Clinical and pathogenetic relationship between IL-1β and IL-8 in melanoma

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Research Article

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Abstract

Immune checkpoint inhibitors (ICI) are mostly used for melanoma treatment, however, the efficacy is achieved not for every patient. The cause of therapy failure can be explained by local immune suppression, which might be induced by different cytokines, including IL-1β. IL-1β is difficult to detect in peripheral blood, meanwhile, the high concentrations of IL-8 are frequently reported. IL-8 production is known to be induced by IL-1β in many cell types, however, there is no data on melanoma cells. This study aims to determine the relationship between IL-1β and IL-8 in patients with metastatic (mts) melanoma and assess the effect of IL-1β on IL-8 production by melanoma cells in vitro. The study involved 28 patients (pts) with mts melanoma taking ICI. The level of IL-1β and IL-8 in blood serum was determined using the ELISA method. In the experiments SK-MEL cells were incubated with/without IL-1β (1-1-2-4 ng/ml) for 9 days, every 2 days the cell media was collected. According to the study, with an IL-8 concentration of more than 42.31 pg/ml in patients with mts melanoma, the presence of IL-1β in the blood serum can be expected. At the same time, the level of IL-8 correlated with the level of IL-1β. The study also showed a concentration-dependent increase in the production of IL-1β and IL-8 by human melanoma cells with external exposure to IL-1β. The data obtained can allow us to assume, that high expression of IL-1β contributes to IL-8 production in tumor microenvironment (TME), which can be observed in peripheral blood and serve as a biomarker of high IL-1β expression in TME and local immune suppression. A high IL-8 level might be associated with a low ICI efficacy, but it`s needed to be studied in the following research.

Introduction

Immune checkpoint inhibitors (ICI) are mostly used for melanoma treatment, however, the efficacy is achieved not for every patient [1]. The cause of therapy failure can be explained by local immune suppression, which might be induced by different cytokines, including IL-1β [2].

The immunosupressive effect of IL-1β was shown in several *in vivo* studies with the use of IL-1β inhibitors [3, 4]. An increased effecacy of checkpoint inhibitors was observed in mouse models of breast cancer due to the combination with the drug "Anakinra", IL-1β inhibitor [3]. The use of "Anakinra" resulted in a decrease of immunosuppression, mediated mainly by macrophages, and thereby an increase in antitumor immunity, mediated by increased dendritic cell function and activated CD8 cytotoxic lymphocytes. It is important to note that the anti-PD-1 treatment reduced the growth of tumor cells, while the combination of anti-IL-1β and anti-PD-1 completely destroyed the tumor [3].

Similar results were obtained in mouse models of renal cell carcinoma with anti-PD-1 drug. Anti-IL-1β reduced the infiltration of polymorphonuclear myeloid-derived suppressors and tumor-associated macrophages. Combination treatment of anti-IL1β with anti-PD-1 showed increased antitumor activity, which was associated with a decrease in immunosuppressive cells and an increase in M1-type macrophages [4].

Considering the pathogenetic role of IL-1β in immune supression and association with low immune therapy efficacy, it can be assumed that an increased IL-1β serum level can serve as a biomarker of progression or a predictor of low efficacy of ICI. However, the clinical studies on diagnostic value of IL-1β in cancer patient showed contradictory results. The spectrum of interleukins (IL-1α, IL-6, IL-8, IL-12p40, IL-13) was found to be increased relative to healthy individuals [5], also a high IL-1β concentration was associated with a poor prognosis [6,7]. In other tumor localizations an increased cytokine expression in the tissue was more often observed in comparison with the elevation of IL-6 and IL-8 levels in the blood serum, for example, in colorectal [8–12, 13] and gastric [14–17] cancers.

It is known that IL-1β activates the production of IL-8 in various cells such as endothelial cells, epithelial cells and smooth muscle cells, macrophages by stimulating p38-mitogen-activated protein kinase (MAPK) and MAPK-activated protein kinase 2 [18–22], which has also been shown in TMK-1 human gastric cancer cells [23].

