RESEARCH ARTICLE

Simultaneous Increase in Serum Levels of IL-37 and IL-18 Binding Protein In Low-Grade and High-Grade Brain Tumors

Mohammad Reza Haghshenas[1], Arash Saffarian[2], Aida Khademolhosseini[1], Amir Reza Dehghanian[3], Abbas Ghaderi[1], Abdoleza Sotoodeh Jahromi[4]*

Abstract

Background: IL-18binding protein (IL-18BP) might play a role in tumor escape from immune surveillance through interacting with IL-37. Such interactions modulate the antitumor activity of IL-18 and affect regulatory T cell (Treg) function. However, the biological roles of IL-37 and IL-18BP have not yet been explored in brain tumors. This study aimed to investigate serum levels of IL-37 and IL-18BP in high-grade and low-grade brain tumors and determine their associations with pathological characteristics of the patients. **Subjects and methods:** This case-control study consisted of 60 patients with brain tumors (40 low-grade and 20 high-grade) and 30 healthy controls. Enzyme-linked immunosorbent assay (ELISA) kits were used to measure the levels of IL-37 and IL-18BP in serum. **Results:** Our results indicated that serum levels of IL-37 and IL-18BP were significantly higher in patients with brain tumors (109.02, 426.37 pg/mL), high-grade (104.44, 428.87 pg/mL), and low-grade (113.88, 426.37 pg/mL) tumors in compared to healthy controls (35.03, 362.00 pg/mL), (P<0.05). Interestingly, our results revealed a significant positive correlation between IL-37 and IL-18BP serum levels in brain tumors (n=60, R=0.42, P=0.001). Our study also showed that serum levels of IL-37 and IL-18BP in glioblastoma grade IV were approximately similar to those in astrocytoma grade II, meningioma type I, and pituitary adenoma. Furthermore, no significant differences were found in serum levels of IL-37 and IL-18BP between patients with low-grade and high-grade tumors (P=0.24 and P=0.61, respectively). **Conclusion:** The simultaneous increase in IL-37 and IL-18BP serum levels and their positive correlation may facilitate disease progression in low-grade and high-grade brain tumors by inhibiting antitumor immune responses.

Keywords: IL-37- IL-18BP- brain tumors

Introduction

Brain tumors are comprised of a rare but diverse group of malignancies leading to a substantial cancer death (Butowski, 2015). The World Health Organization (WHO) Classification of Tumors of the Central Nervous System defined a classification and grading system according to molecular parameters and histological features of tumors (Louis et al., 2016). Glioblastoma, astrocytoma, meningioma, and pituitary adenoma are among the common and important subtypes of brain tumors (Ricard et al., 2012). Brain tumors are classified from grade I to IV. Grade I and II are low-grade, and grades III and IV are high-grade brain tumors (Barnholtz-Sloan et al., 2018). The components of the immune system, particularly cytokines, play critical roles in cancer progression and/ or cancer protection (Gonzalez et al., 2018). Since the brain is an immune-privileged organ, the function of the immune system in brain tumors is unique (Tomaszewski et al., 2019). Therefore, there is a growing interest in discovering the exact role of immune system components in brain tumors (Albulescu et al., 2013; Mostofa et al., 2017; Yeo et al., 2021). Dysregulation of some cytokines, including IL-6, TNF-α, IL-1β, IL-10, IL-8, and IL-2, was shown in sera of patients with glioblastoma (Albulescu et al., 2013). Cytokines of the IL-1 family possess a broad range of functionality, from pro-inflammatory to anti-inflammatory. In this regard, interleukin-37 (IL-37), as a new member of IL-1 family, has anti-inflammatory properties, while IL-18 is considered as a strong pro-inflammatory cytokine (Su and Tao, 2021; Vecchié et al., 2021). Since IL-37 shares sequence homology with IL-18, it exerts its biological functions via binding to the α-subunit of the IL-18 receptor (IL-18Rα) or IL-18 binding

