



Evolution in Immune Gene Therapy of Glioblastoma; Interleukin-37 as a Novel Candidate

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Abstract

Glioblastoma (GBM), as grade IV of glioma in nervous system, is one of the most invasive cancers which its survival rate is about 12 to 15 months. In spite of main therapeutics or preventive procedures such as surgery, radiotherapy and chemotherapy for this aggressive tumor, there is no confirmed explicit advancement. Thus, nowadays more investigations on appropriation of efficient strategies for those kinds of tumors, is of particular importance. Fortunately, exponential growth of target therapies especially with immunological perspectives has opened glittering windows to our significant challenges. One of these lately a novel method is immune gene therapy in which, cytokine genes majorly is being administrated in order to immune regulation. Interleukin-37 (IL-37) is one of those cytokines which displays anti-tumor function and has been focused in attraction of basic scientist's attention. Here, we propose that it could be rational to investigate anti-tumoral role of IL-37 by utilizing CNS-1 cell line in GBM-induced microenvironment of a syngeneic Lewis rat in order to diminish patients' sufferings, oncologist's considerations and exorbitant social expenditures.

Keywords: Glioblastoma; Interleukin-37; Immune gene therapy; Anti-angiogenesis; Immune regulation; Immunotherapy

Glioma

As one of the nervous system malignancies, glioma which is derived from glial or its precursor cells [1], involves in 81% of malignant brain tumors [2]. The most common symptoms that depend on the site of the tumor in nervous system include in: headache, seizure, cognitive disorders, imbalance and incontinency [3]. Common types of glioma consist of: Astrocytoma, Oligodendroglioma and Ependymoma that are categorized as follows: 1. Low grade (I-II) 2. High grade (III-IV) and the last one (grade IV), is being considered as Glioblastoma Multiform (GBM) [1,4].

Despite the identical histology features that they have, GBM is the most devastating type [5-7]. The survival rate of mentioned tumor is less than 10% in five years and the average survival rate is almost 12 to 15 months [5,7,8].

Glioma treatment challenges

The main therapeutics or preventive procedures for this aggressive tumor are: surgical resections, followed by radiotherapy and/or chemotherapy, radio surgery, corticosteroids, and anti angiogenic agents administration [7-9]. In spite of progressions that have been widely done in GBM treatment, the current treatment protocols could not be able to improve the survival rate, yet [9].

Shortly after surgical resection, rapid proliferation of the tumor will be appeared [10]. Glioma microenvironment is under some circumstances, aiding to heterogeneous phenotype manifestation of the tumor [11-13]; All in all, these will lead the microenvironment toward being resistant to treatment procedures and therapy processes will be more challenging [12].

Nowadays, it is demonstrated that novel gene based therapeutic processes have been successful for cancer worldwide dilemma. They are examined to improve the GBM treatment's outcome and according to recent studies, focus on immune gene therapy is considered as one of the efficient therapeutic procedures for cancers [14-21].

Glioma microenvironment

The tumor site is surrounded by Blood-Brain Barriers (BBBs) in nervous system of human body which will be as an obstacle, limiting the distribution and delivery of pharmaceutical agents to the

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tumoral space [9,10,13,22,23].

Most existing cells in GBM microenvironment are: a) Dendritic Cells (DCs) as Antigen Presenter Cells (APC) to T lymphocytes that settled in brain parenchyma and cervical lymph nodes, and b) immune cells which migrate to tumor localized site by chemotaxis [9].

Immuno pathophysiology of the GBM

Altogether, microenvironment that is developed around the tumor mass is featured immunosuppressive due to production of some suppressor cytokines [9,24,25].

Increase in production of immunosuppressive cytokines: As mentioned before, GBM microenvironment is immunosuppressive and the major reason is production of some cytokines such as: Interleukin-6 (IL-6) (from source of T helper 2), Interleukin-10 (IL-10), Transforming Growth Factor Beta (TGF-B) and Prostaglandin E₂ (PGE₂) [9,23-25].

