomatous hyperplasia by multiplex qRT-PCR. Modern Pathology. 2013; 26: 1433-1437.
4. Guy Jr GP, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and Costs of Skin Cancer Treatment in the US, 2002-2006 and 2007-2011. American journal of preventive medicine. 2015; 48: 183-187.
5. Elmore S. Apoptosis: a review of programmed cell death. Toxicologic pathology. 2007; 35:495-516.
6. Bottomley MJ, Thomson J, Harwood C, Leigh I. The role of the immune system in cutaneous squamous cell carcinoma. International journal of molecular sciences. 2019; 20: 2009.
7. Joseph K. Non-Melanoma Skin Cancer-Overview. Current Cancer Therapy Reviews. 2016; 12: 142-151.
8. Tufaro AP, Chuang JC-M, Prasad N, Chuang A, Chuang TC, et al. Molecular markers in cutaneous squamous cell carcinoma. International journal of surgical oncology. 2011; 2011: 231475.
9. Gupta P, Su Z-z, Lebedeva IV, Sarkar D, Sauane M, et al. mda-7/IL-24: multifunctional cancer-specific apoptosis-inducing cytokine. Pharmacology & therapeutics. 2006; 111: 596-628.
10. Mitsui H, Suarez-Farinas M, Gulati N, Shah KR, Cannizzaro MV, et al. Gene expression profiling of the leading edge of cutaneous squamous cell carcinoma: IL-24-driven MMP-7. Journal of Investigative Dermatology. 2014; 134: 1418-1427.
11. van Hogerlinden M, Rozell BL, Ahrlund-Richter L, ToftgArd R. Squamous cell carcinomas and increased apoptosis in skin with inhibited Rel/nuclear factor-κB signaling. Cancer research. 1999; 59: 3299-3303.
12. Kopecki Z, Yang GN, Jackson JE, Melville EL, Calley MP, et al. Cytoskeletal protein Flightless I inhibits apoptosis, enhances tumor cell invasion and promotes cutaneous squamous cell carcinoma progression. Oncotarget. 2015; 6: 36426.
13. Xia A, Zhang Y, Jiang X, Tailang Y, Lu XJ. T cell dysfunction in cancer immunity and immunotherapy. Frontiers in immunology. 2019; 10: 1719.
14. Ji J, Fan Z, Zhou F, Wand X, Shi L, et al. Improvement of DC vaccine with ALA-PDT induced immunogenic apoptotic cells for skin squamous cell carcinoma. Oncotarget. 2015; 6: 17135-17146.
15. Ratushny V, Gober MD, Hick R, Ridky TW, Seykora JT. From kera-

tinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma. The Journal of clinical investigation. 2012; 122: 464-472.

16. Juba BA, Sovrea A, Crisan D, Melincovici C, Coneac A, et al. Apoptotic markers in photoinduced cutaneous carcinoma. Romanian Journal of Morphology and Embryology. 2013; 54(3 Suppl): 741-747.

17. Voiculescu V, Calenic B, Ghita M, Lupu M, Caruntu A, et al. From normal skin to squamous cell carcinoma: A quest for novel biomarkers. Disease markers. 2016; 2016: 4517492.

18. Huang PY, Balmain A. Modeling cutaneous squamous carcinoma development in the mouse. Cold Spring Harbor perspectives in medicine. 2014; 4: a013623.

19. Yamada S, Jinnin M, Kajihara I, Nakashima T, Aoi J, et al. Cytokine expression profiles in the sera of cutaneous squamous cell carcinoma patients. Drug discoveries & therapeutics. 2016; 10: 172-176.

20. Neville JA, Welch E, Leffell DJ. Management of nonmelanoma skin cancer in 2007. Nature clinical practice Oncology. 2007; 4: 462-469.

21. Lacouture ME, Morris JC, Lawrence DP, Tan AR, Olencki TE, et al. Cutaneous keratoacanthomas/squamous cell carcinomas associated with neutralization of transforming growth factor β by the monoclonal antibody fresolimumab (GC1008). Cancer Immunology, Immunotherapy. 2015; 64: 437-446.

22. Esmaeilzadeh A, Farshbaf A. Mesenchymal stem cell as a vector for gene and cell therapy strategies. Glob J Stem Cell Biol Transp. 2015; 6: 17-18.