[1]Shiraz Institute for Cancer Research, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [2]Department of Neurosurgery, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [3]Molecular Pathology and Cytogenetics Division, Department of Pathology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [4]Research Center for Non-Communicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran.*For Correspondence: sotoodehj2002@yahoo.com

protein (IL-18BP) (Su and Tao, 2021). Interaction of IL-37 with IL-18BP increases the affinity of IL-18BP for binding to IL-18. These interactions lead to the suppression of IL-18 pro-inflammatory functions (Cavalli and Dinarello, 2018; Su and Tao, 2021). Investigations regarding the role of IL-37 in tumors are limited. IL-37 was reported to inhibit tumor growth in non-small lung cancer, renal cell carcinoma, colon cancer, and cervical cancer. At the same time, elevated levels of IL-37 may persuade tumor progression and unfavorable prognosis in ovarian and gastric cancers (Jiang et al., 2015; Wang et al., 2015; Mora et al., 2016; Huo et al., 2017; Yan et al., 2017; Jiang et al., 2018; Zhang et al., 2019). However, whether IL-37 is involved in the protection and/or the progression of brain tumors remains to be clarified. More recently, it was shown that the expression of IL-37 was higher in tumor tissue of patients with glioma compared to normal tissue. Moreover, there was a negative relationship between the expression of IL-37 and tumor grade in these patients (Liu et al., 2021). IL-18BP is a natural antagonist of IL-18. Interaction of IL-37 with IL-18BP has an essential role in the anti-inflammatory function of IL-37 (Cavalli and Dinarello, 2018). It has been reported that IL-18BP is produced from prostate cancer cells and prostate cell lines, and it might be employed as a tumor marker and even a therapeutic target in prostate cancer (Fujita et al., 2011). However, the role of IL-18BP has not yet been investigated in brain tumors. Since function of IL-37 depends on its interaction with IL-18BP; our study aimed to investigate both IL-37 and IL-18BP in sera of patients with brain tumors and explore their relationship with the pathological characteristics of the patients.

Materials and Methods

Study subjects

This case-control study consisted of 60 patients with different types and grades of brain tumors (32 males and 28 females, mean age 48.08 ±13.38 years, ranging from 21-75 years) and 30 healthy individuals (16 males and 14 females, mean age 49.93±12.48 years, ranging from 20-75 years). The diagnosis was confirmed by both the clinician and the pathologist at Chamran hospital, Shiraz University of Medical Sciences, Shiraz, Iran. Patients were excluded if they had a history of tumors of other organs, immune disorders, and infectious diseases during the previous month. The sample collection was accomplished before any medical intervention, including surgery, chemotherapy, or radiotherapy. Of 60 patients, 40 patients (66.7%) were histologically low-grade and 20 patients (33.3%) were high- grade. High-grade brain tumors consisted of glioblastoma grade IV (25%), anaplastic astrocytoma grade III (3.3%), anaplastic meningioma type III (1.7%), anaplastic ependymoma type III (1.7%) and medulloblastoma type IV (1.7%). Low-grade brain tumors were comprised of meningioma type I (26.6%), pituitary adenoma (25%), and astrocytoma grade II (15%). The pathological characteristics of patients are summarized in Table 1. Healthy individuals were considered the control group. They had no family history of cancers, immune disorders, infectious diseases, and no anti-inflammatory

drug administration within the month before the study.

Written informed consent was obtained from each participant. The ethics local committee approved the study at Jahrom University of Medical Sciences, Jahrom, Iran (IR.JUMS.REC.1398.107).

Cytokine Measurements

Five mL of peripheral blood was obtained from each patient. To collect the serum, blood samples were centrifuged at 2,500 × g for 10 minutes at 4°C. The serum samples were stored at -80°C for further analysis. To measure IL-37 and IL-18BP in serum, enzyme-linked immunosorbent assay (ELISA) kits (SHANGHAI CRYSTAL DAY BIOTECH CO., LTD) were used. The IL-37 and IL-18BP ELISA kits had an assay range of 7 to 400 pg/mL and 5 to 2000 pg/mL, respectively. The sensitivity of kits was 4.5 pg/mL for IL-37 pg/mL and 2.43 pg/mL for IL-18BP.

Statistical Analysis

All statistical analyses were performed using the SPSS software (version 11.5). The normal distribution of data was determined using the Kolmogorov–Smirnov test. The serum levels of IL-37 and IL-18BP between the patients and control groups and their association with tumor grade and tumor subtypes were compared using non-parametric tests, including Mann–Whitney U and Kruskal–Wallis H. Spearman's correlation was used to study the correlations between serum IL-37 and IL-18BP levels and age. All of the values were given as the mean± SEM and median. A p value ≤0.05 was considered to be statistically significant.