TGF-B does its immuno suppression action, as follows; [9,25]

1. Blocking proliferation of T lymphocytes.
2. Inhibition of Interlekin-2 (IL-2) production.
3. Blocking of Natural Killer Cells (NK) activities.
4. Promotion of T regulatory cells.

It is worth saying that the dominant iso form in GBM microenvironment is TGF-B2 which stimulates tumor cells proliferation [26].

IL-10 is a cytokine that its level is high in many neoplasms such as GBM, this cytokine carries out its immunosuppressive activity according to below [9].

1. Amplification in production of Interferon Gamma (IFN- γ) and Tumor Necrosis Factor alpha (TNF- α).
2. Reduction in the expression of Major Histo Compatibility (MHC) class II molecules in monocytes.

Reduction of T cells' activities: The tumor microenvironment enhances T cell's tendency toward apoptosis. First of all, the interaction between CD70 and CD27 which is TNF receptor will increase the amount of T cell's apoptosis. Secondly, some immune inhibitor ligands will develop apoptosis rate; one of them is Programmed Cell Death Protein-1 ligand (PD-L1) which is highly expressed in such a tumor microenvironment. The other ligand is FasL that it recruits apoptosis processes as well [9].

Increase in activation of T regulatory cells (Tregs): Tregs are actually immune response modulators. FOXP3 is one of the essential surface marker in Tregs which is expressed increasingly in such a microenvironment; leading to more immuno suppressory state [9,24,27].

Hypoxia: Hypoxia induction is result of improper neovascularization and excessive usage of oxygen by tumor cells. Furthermore, this condition itself will enhances the expression of genes involving in tumor growth via Signal Transducer and Activator of Transcription 3 (STAT3) pathway; this pathway is an immunosuppressive one that will amplifies activation of Hypoxia Induced Factor-1 α (HIF-1 α) which enhances Tregs activation and Vascular Endothelial Growth Factor (VEGF) production [9,24].

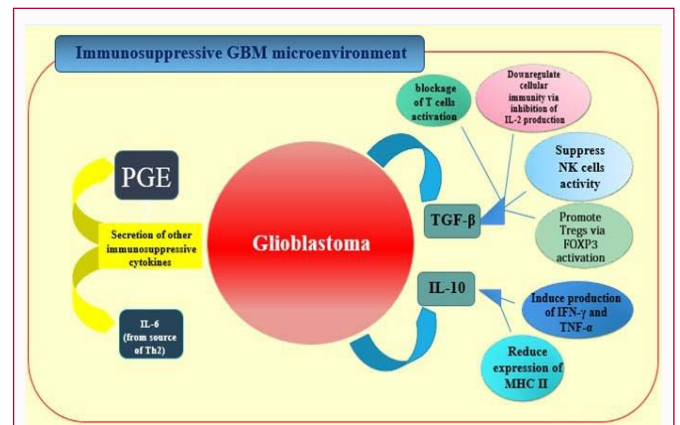


Figure 1: Glioblastoma microenvironment [17].

Abbreviations: TGF-B: Transforming Growth Factor Beta; IL-2: Interlekin-2; NK: Natural Killer Cells; Tregs: T-Regulatory Cells; IL-10: Interleukin-10; IFN- γ : Interferon Gamma; TNF- α : Tumor Necrosis Factor Alpha; PGE2: Prostaglandin E₂; I-6: Interleukin-6; Th2: T helper 2; FOXP3: Forkhead Box Protein P3

Furthermore, hypoxic condition forces brain macrophages conversion into Tumor-Associated Macrophages (TAMs) which is tumor supportive phenotype (M₂) [9,25].

All in all, GBM environment is an area that induces an immunosuppressive state which increases T lymphocytes tendency to apoptosis [9,24], and promotes Tregs [24,27] (Figure 1).

Interleukin-37 (IL-37)

At first stage, Interleukin-37 (IL-37) was discovered in 2000 in silico research from gene data banks [28,29]. IL-37 gene has been located on long arm of chromosome 2 (2q) [29-31].