23. Hengge U. Gene therapy progress and prospects: the skin-easily accessible, but still far away. Gene therapy. 2006; 13: 1555-1563.

24. Johansen C, Usher P, Kjellerup R, Lundsgaard D, Iversen L, et al. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. British Journal of Dermatology. 2009; 160: 319-324.

25. Tang W, Smith SG, Beaudin S, Dua B, Howie K, et al. IL-25 and IL-25 receptor expression on eosinophils from subjects with allergic asthma. International archives of allergy and immunology. 2014; 163: 5-10.

26. Petersen BC, Budelsky AL, Baptist AP, Schaller MA, Lukacs NW. Interleukin-25 induces type 2 cytokine production in a steroid-resistant interleukin-17RB+ myeloid population that exacerbates asthmatic pathology. Nature medicine. 2012; 18: 751-758.

27. Corrigan CJ, Wang W, Meng Q, Fang C, Eid G, et al. Allergen-induced expression of IL-25 and IL-25 receptor in atopic asthmatic airways and late-phase cutaneous responses. Journal of Allergy and Clinical Immunology. 2011; 128: 116-124.

28. Furuta S, Jeng Y-M, Zhou L, Huang L, Kuhn I, et al. IL-25 causes apoptosis of IL-25R-expressing breast cancer cells without toxicity to nonmalignant cells. Science translational medicine. 2011; 3: 78ra31.

29. Angkasekwinai P, Sodthawon W, Jeerawattanawart S, Hansakon A, Pattanapanyasat K, et al. ILC2s activated by IL-25 promote antigen-specific Th2 and Th9 functions that contribute to the control of Trichinella spiralis infection. PloS one. 2017; 12: e0184684.

30. Beale J, Jayaraman A, Jackson DJ, Macintyre J, Edwards MR, et al. Rhinovirus-induced IL-25 in asthma exacerbation drives type 2 immunity and allergic pulmonary inflammation. Science translational medicine. 2014; 6: 256ra134-256ra134.

31. Salimi M, Barlow JL, Saunders SP, Xue L, Owsiak DG, et al. A role for IL-25 and IL-33–driven type-2 innate lymphoid cells in atopic dermatitis. Journal of Experimental Medicine. 2013; 210: 2939-2950.

32. Xu M, Dong C. IL-25 in allergic inflammation. Immunological reviews. 2017; 278: 185-191.

33. Piri Z, Esmaeilzadeh A, Hajikhanmirzaei M. Interleukin-25 as a candidate gene in immunogene therapy of pancreatic cancer. Journal of Medical Hypotheses and Ideas. 2012; 6: 75-79.

34. Lim WA, June CH. The principles of engineering immune cells to treat cancer. Cell. 2017; 168: 724-740.

35. Elahi R, Khosh E, Tahmasebi S, Esmaeilzadeh A. Immune Cell Hacking: Challenges and Clinical Approaches to Create Smarter Generations of Chimeric Antigen Receptor T Cells. Frontiers in immunology. 2018; 9: 1717.

36. Esmaeilzadeh A, Farshbaf A, Erfanmanesh M. Autologous Hematopoietic Stem Cells transplantation and genetic modification of CCR5 m303/m303 mutant patient for HIV/AIDS. Medical hypotheses. 2015; 84: 216-218.

37. Marofi F, Vahedi G, Biglari A, Esmaeilzadeh A, Athari SS. Mesenchymal stromal/stem cells: a new era in the cell-based targeted gene therapy of cancer. Frontiers in Immunology. 2017; 8: 1770.

38. Stagg J. Mesenchymal stem cells in cancer. Stem cell reviews. 2008; 4: 119-124.

39. Wang Y, Chen X, Cao W, Shi Y. Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. Nature immunology. 2014; 15: 1009.

40. Ma S, Xie N, Li W, Yuan B, Shi Y, et al. Immunobiology of mesenchymal stem cells. Cell death and differentiation. 2014; 21: 216.

41. Yin H, Kanasty RL, Eltoukhy AA, Vegas AJ, Dorkin JR, et al. Non-viral vectors for gene-based therapy. Nature Reviews Genetics. 2014; 15: 541-555.