Results

IL-37 and IL-18BP Serum Levels in Patients and Controls

As shown in Table 2, serum levels of IL-37 were significantly higher in patients with brain tumor in comparison to controls (P=<0.001). There was also a significant increase in IL-18BP serum levels in the patients compared to the control groups (P=0.002). Moreover, a significant increase in serum levels of IL-37 was found in both the patients with low-grade and high-grade tumors in comparison to controls (P=<0.001 for both comparisons). The same results were observed for IL18BP serum levels, which were significantly higher in both the patients with low-grade and high-grade tumors compared to controls (P=0.006 and P=0.008, respectively). However, there was no statically significant difference in serum levels of IL-37 and IL-18BP between patients with low-grade and high-grade tumors (P=0.24 and P=0.61, respectively). Statistical analysis also indicated no significant difference in IL-37 and IL-18BP serum levels between male and female patients.

IL-37 and IL-18BP serum Levels in different pathological types of tumors

Our results indicated that the serum levels of IL-37 and IL-18BP were approximately similar among all studied subtypes (P≥0.05). Among comparisons, IL-37 and IL-18BP serum levels were higher in patients with astrocytoma grade II than patients with

Table 1. The Pathological Characterization of Patients with Brain Tumors

Characteristic	Classification	Frequency	Percent
Gender	Male	32	53.3
	Female	28	46.7
Histological tumor type	Glioblastoma grade IV	15	25.0
	Anaplastic astrocytomas grade III	2	3.3
	Anaplastic meningiomas type III	1	1.7
	Anaplastic ependymomas type III	1	1.7
	Medulloblastomas type IV	1	1.7
	Meningioma type I	16	26.6
	Pituitary adenoma	15	25.0
	Astrocytoma grade II	9	15.0
Brain tumor grade	High grade	20	33.3
	Low grade	40	66.7

glioblastoma grade IV; however, the differences were not statistically significant (P=0.09 and P=0.35, respectively). Additionally, the statistical analysis revealed no significant differences in IL-37 and IL-18BP between meningioma type I or pituitary adenoma compared to glioblastoma grade IV (P>0.05). Moreover, the same results regarding IL-37 and IL-18BP serum levels were observed in comparisons between astrocytoma grade II, meningioma type I, and pituitary adenoma as low-grade tumors (P>0.05). However, compared to patients with meningioma type I, patients with astrocytoma grade II indicated an increasing tendency in IL-18BP serum levels (P=0.05). Since brain tumors can be intra-axial (e.g., glioblastoma, astrocytoma, ependymoma, and medulloblastoma) or extra-axial (e.g., meningioma and pituitary adenoma), we then compared IL-37 and IL-18BP serum levels in these two groups. Our results indicated no significant difference in IL-37 and IL-18BP serum levels between intra-axial and extra-axial brain tumors (P=0.90 and P= 0.11). The data are summarized in Table 3.

Correlation Analysis between IL-37, IL-18BP, Age, and Tumor Size

Spearman's Rho analysis revealed a significant positive correlation between IL-37 and IL-18BP serum levels in all brain tumors (n=60, R=0.42, P=0.001) and patients with low-grade tumors (n=40, R=0.38, P=0.02). The statistical analysis indicated a near-significant correlation between IL-37 and IL-18BP serum levels in patients with high-grade tumors (n=20, R=0.43, P=0.057). However, no significant correlation was found between the IL-37 or IL-18BP serum levels and the age and tumor size in brain tumors, patients with low-grade tumors, and patients with high-grade tumors.

Discussion

In the current study, serum levels of IL-37 and IL-18BP were investigated between patients with brain tumors and healthy individuals. IL-37 and IL-18BP were significantly higher in patients with a brain tumor than in healthy controls. Moreover, both the patients with high-grade and low-grade tumors indicated a significant increase in serum levels of IL37 and IL-18BP than those in healthy subjects. Interestingly, our results showed a significant positive correlation between IL-37 and IL-18BP serum levels in brain tumors.

IL-37 serum levels were significantly higher in patients with gastric, ovarian, and bladder cancers, and its overexpression was associated with unfavorable outcomes and tumor progression (Huo et al., 2017; Zhang et al., 2019; Haghshenas et al., 2021). In contrast, serum levels of IL-37 were shown to be decreased in renal cell carcinoma. Moreover, IL-37 expression was negatively associated with disease progression in this cancer (Jiang et al., 2015).