This cytokine is categorized in interleukin-1 family which is member 7 (IL-1F7) [29,32], IL-1 family which has some sub families according to their precursor's length [29], play a role in relation to immune system function, some members are important, in terms of angiogenesis and inflammation processes [31].

In the following, the name of the cytokine was changed from IL1F7 to IL-37, in 2010 [31].

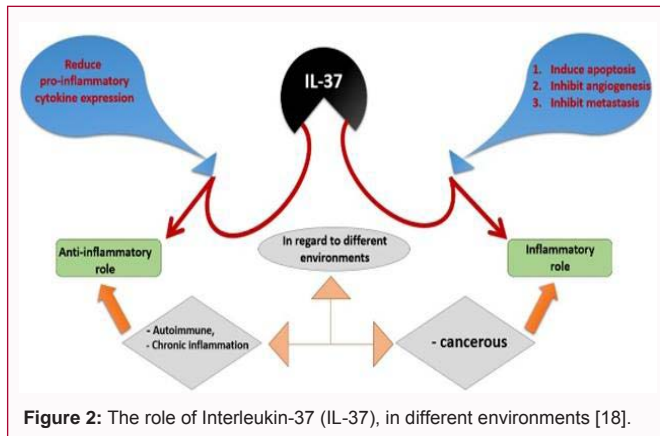
IL-37 have 5 isoforms (IL-37 a-e) [28-30,33,34], the active forms are a, b and d. thus, c and e isoforms are inactive forms due to not having the entire IL-1 sequence [33,34].

Each iso form is expressed by various tissues [29,33,35], however just IL-37 a which has 30 kDa mass weight is expressed in brain [33].

The function of IL-37

Many studies have been carried out since its recent discovery, to realize its function in immune system [29]. It was predicted that, this cytokine may set a new pattern for alignment of inflammation [33].

IL-37 and IL-18 are structurally similar to each other [29], therefore, IL-37 binds to IL-18 receptor α chain (IL-18R α) and conduct its anti-inflammatory role *via* effect on this receptor [28,29,33,34,36]. Furthermore, IL-37 binds to an orphan receptor that named Single Ig IL-1-Related Receptor (SIFGIRR) OR IL-1R8 in order to act the anti-inflammatory role [28,29,33,34,36]. Thus, Triad complex of IL-37/IL-18R α /IL-1R8 lead to suppress inflammation *via* reduction of pro-inflammatory cytokine expression (TNF, IL-1 β) [29,33,36]. Actually, the anti-inflammatory role is done *via* increasing



the activation of STAT3 and Phosphatase and Tensin homolog (PTEN) signaling pathways and also, inhibiting the transcription of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) which affects the production of pro-inflammatory cytokines [29,32]. IL-37 acts as a link between innate and adaptive immunity, which complicates its function in different environments [37,38].

In fact, IL-37 as a key regulator cytokine has duality function which depends on the IL-37 cytokine condition. It has been assessed that, IL-37 might have an anti-inflammatory role in sphere of auto immune diseases and chronic inflammation [28,29,33-36]. On the other side, there are some unknown issues about its anti-cancerous role [29]; It is supposed that this cytokine has a protective role in tumor progression [28,29,34,35] (Figure 2). There are some publications and documentations which have been done by medical researchers in various aspects on the role of IL-37, such as fibro sarcoma, hepatocellular carcinoma, and cervical cancer [29,31,35]. In regards to accumulated evidences, IL-37 may be a novel candidate for tumor immune gene therapy [30,31,34,35,37].

Hypothesis

Glioblastoma (GBM) is one of the most invasive tumors of nervous system's malignancies. Actually, its micro environment is a heterogeneous one and makes it resistant to treatment. Despite the routine treatment strategies such as surgery, chemotherapy and radiotherapy, its survival rate has not increased. So, demands for figuring out new treatment protocols have been risen and progression in these fields is instantly needed. Here, we suggest inducing the expression of IL-37 gene in the CNS-1 cell line in GBM-induced microenvironment of a syngeneic Lewis rat. We expect that IL-37 can improve immune condition in GBM microenvironment through induction of tumor cells apoptosis and angiogenesis inhibition and leading to metastasis diminution.