42. Lichty BD, Breitbach CJ, Stojdl DF, Bell JC. Going viral with cancer immunotherapy. Nature Reviews Cancer. 2014; 14: 559-567.

43. Kay MA, Glorioso JC, Naldini L. Viral vectors for gene therapy: the art of turning infectious agents into vehicles of therapeutics. Nature medicine. 2001; 7: 33-40.

44. Thomas CE, Ehrhardt A, Kay MA. Progress and problems with the use of viral vectors for gene therapy. Nature Reviews Genetics. 2003; 4: 346-358.

45. Luo J, Luo Y, Sun J, Jhou Y, Zhang Y, et al. Adeno-associated virus-mediated cancer gene therapy: current status. Cancer letters. 2015; 356: 347-356.

46. Tomar RS, Matta H, Chaudhary PM. Use of adeno-associated viral vector for delivery of small interfering RNA. Oncogene. 2003; 22: 5712-5715.

47. Esmaeilzadeh A, Mohammadzadeh A, Bahmaie N. New Generation of Promising Immunotherapeutics Approaches for Psoriasis Dilemma; IL-35 Gene as a Potentiated Candidate. Inflammation and Cell Signaling. 2018; 5.

48. Santiago-Ortiz JL, Schaffer DV. Adeno-Associated Virus (AAV) vectors in cancer gene therapy. Journal of Controlled Release. 2016; 240: 287-301.

49. Baghaei K, Hashemi SM, Tokhanbigli S, Rad AA, Aghdaei HA, et al. Isolation, differentiation, and characterization of mesenchymal stem cells from human bone marrow. Gastroenterology and Hepatology from bed to bench. 2017; 10: 208-213.

50. Wang Y, Mao Y, Zhang J, Shi G, Chang L, et al. IL-35 recombinant protein reverses inflammatory bowel disease and psoriasis through regulation of inflammatory cytokines and immune cells. Journal of cellular and molecular medicine. 2018; 22: 1014-1025.

51. Li J, Liu L, Rui W, Li X, Xuan D, et al. New interleukins in psoriasis and psoriatic arthritis patients: the possible roles of interleukin-33 to interleukin-38 in disease activities and bone erosions. Dermatology. 2017; 233: 37-46.

52. Zhang J, Lin Y, Li C, Zhang X, Cheng L, et al. IL-35 decelerates the inflammatory process by regulating inflammatory cytokine secretion and M1/M2 macrophage ratio in psoriasis. The Journal of Immunology. 2016; 197: 2131-2144.

53. Mazaheri T, Esmaeilzadeh A, Mirzaei MHK. Introducing the immunomodulatory effects of mesenchymal stem cells in an experimental model of Behcet's disease. Journal of Medical Hypotheses and Ideas. 2012; 6: 23-27.

54. Manesh ME, Esmaeilzadeh A, Mirzaei MH. IL-24: A novel gene therapy candidate for immune system upregulation in Hodgkin's lymphoma. Journal of Medical Hypotheses and Ideas. 2015; 9: 61-66.

55. Chatrabnous N, Ghaderi A, Ariafar A, Razeghinia MS, Nemati M, et al. Serum concentration of interleukin-35 and its association with tumor stages and FOXP3 gene polymorphism in patients with prostate cancer. Cytokine. 2018; 113: 221-227.

56. Mirzaei MH, Esmaeilzadeh A. Overexpression of MDA-7/IL-24 as an anticancer cytokine in gene therapy of thyroid carcinoma. Journal of Medical Hypotheses and Ideas. 2014; 8: 7-13.

57. Benatar T, Cao MY, Lee Y, Lightfoot J, Feng N, et al. IL-17E, a proinflammatory cytokine, has antitumor efficacy against several tumor types in vivo. Cancer Immunology, Immunotherapy. 2010; 59: 805-817.

58. Esmaeilzadeh A, Reyhani E, Bahmaie N. Immunobiology of Dental Tissue-Derived Stem Cells; As a Potentiated Candidate for Cell Therapy. trials. 3: 28-29.

59. Moghadam S, Erfanmanesh M, Esmaeilzadeh A. Interleukin 35 and Hepatocyte Growth Factor; as a novel combined immune gene therapy for Multiple Sclerosis disease. Medical hypotheses. 2017; 109: 102-105.