Limited studies investigated serum levels of IL-18BP in patients with cancer. However, it has been found that IL-18BP levels in urine and serum might be positively related to Gleason score and tumor status in prostate cancer. Additionally, IL18BP may facilitate tumor scape from immune surveillance in prostate cancer (Fujita et al., 2011). Interaction of IL-18 with IL-18BP inhibits the binding of IL-18 to its receptor, therefore restricts the pro-inflammatory effects of this cytokine. IL-37 can also bind to IL-18BP. Interaction of IL-18BP with IL-37 increases its affinity for binding to IL-18 (Cavalli and Dinarello, 2018; Su and Tao, 2021). Thus, IL-37 can suppress pro-inflammatory responses by restricting IL-18 functions. As the primary function, IL-18 strongly stimulates the secretion of IFN-γ by natural killer cells (NK cells) and Th1 cells (Esmailbeig and Ghaderi, 2017).

On the other hand, IL-18 has a predominant role in priming the human NK cells. In cooperation with dendritic cells (DCs), it can promote the recruitment of cytotoxic CD8+ T cells (CTL) into the tumor microenvironment (Wong et al., 2013; Fabbi et al., 2015). NK cells and CTLs are the essential components of the immune system in antitumor responses (Ohtani et al., 2014; Peterson and Barry, 2020). The simultaneous increase in IL-37 and IL-18BP in both high-grade and low-grade tumors and the significant positive correlation between IL-37 and IL-18BP serum levels in brain tumors could dampen anti-tumor immune responses in brain tumors, consequently leading to tumor development and progression. IL-37 is highly expressed in regulatory T cells (Tregs), showing that IL-37 levels are positively associated with Foxp3

Table 3. IL-37 and IL-18 BP Serum Levels in Different Tumor Types of Brain Tumors

Protein investigation	Statistics	Serum concentration (pg/mL)			
		Glioblastoma grade IV (n=15)	Meningioma type I (n=16)	Pituitary adenoma (n=15)	Astrocytoma grade II (n=9)
IL-37	Mean± SEM	118.50±18.77	115.55±5.27	119.04±8.47	143.10±24.57
	Median	102.91	110.83	105.97	115.97
	Minimum	68.19	90.69	85.14	65.69
	Maximum	362.08	165.69	189.31	322.08
IL-18BP	Mean± SEM	497.91±69.67	405.20±23.74	470.75±31.75	563.11±97.50
	Median	425.75	406.37	428.25	465.75
	Minimum	293.25	180.75	349.5	384.5
	Maximum	1423.25	630.75	718.25	1302

Tumor types comprised of 2 patients or less, are not included in comparisons. P-values in all comparisons were 0.05 or more than 0.05.

Table 2. IL-37 and IL-18 BP Serum Levels in Patients with Brain Tumors and Control Group

Protein investigation	Statistics	Serum concentration (pg/mL)						P value (2tailed)					
		Brain tumors (n=60)	High grade brain tumors (n=20)	Low-grade brain tumors (n=40)	Intra-axial brain tumors	Extra-axial brain tumors	Healthy control subjects (n=30)	Comparison between brain tumors and controls	The global p-value for comparison between three groups	Comparison between High grade and low-grade tumors	Comparison between high-grade tumors and controls	Comparison between Low-grade tumors and controls	Comparison between intra-axial and extra-axial brain tumors
IL-37	Mean± SEM	123.79±7.39	125.25±18.01	123.06±6.69	131.28±14.93	117.23±4.69	40.40±3.90	<0.001	<0.001	0.24	<0.001	<0.001	0.9
	Median	109.02	104.44	113.88	111.11	108.33	35.03						
	Minimum	46.25	46.25	65.69	46.25	85.14	6.67						
	Maximum	362.08	362.08	322.08	362.08	189.31	99.95						
IL-18BP	Mean± SEM	495.79±34.51	556.75±87.82	465.31±27.45	564.18±68.92	435.94±19.60	378.24±39.59	0.002	0.007	0.61	0.008	0.006	0.11
	Median	426.37	428.87	426.37	443.25	408.25	362						
	Minimum	180.75	293.25	180.75	293.25	180.75	2.5						
	Maximum	1895.75	1895.75	1895.75	1895.75	718.25	1119.5						