It can be noted that overexpression of IL-1β and IL-8 is observed in the tissues of the most tumors, while in the blood an increase of IL-8 is more often observed. However, there is no data on diagnostic significane of IL-1β and IL-8 during ICI therapy of melanoma and the effect of IL-1β on melanoma cells.

This study aims to assess the diagnostic significance of IL-1β and IL-8 determination in patients with metastatic (mts) melanoma and the effect of IL-1β on IL-8 production by melanoma cells *in vitro*, which could show the possibility of using IL-8 as a biomarker of high IL-1β expression in the tumor microenvironment (TMO), local immune suppression and low therapy efficacy.

Materials And Methods

1. Clinical study

A study involved 31 patients with metastatic melanoma, taking the treatment in the City oncology centre. All patients signed the Informed Consent Statement, which was approved by the Ethics Committee (protocol code № 115-02-6, 23.09.2020). Because of the disease progression, these patients were prescribed therapy with checkpoint inhibitors. All patients underwent a standard set of clinical, laboratory and instrumental medical examinations required in the diagnosis of oncological diseases, including: history taking, physical assessment of clinical symptoms, clinical and biochemical blood tests, multi-slice computed tomography (MSCT), histological verification of the neoplasm. According to the design of the study, the inclusion criteria were: the age of patients from 18 to 80 years, the diagnosis of "Metastatic melanoma", requiring systemic therapy. The exclusion criteria were the presence of HIV infection, syphilis, decompensated diabetes mellitus. Patients characteristics are presented in Table 1.

Table 1
Characteristics of patients with metastatic melanoma

Characteristics		The number of pts %(n)
Age, years	20–50	12.9% (4)
	50–60	32.2% (10)
	60–70	32.2% (10)
	> 70	22.6% (7)
The drug	Nivolumab	51.6% (16)
	Pembrolizumab	29.0% (9)
	Prolgolimab	3.2% (1)
	Nivolumab + Ipilimumab	16.1% (5)
Presence of prior anticancer therapy	Chemotherapy	48.3% (15)

Before the start of ICI therapy, 2–3 months after blood sera were obtained by centrifugation of whole peripheral venous blood, the biomaterial was stored at -20°C. The level of IL-1β and IL-8 in blood serum was determined by using ELISA kits for respective cytokine (Vector-best, Russia). All measurements were carried out on a multifunctional plate reader Varioskan LUX (Thermo Fisher Scientific, USA). When determining the concentration of IL-1β, the linear concentration range is 0-250 pg/ml, the upper limit of values is 11.00 pg/ml, when determining the concentration of IL-8, the linear concentration range is 0-250 pg/ml, the upper limit of values is 10.00 pg/ml (Instructions for the use of a set of reagents for enzyme immunoassay for determining the concentration of human interleukin-1 beta//ZAO "Vector-Best". - Novosibirsk, 15.10.08. – 23 p.).

After 3 months the effect of therapy was assessed: regression, partial regression, stabilization, progression. Regression, partial regression/stabilization were combined into the disease control group.

2. *In vitro* study

We used a melanoma cell line (SK-MEL-1). The cells were cultured in flasks for adhesive cell cultures with ventilated caps, in a CO_2 incubator at 95% humidity, containing 21% O_2 and 5% CO_2 at 37°C in DMEM culture medium (Paneco, Russia) supplemented with 10 mM HEPES-Na (Paneco, Russia), 2 mM glutamine (Paneco, Russia), 10% fetal bovine serum (FBS; (HyClone ™, USA) and 1% penicillin-streptomycin (10 IU ml^{-1}–100 μg ml^{-1}; Paneco, Russia).

To assess the effect of IL-1β on the production of IL-8 by melanoma cells, the following reagents were used: a solution of interleukin-1 beta (0.5 mM) and ELISA kits for determining the concentration of IL-1β and IL-8.

The experiment was carried out according to the following protocol (Fig. 1)

1. SK-MEL-1 melanoma cells were cultured in 25 cm^2 flasks for 9 days, IL-1β solution (1 ng/ml) was added to the cell line at each passage.
2. At each passage the cell medium was aspirated, alliquoted in 2 ml, after which it was frozen and stored at -4°C.
3. The level of IL-1β and IL-8 in the culture medium was determined by ELISA.