Evaluation of the hypothesis

To evaluate this hypothesis that is combination of gene therapy and animal model usage, first of all, culturing the CNS-1 cell line is demanded. Then, murine IL-37 gene accompanied by adenovirus vectors is being delivered in cell cultures, respectively. Therefore, transected cells will be screened from untransfected cells.

The animal model which has been used in this tumor is Lewis rat that syngeneic transport will be conducted. In order to create a GBM tumor in these rats, CNS-1 cell line accompanied by Methyl Nitrous Urea (MNU) is being injected in order to place the tumor in rat's brain; furthermore, it will be injected weekly and within six months

[40,41].

The injections will be done through Bregma regarding specified axis. Also, the utilization of stereotaxic method for giving accurate injections is suggested to prevent the obstacle cause of blood-brain barrier function, actually stereotaxic method has caused fewer invasions and will be more trustable to penetrate the tumor microenvironment.

We need four groups Lewis rats for administration:

First group: is a control group, and have not given any injections.

Second group: Only CNS-1 cell line will be injected, therefore they will be checked through biopsy whether GBM has been induced or not.

Third group: They will be delivered CNS-1 cell line with plasmid vector to realize whether latter transformation is related to vectors or not.

Fourth group: They will be delivered CNS-1 cell line accompanied by vector in which murine IL-37 gene was introduced (Figure 3).

In order to assess the goal of the hypotheses, the laboratory tests will be used as follows;

Real Time PCR: Checking murine IL-37 gene expression for transportation assurance.

ELISA (Enzyme-Linked Immunosorbent Assay): Checking the amount of cytokine production in tumor microenvironment.

TUNEL (Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling) assay: Checking the apoptosis rate of tumor cells in microenvironment.

At the end, utilization of imaging tests such as Brain Computerized Tomography (CT), Magnetic Resonance Imaging (MRI) will be provided to check if there is any diminution in tumor size or not.

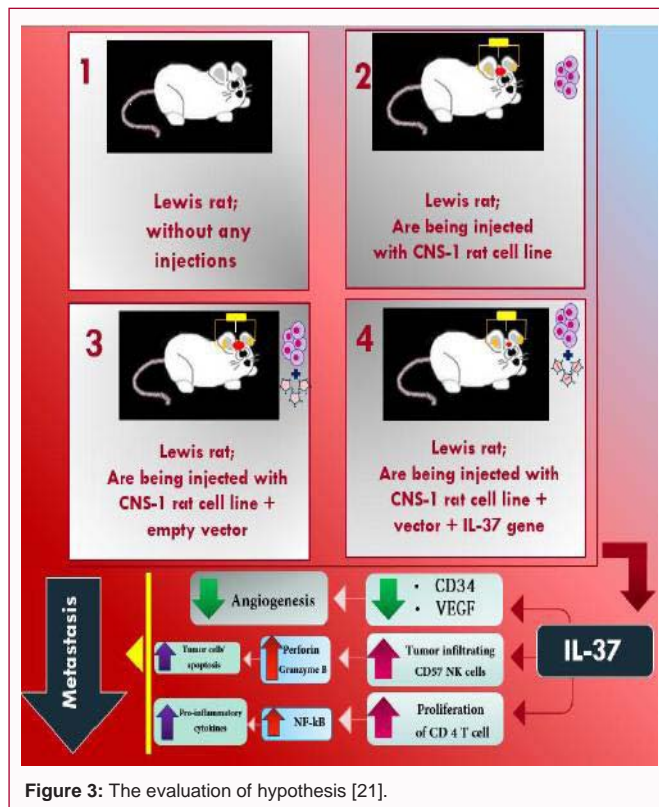
Discussion

Our hypothesis suggests that IL-37 can induce apoptosis, inhibit angiogenesis and decrease metastasis in glioma CNS-1 cells in tumor-bearing Lewis rat [34].