P-values less than 0.05 are considered a significant level.

expression and immunosuppressive function of Tregs (Shuai et al., 2015; Osborne et al., 2019). Accordingly, IL-37 could down-regulate both innate and adaptive immunity and may consequently modulate antitumor responses in various types of disorders, as reported in melanoma (Osborne et al., 2019). In addition to the effect on Tregs, IL-37 can also suppress the immune responses through down-regulation of DCs activity (Nold et al., 2010). Therefore, IL-37 could be considered as a novel marker for tumor-induced immunosuppression, and thereby IL-37 targeting might be serves as a therapeutic tool in certain cancers such as brain tumors. However, it has been shown that IL-37 could play a protective role in several cancers. It was indicated that IL-37 inhibits tumor progression in non-small cell lung cancer and colorectal cancer through suppression of the IL-6/STAT-3 signaling pathway and β-catenin, respectively (Yan et al., 2017; Jiang et al., 2018). Dual role of IL-37 in cancer can be explained by different cell types, depending on their milieu, context, and differentiation state, among others (Abulkhir et al., 2017).

In continue, we also investigated the association of IL-37 and IL-18BP serum levels with pathological characteristics of patients. Our study showed that serum levels of IL-37 and IL-18BP in low-grade brain tumors were approximately similar to those in high-grade brain tumors. Additionally, our results indicated that although IL-37 and IL-18BP serum levels were higher in astrocytoma grade II than in glioblastoma grade IV, the differences were not statistically significant. Accordingly, the same results were also observed in serum levels of IL-37 and IL-18BP between meningioma type I, pituitary adenoma, and glioblastoma grade IV. On the other hand, our result indicated that serum levels of IL-37 and IL-18BP were not different between high-grade and low-grade brain tumors or different subtypes of brain tumors, and thereby, they may have the same functions in all types of brain tumors.

In conclusion, our results show the simultaneous increase in IL-37 and IL-18BP in both high-grade and low-grade tumors and a significant positive correlation between IL-37 and IL-18BP serum levels in brain tumors. The interaction between IL-37 and IL18BP may lead to tumor growth by inhibiting antitumor immune responses. However, more studies in a larger population are needed to precisely define the role of IL-37 and IL-18BP in low- and high-grade brain tumors.

Author Contribution Statement

A. Gh., M.R. H., A.R. S.J.; Contributed to the conception and study design. A. Kh., M.R. H., A.R. S.J.; Contributed to lab experiments, statistical analysis, and the data interpretation. A. S., A.R. D.; Contributed to patient's diagnosis and sample collection. A. Gh., M.R. H.; A.R. S.J.; Supervised the project. A. Kh., M.R. H.; Drafted the manuscript, and then it was revised by A.R. S.J., A. Gh., A. S., A.R. D.; All authors read and approved the final manuscript. Authors state that there was no conflict of interest.

References

Abulkhir A, Samarani S, Amre D, et al (2017). A protective role of IL-37 in cancer: a new hope for cancer patients. *J Leukoc Biol*, **101**, 395-406.

Albulescu R, Codrici E, Popescu ID, et al (2013). Cytokine patterns in brain tumour progression. *Mediators Inflamm*, **2013**, 979748.

Barnholtz-Sloan JS, Ostrom QT, Cote D (2018). Epidemiology of brain tumors. *Neurol Clin*, **36**, 395-419.

Butowski NA (2015). Epidemiology and diagnosis of brain tumors. *Continuum (Minneap Minn)*, **21**, 301-13.

Cavalli G, Dinarello CA (2018). Suppression of inflammation and acquired immunity by IL-37. *Immunol Rev*, **281**, 179-90.

Esmailbeig M, Ghaderi A (2017). Interleukin-18: a regulator of cancer and autoimmune diseases. *Eur Cytokine Netw*, **28**, 127-40.

Fabbi M, Carbotti G, Ferrini S (2015). Context-dependent role of IL-18 in cancer biology and counter-regulation by IL-18BP. *J Leukoc Biol*, **97**, 665-75.

Fujita K, Ewing CM, Isaacs WB, et al (2011). Immunomodulatory IL-18 binding protein is produced by prostate cancer cells and its levels in urine and serum correlate with tumor status. *Int J Cancer*, **129**, 424-32.

Gonzalez H, Hagerling C, Werb Z (2018). Roles of the immune system in cancer: from tumor initiation to metastatic progression. *Genes Dev*, **32**, 1267-84.