Statistical analysis was carried out using GraphPad Prism 6 (Graph Pad Software, USA) Nonparametric Fisher, Mann-Whitney tests, Spearman correlation analysis, ROC, Wilcoxon matched-pairs signed rank test analysis were applied. Differences were considered statistically significant at a significance level of the tested hypothesis p less than 0.05.

Results

Determining the concentrations of IL-1β and IL-8 in patients with mts melanoma

IL-1β was detected in 35.5% (11/31) of patients before therapy, while an elevated level of IL-1β was observed in only one patient. The average concentration of IL-1β before the start of therapy was 3.43 ± 2.64 pg/ml, 2–3 months after – 0.49 ± 0.36 pg/ml, respectively. IL-8 was determined in all patients blood samples, an elevated level before therapy was observed in 64.5% (20/31) of cases, after 2–3 months - in 35.5% (11/31). The average concentration of IL-8 before the start of therapy was 71.74 ± 26.93 pg/ml, 2–3 months after – 22.75 ± 6.47 pg/ml. It should be noted that after 2–3 months of therapy, the elevation of IL-8 concentration was observed in 25.8% (8/31) of patients.

According to Wilcoxon matched-pairs signed rank test after the therapy a statistically significant decrease in the concentration of IL-1β was observed (p = 0.0498). The IL-8 concentration statistically significant decreased in 74.2% (23/31) of patients (p = 0.0002) and statistically significant increased in 25.8% (8 /31) of patients (p = 0.0078) (Fig. 2).

An analysis of the relationship between the concentrations of IL-1β and IL-8 was performed. Depending on the presence of IL-1β in the blood serum, the patients were divided into two groups. According to the Mann Whitney test, when IL-1β was detected, the level of IL-8 was statistically higher and amounted to 139.6 ± 65.26 pg/ml (p = 0.024), while in patients with undetectable IL-1β, the average concentration of IL-8 was 34.39 ± 18.31 pg/ml (Fig. 3).

According to correlation analysis using the Spearman coefficient in patients with detectable IL-1β, an average positive correlation was found between the concentrations of IL-1β and IL-8 (R = 0.6469, p = 0.035) (Fig. 4).

According to ROC analysis (Area = 0.76), with an increase in the concentration of IL-8 more than 42.31 pg/ml with a diagnostic sensitivity of 66.67% and a specificity of 90.00%, it can be assumed that the patient will have an increased level of IL-1β (p = 0.025).

Analysis of the association between interleukin concentrations and the therapy efficacy did not reveal statistically significant results. Although the level of IL-8 in the tumor regression group was significantly lower compared to the progression group (Table 2).

Table 2
The concentration of IL-8 in patients groups divided according to therapy efficacy

	The group of regression (n = 10)	The group of progression (n = 9)	The group of stabilisation (n = 12)
Mean ± M	41.6 ± 19.1	120.6 ± 67.6	60.2 ± 46.1
Median	18.19	28.00	12.31
95% CI	0-84.72	0-276.6	0-161.6

Evaluation of the chronic effect of IL-1β on IL-8 production in vitro

Addition of exogenic IL-1β into cell culture medium (1-1-2-4 ng/ml) for 9 days contributed to an increase in the level of IL-1β (p = 0.029), and IL-8 (p = 0.029), in culture medium of SK-MEL cells, which may reflect increased secretion of these cytokines by tumor cells (Fig. 5).

At the same time, the concentration of injected IL-1β correlated non-linearly with the level of IL-8 (R = 0.949) and linearly with the level of IL-1β (R = 0.949) in the culture medium.

Discussion

According to data obtained during a clinical study, IL-1β was not detected in the blood of patients with mts melanoma, while 64% of patients had elevated levels of IL-8. The concentration of both cytokines in most cases decreased during the therapy. The level of IL-8 before the start of therapy was not associated with the therapy efficacy, although this parameter was higher in patients with disease progression. *In vitro* experiments showed a concentration-dependent increase in the production of IL-1β and IL-8 by human melanoma cells in presence of exogenic IL-1β.