According to recent studies, It was demonstrated that multiple intra tumoral injection of adenovirus IL-37 (Ad-IL-37), in fibro carcinoma animal model environment, suppressed the tumor growth significantly, also represented that the anti-tumor function of IL-37 has linked to proper activity of B and T cells. "IL-37 mediates antitumor effects in the same manner of IL-12 and IL-18, which indicates that IL-37 has a significant role in the connection between innate and adaptive immunity [29-31,34,35]".

Also, evidences have shown that IL-37 converts Smad3 phospho-isoform signaling from JNK/pSmad3L/c-myc oncogenic signaling to pSmad3c/p21 signaling which is tumor suppressive [40].

The expression of IL-37 reduces in tumor tissue [29,37]. So, with administration of intra tumoral injections of exogenous IL-37 in Hepatocellular Carcinoma (HCC) environment, the following fact has been proved, which the more level of IL-37 that exists in tumor environment, the smaller size of tumor is. Then, it will be an indirect relation between amounts of IL-37 and tumor size. Also, it was revealed that, IL-37 increased the amount of tumor-infiltrating CD57⁺ Natural Killer (NK) cells, in this way; it will protect normal



hepatocytes against tumor cells. But, IL-37 is not related with CD3⁺ and CD8⁺ T cells [29,31,34,35,37]. Recent studies have shown that IL-37 enhanced autophagy and apoptosis in SMMC-7721 and Huh-7 cell lines which is related to HCC [41].

According to accumulated evidences, when IL-37 was expressed in cervical cancer environment, the proliferation and invasion of the tumor reduced. It is probable that IL-37 does it through inhibition of STAT3 [29,31,34].

In addition, it was represented that IL-37 has a role on activation and proliferation of CD4⁺ T cells but not on CD8⁺ T cells in breast cancer micro environment [29,35].

Moreover, IL-37 seems to induce tumor cell apoptosis in Renal Cell Carcinoma (RCC). Also, this novel cytokine inhibits proliferation and migration of RCC cells via inhibiting IL-6/STAT3 signaling, it suppresses expression of IL-6 in tumor microenvironment, as well [29].

Recent studies have informed that IL-37 therapy induces reduction in CD34 levels in Non-Small Cell Lung Cancer (NSCLC), which is related to angiogenesis; thus, tumor angiogenesis will be inhibited. Since angiogenesis is a major factor for tumor progression; so, if angiogenesis is suppressed in tumor microenvironment, metastasis and progression will be reduced. Furthermore, IL-37 would decrease tumor cell proliferation and induce apoptosis via inhibiting IL-6/STAT3 signaling pathway [29,39,42].

Moreover, recent documents have demonstrated that IL-37 could be as a radio sensitizer agent in prostate cancer; then, the lower dosage of radiotherapy will be needed and side effects will be decreased as well [43].

All in all, the role of exogenous IL-37 in tumor microenvironment is as follows;

This cytokine will set some tumor-suppressive signaling pathways such as pSmad3c/p21 signaling pathway [41]. Also, IL-37 will inhibit STAT3 pathway which was the main pathway for anti-inflammatory role of this cytokine [29,32]. Furthermore, IL-37 involves in activating the proliferation of CD4⁺ T cells that can increase the amount of NF-KB which is a transcription factor that has a relation with pro-inflammatory cytokine production [35].

On the other side the amount of tumor-infiltrating CD57⁺ NK cells will be increased via intervention of IL-37; thus, tumor microenvironment will be replete with NK cells' products such as perforin and granzyme B that lead tumoral cells toward apoptosis [37].

Also, levels of CD34 cells will be diminished with intra tumoral injections of exogenous IL-37, the diminution in CD34 cells' level will be defined [34].

In conclusion, according to recent evidences on other type of cancers, IL-37 can be as an effective promising candidate in cytokine gene therapy in glioblastoma microenvironment. It will conduct its function via inducing apoptosis, reducing angiogenesis and reducing metastasis forwards. It is going to do its role, in such a microenvironment that T cells have been blocked and is full of T regulatory cells.

With considering all of these, IL-37 possibly may have an anti-tumoral role.

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