Haghshenas MR, Hosseini SR, Fattahi MJ, et al (2021). Elevated IL-37 Serum Levels in Patients with Transitional Cell Carcinoma of Bladder. *Iran J Immunol*, **18**, 346-53.

Huo J, Hu J, Liu G, et al (2017). Elevated serum interleukin-37 level is a predictive biomarker of poor prognosis in epithelial ovarian cancer patients. *Arch Gynecol Obstet*, **295**, 459-65.

Jiang M, Wang Y, Zhang H, et al (2018). IL-37 inhibits invasion and metastasis in non-small cell lung cancer by suppressing the IL-6/STAT3 signaling pathway. *Thorac Cancer*, **9**, 621-9.

Jiang Y, Wang Y, Liang L, et al (2015). IL-37 mediates the antitumor activity in renal cell carcinoma. *Med Oncol*, **32**, 250.

Liu S, Ba Y, Li C, et al (2021). Interleukin 37 expression was negatively associated with pathological grading in human gliomas. https://doi.org/10.21203/rs.3.rs-318636/v1.

Louis DN, Perry A, Reifenberger G, et al (2016). The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*, **131**, 803-20.

Mora J, Schlemmer A, Wittig I, et al (2016). Interleukin-38 is released from apoptotic cells to limit inflammatory macrophage responses. *J Mol Cell Biol*, **8**, 426-38.

Mostofa AG, Punganuru SR, Madala HR, et al (2017). The

process and regulatory components of inflammation in brain oncogenesis. *Biomolecules*, **7**.

Nold MF, Nold-Petry CA, Zepp JA, et al (2010). IL-37 is a fundamental inhibitor of innate immunity. *Nat Immunol*, **11**, 1014-22.

Ohtani T, Yamada Y, Furuhashi A, et al (2014). Activated cytotoxic T-lymphocyte immunotherapy is effective for advanced oral and maxillofacial cancers. *Int J Oncol*, **45**, 2051-7.

Osborne DG, Domenico J, Luo Y, et al (2019). Interleukin-37 is highly expressed in regulatory T cells of melanoma patients and enhanced by melanoma cell secretome. *Mol Carcinog*, **58**, 1670-9.

Peterson EE, Barry KC (2020). The natural killer-dendritic cell immune axis in anti-cancer immunity and immunotherapy. *Front Immunol*, **11**, 621254.

Ricard D, Idbaih A, Ducray F, et al (2012). Primary brain tumours in adults. *Lancet*, **379**, 1984-96.

Shuai X, Wei-min L, Tong YL, et al (2015). Expression of IL-37 contributes to the immunosuppressive property of human CD4+CD25+ regulatory T cells. *Sci Rep*, **5**, 14478.

Su Z, Tao X (2021). Current understanding of IL-37 in human health and disease. *Front Immunol*, **12**, 696605.

Tomaszewski W, Sanchez-Perez L, Gajewski TF, et al (2019). Brain tumor microenvironment and host state: Implications for Immunotherapy. *Clin Cancer Res*, **25**, 4202-10.

Vecchié A, Bonaventura A, Toldo S, et al (2021). IL-18 and infections: Is there a role for targeted therapies?. *J Cell Physiol*, **236**, 1638-57.

Wang S, An W, Yao Y, et al (2015). Interleukin 37 expression inhibits STAT3 to suppress the proliferation and invasion of human cervical cancer cells. *J Cancer*, **6**, 962-9.

Wong JL, Berk E, Edwards RP, et al (2013). IL-18-primed helper NK cells collaborate with dendritic cells to promote recruitment of effector CD8+ T cells to the tumor microenvironment. *Cancer Res*, **73**, 4653-62.

Yan X, Zhao J, Zhang R (2017). Interleukin-37 mediates the antitumor activity in colon cancer through β-catenin suppression. *Oncotarget*, **8**, 49064-75.

Yeo ECF, Brown MP, Gargett T, et al (2021). The role of cytokines and chemokines in shaping the immune microenvironment of glioblastoma: Implications for immunotherapy. *Cells*, **10**.

Zhang Y, Tang M, Wang XG, et al (2019). Elevated serum levels of interleukin-37 correlate with poor prognosis in gastric cancer. *Rev Esp Enferm Dig*, **111**, 941-5.