The significance of measurements of IL-8 concentration is confirmed in a meta-analysis on the study of colorectal cancer. The study analyzed 18 articles, the number of examined patients was 1509 patients to assess clinical and pathological characteristics, prognosis and 725 participants to assess diagnostic significance. The results showed that IL-8 overexpression is significantly associated with poor prognosis, especially in stage IV patients, and there is a significant correlation between high IL-8 expression and lymphatic and liver metastases [24]. In our study most of the patients with mts melanoma had elevated

level of IL-8, however we can`t consider this parameter as a biomarker of progression without a comparison with a control group.

In the study of Schalper et al [25] the elevated baseline serum levels of IL-8 were associated with lower overall survival of patients (n = 1344) with advanced cancers treated with nivolumab and/or ipilimumab, everolimus, or docetaxel in phase 3 clinical trials. Despite we found high concentrations of IL-8 in serum of patients with mts melanoma, it wasn't associated with the therapy efficacy. We assume that our results might be connected with a small sample and the short observational period.

One of the alternative hypothesis of difference in cytokine levels in the peripheral blood might be the metabolism processes. IL-1β is believed to have a very short half-life [26,27], while IL-8 can be detected in the blood for up to 4 h [28].

The obtained results in our study support the hypothesis based on the literature review. It can be assumed that with increased synthesis of IL-1β in the melanoma TME induces the IL-8 secretion, which correlates with an increase in IL-8 in the blood (Fig. 6).

Conclusions

According to the study, with an IL-8 concentration of more than 42.31 pg/ml in patients with mts melanoma, the presence of IL-1β in the blood serum can be expected. At the same time, the level of IL-8 correlated with the level of IL-1β. The *in vitro* study might confirm our hypothesis. It showed a concentration-dependent increase in the production of IL-1β and IL-8 by human melanoma cells with external exposure to IL-1β.

The data obtained can allow us to assume, that high expression of IL-1β contributes to IL-8 production in TME, which can be observed in peripheral blood and serve as a biomarker of high IL-1β expression in TME and local immune suppression. A high IL-8 level might be associated with a low ICI efficacy, but it`s needed to be studied in the following research.

Declarations

Author Contributions

A.M.: conceptualization, formal analysis, investigation, writing—original draft preparation; R.O.: conceptualization, writing—review and editing, supervision, project administration; N.Z.: resources, data curation; E.K.: resources, data curation; A.D.: resources, data curation; N.P.: resources, data curation; V.S.: conceptualization, writing—review and editing, supervision, project administration. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Saint Petersburg State University (protocol code № 115-02-6, 23.09.2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the presence of private information about patients.

Conflicts of Interest: The authors declare no conflict of interest.

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Figures

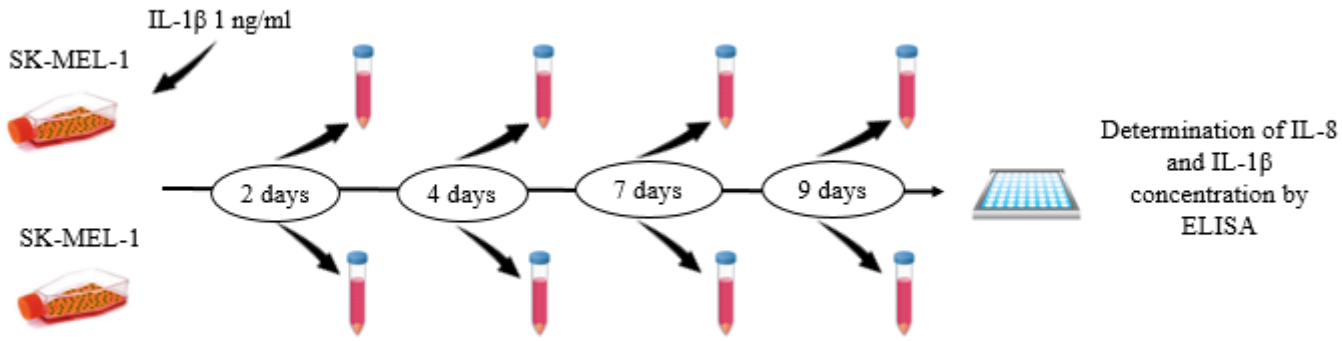

Figure 1

The design of the experiment to assess the chronic effect of IL-1β on IL-8 production by SK-MEL-1 melanoma cells

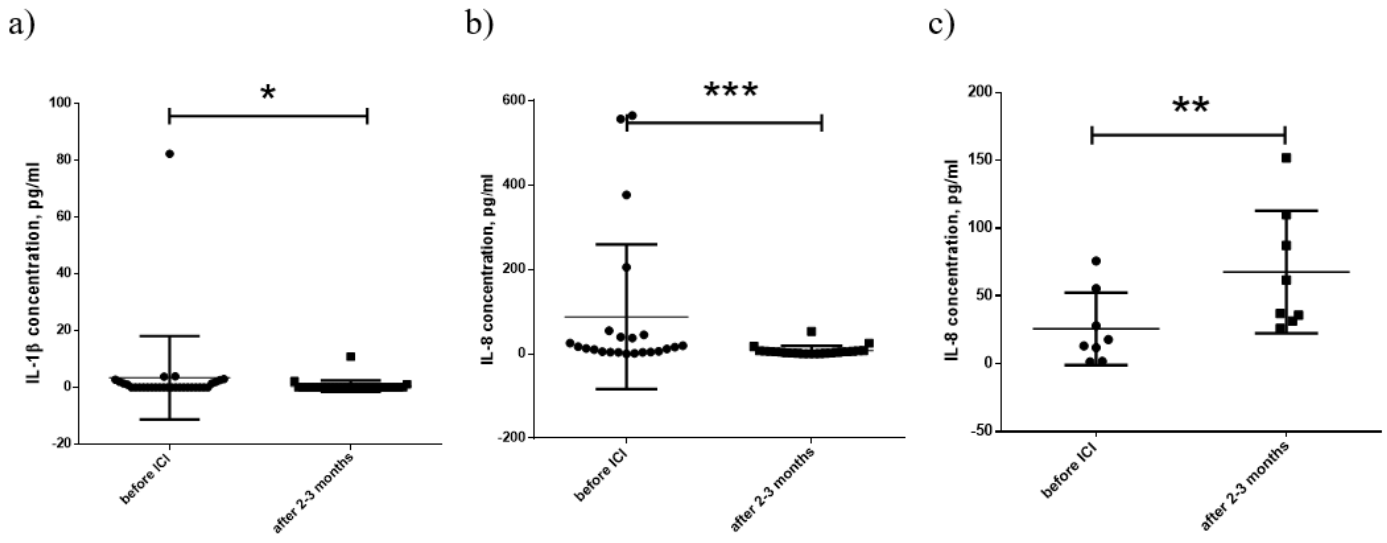

Figure 2

Change in IL-1β (a), IL-8 concentration after 2-3 months: decrease (b), increase (c). A) Change in IL-1β concentration after 2-3 months of treatment; b) Patients with a decrease in IL-8 (n=23); c) Patients with an increase in IL-8 (n=8).

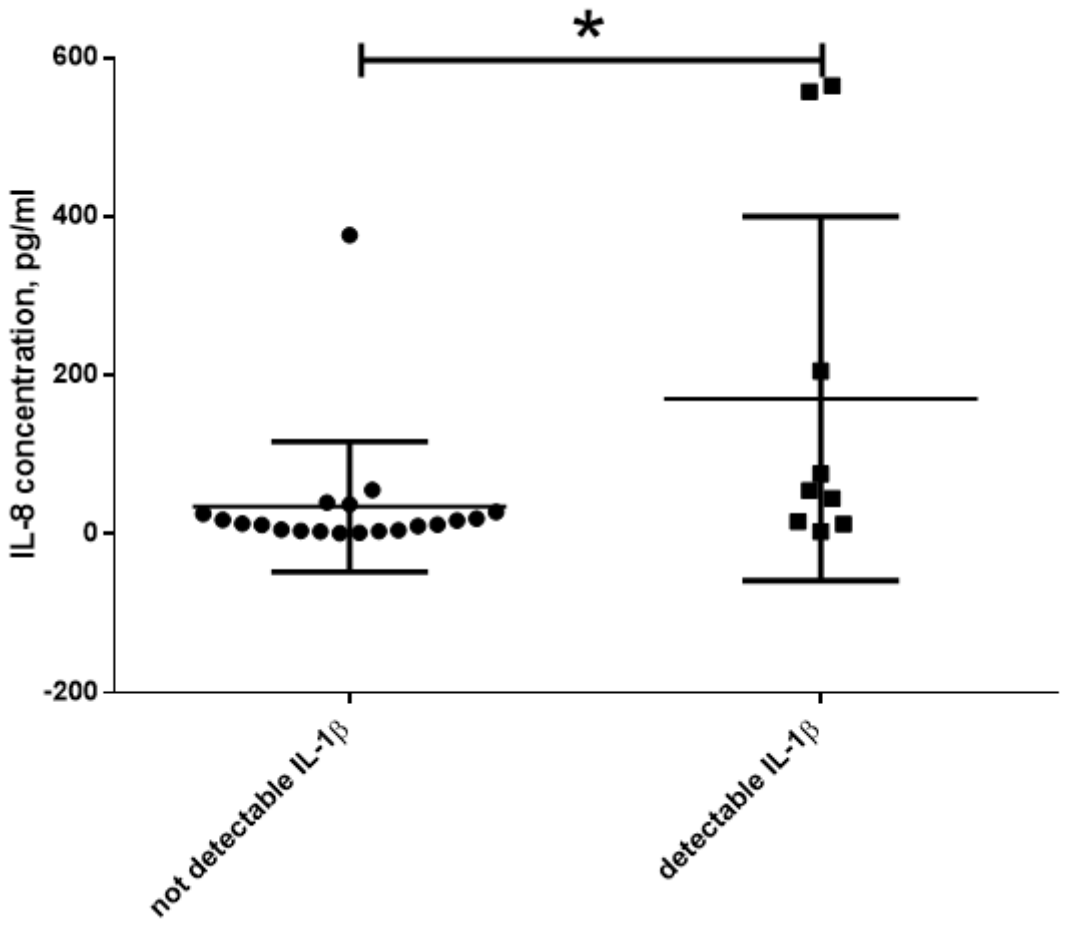

Figure 3

Level of IL-8 depending on the presence of IL-1β in blood serum.

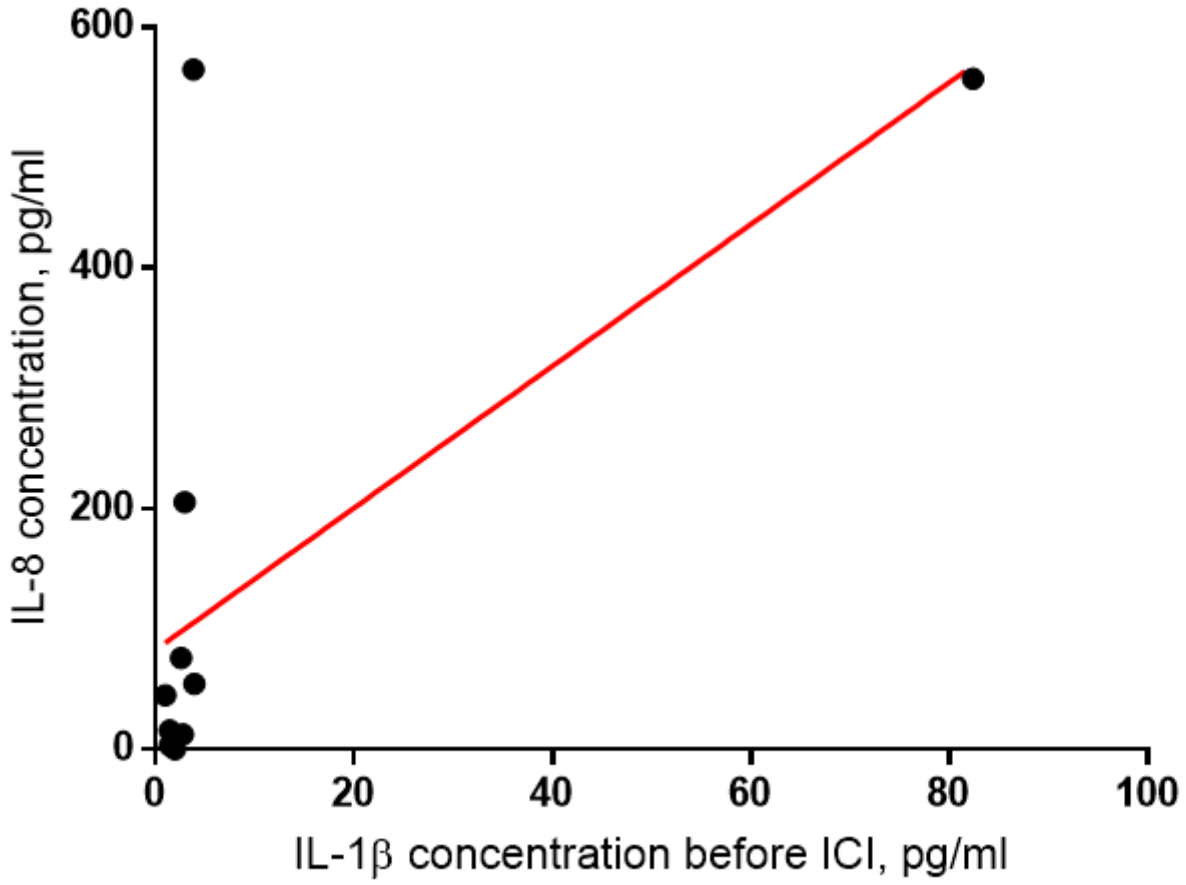

Figure 4

Correlation dependence of IL-8 and IL-1β.

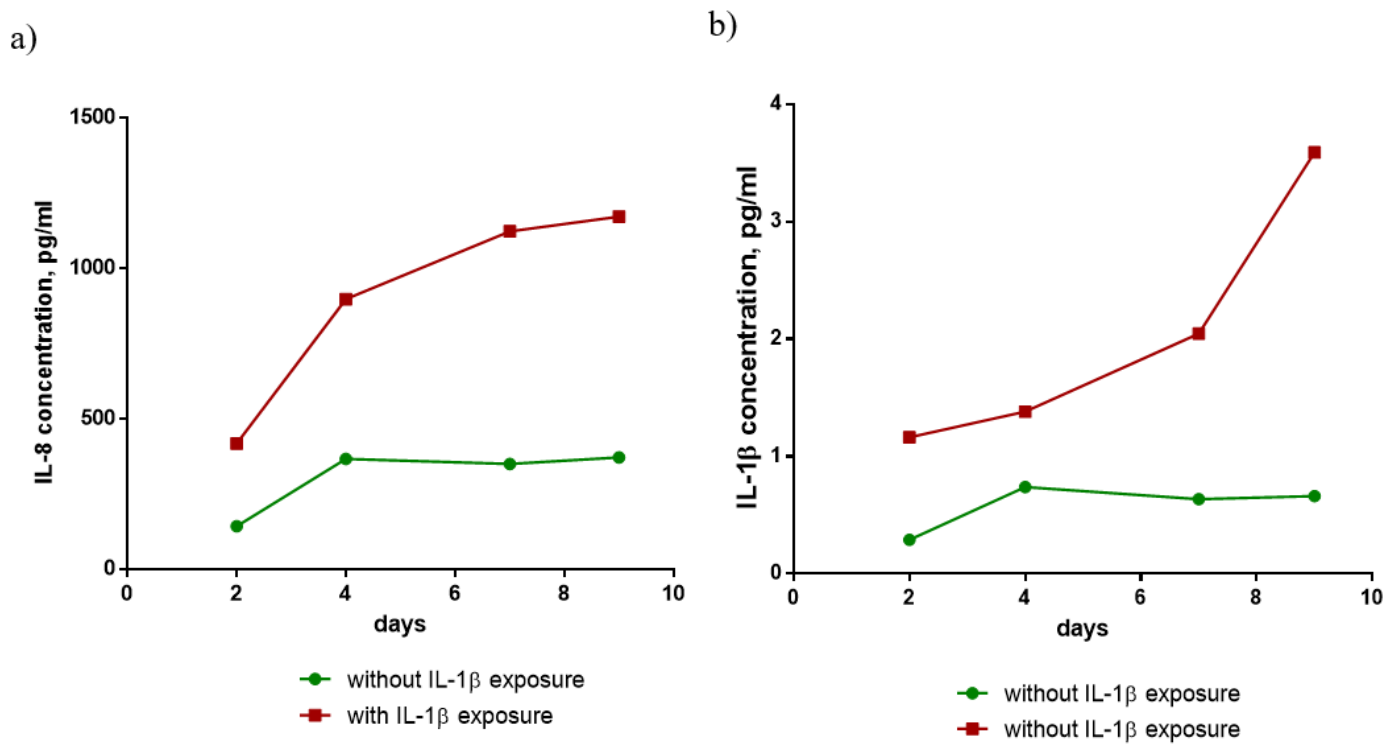

Figure 5

Dynamics of changes in the concentration of IL-8 (a) and IL-1β (b) depending on the external influence of IL-1β (1-4 ng/ml). a) Dynamics of changes in the IL-8 concentration; b) Dynamics of changes in the IL-1β concentration

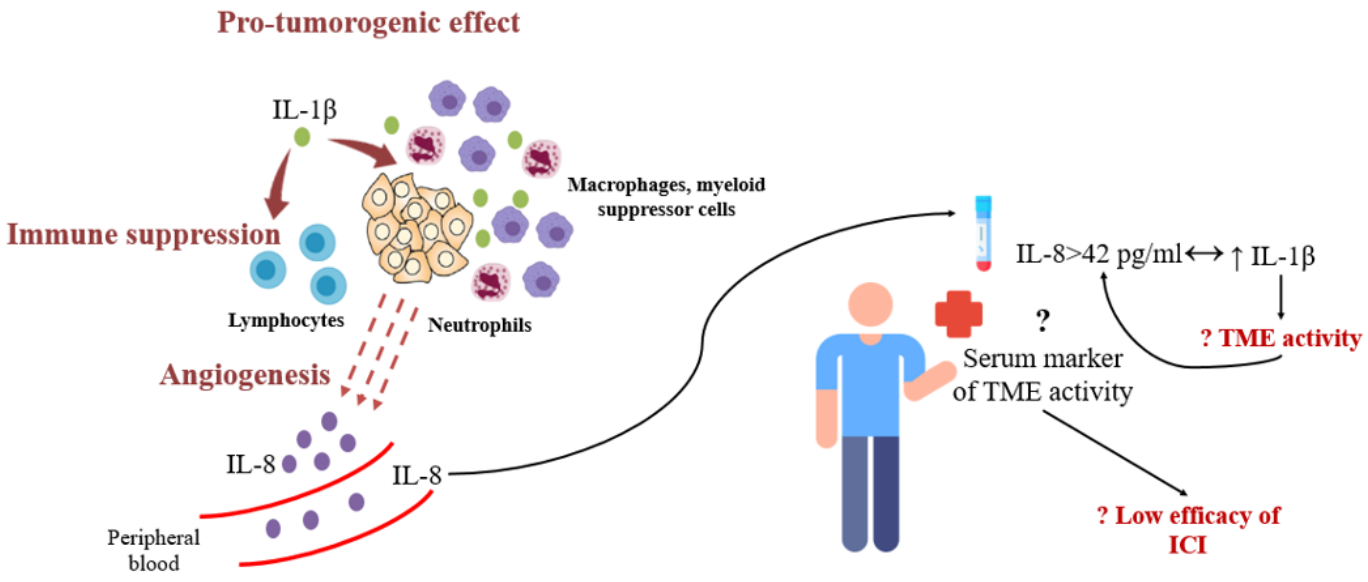

Figure 6

The assumed role of IL-1β in oncogenesis and the impact on ICI therapy, the diagnostic significance of determining IL-1β and IL-8 in patients with mts melanoma taking ICI.