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Original Article

# Human Leptin Hormone Affects TNF-α Production in Mucosal-associated Invariant T Cells

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**Background and Aims:** Mucosal-associated invariant T (MAIT) cells are striking lymphocyte population in the blood and their importance in immune responses is growing fast. The current study was conducted to evaluate leptin hormone effects on MAIT cell functions.

**Materials and Methods:** Five healthy male donors in ages of 22-30 years were selected and peripheral blood mononuclear cells (PBMCs) were enriched by Ficoll-density gradient. The cells were stimulated by different doses of human recombinant leptin. Using anti-CD3, anti-CD161 and anti-Vα7. 2 antibodies, positive CD3/CD161/ Vα7.2 MAIT cells were selected among stimulated PBMCS and proliferation alterations (after 5 days) and intercellular tumor necrosis factor (TNF)-α production (after 24 hours) were determined by flow cytometer.

**Results:** Stimulation of MAIT cells in doses of under 800 ng/ml of leptin did not alter the frequency of the cells significantly. However, in 800 ng/ml of leptin the number of the cells declined substantially, but statically analysis did show a significant difference with unstimulated and other leptin concentrations (p=0.12). When the frequency of intracellular TNF-α positive MAIT cells investigated, it revealed that in doses of 250 and 400 ng/ml of leptin, the number of the TNF-α. positive cells significantly increased compared to other concentrations (p=0.002). In high concentration of leptin (800 ng/ml), the frequency of positive TNF-α cell decreased compared to 400 ng/ml of the hormone.

**Conclusions:** Leptin hormone in doses of 250 and 400 ng/ml has affected MAIT cells' ability to produce TNF-α cytokine. Therefore, in adipose tissue leptin might be considered as a new source of inflammatory cytokines.

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## Introduction

Obesity and related complications are crucial health problem in many countries throughout the world. Obese people are more susceptible to infectious diseases, including pneumonia, bacteremia, nosocomial infections, periodontitis, skin infections and sepsis in comparing to non-obese subjects [1-3]. In addition, obesity has been overwhelmingly implicated in the etiology of different cancers, including colon, renal, gallbladder, pancreatic, endometrial and postmenopausal breast cancers [4, 5]. The increase in adipose tissue in obese people is directly associated with higher levels of inflammation and the increase in oxidative stress [6]. Leptin is a 16 kD peptide hormone, which elevated significantly in serum of obese people. Leptin concentration structurally and functionally is related to the Interleukin (IL)-6 cytokine family. The hormone affects target cells by its receptor, which called Ob-R (or Lepr). Ob-R is a member of the class I cytokine receptor family. Like IL-6 receptor, Ob-R also uses gp-130 to induce signal transduction [7]. Leptin plays pivotal role in regulating food intake and body weight [8]. In humans, leptin is produced by different cells, including adipocytes, stomach, mammary epithelial, chondrocytes and in some situations by lymphocytes. Previous studies have shown that the mutations in leptin and Ob-R genes in human are associated with obesity. Accordingly, obese individuals produce higher plasma leptin levels than do lean ones [9]. Leptin activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway similar to IL-6 cytokine. Leptin also activates phosphatidy linositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) [10]. Indeed, leptin functions in induction of inflammation and innate immune responses have not cleared yet. Consistently with inflammatory role of leptin, some studies have shown Lipopolysaccharides, tumor necrosis factor (TNF)-α and IL-1 increase plasma concentrations of the hormone [11]. However, based on other studies leptin levels in inflammatory conditions, including human immunodeficiency virus (HIV) infection and newborn sepsis [12] and in plasma of tuberculosis patients were significantly reduced [13]. Similarly, mice following intravenous injection of *Staphylococcus aureus* has shown the decreased plasma levels of leptin [14]. Based on plenty of observations, it might be concluded that leptin deficiency constitutes a proinflammatory state.

Recently studies on the effects of leptin on T cells have reported that the hormone stimulates developing T helper 1 (Th1) responses [15]. Furthermore, in humans, leptin deficiency was associated with reduced numbers of circulating Th cells and administration of human leptin reversed the number of the cells in the blood [16]. Innate immune semi-invariant natural killer T (iNKT) cells are enriched in adipose tissue of lean subjects compared with this tissue of obese patients [17]. According to another study, type II NKT cells initiate inflammation

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in the liver and adipose tissue and play considerable role in insulin resistance [18]. Although a few studies investigated leptin effects on T cells and iNKT cells, our knowledge about Mucosal-associated invariant T (MAIT) cells function in obesity and high concentration leptin need to be clear.

MAIT cells are a novel subset of innate-like T cells that in human predominantly was found in peripheral blood, intestinal mucosa, and liver [19]. Like iNKT cells, human MAIT cells express an invariant T cell receptor α chain, the Vα7. 2-Jα33 chain. The cells recognized presented antigens on major histocompatibility complex class I–related molecule MR1 [20]. Vitamin B2 (riboflavin) metabolites produced by bacteria and yeasts are recognized as specific ligands for MAIT cell receptor [21]. Recently, other host-derived small molecules, such as methylglyoxal and glyoxal and other bacterial products such as riboflavin metabolite 5-A-RU are considered as potent MAIT cell ligands [22, 23]. According to the new studies, MAIT cells in the inflammatory bowel disease patients produced significantly more IL-17 than from healthy donors, whereas there was no difference in IL-2 and TNF-α production [24]. Recent study showed MAIT cells accumulate in brain lesions of multiple sclerosis patients [25]. Additionally, MAIT cells implication in HIV-1 and tuberculosis infection are approved [26, 27]. In a study in 2015 it was revealed that MAIT cells are enriched in human adipose tissue and display an IL-17 positive phenotype in both obese adults and children [28]. Indeed, the exact role of MAIT cells in induction of inflammatory responses especially by adipokines is not elucidated. In the present study, for the first time we intend to investigate the TNF-α production in MAIT cells in responses to leptin in human intracellularly.

## Materials and Methods

### Cell preparation

In the experimental study, 5 healthy donors were selected. All the subjects were evaluated for concurrent infection, including influenza and common cold. Also, all donors did not receive immune suppressor drugs in one month before taking blood. 20 ml heparinized vein blood were taken from each attendant and transferred immediately to lab. Ficoll-paque density gradient centrifugation was used to enrich peripheral blood mononuclear cells (PBMCs).

### PBMCs culture and leptin stimulation

Isolated PBMCs were suspended in complete medium Roswell Park Memorial Institute (RPMI) 1640, 10 mM HEPES buffer, 200 Mm L-glutamine, 50 U of streptomycin-penicillin/ml (all from Gibco-BRL, Rockville, Md) supplemented with 10% human male AB serum (Sigma, St. Louis, Mo) and were cultured in 200 µl in 48-well microplate in 1000,000 cells per well in 37˚ C and 5% Co2.

### Intracellular TNF-α assay

PBMCs were stimulated with 1 µM Ionomycin and 20 ng/mL Phorbol 12-myristate 13-acetate (Sigma-Aldrich, St. Louis, MO, USA) as positive control and 20, 50, 100, 200, 400 and 1000 ng/ml of leptin (R

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& D systems, Minneapolis, MN, USA). The stimulated cells were analyzed at 24, 48 and 72 hours in the presence of 2 µM Brefeldin A (Sigma-Aldrich, St. Louis, MO, USA) for 5 hours. To evaluate the proliferation responses, PBMCs' culture continued up to 5 days. The cells were stained with anti-CD3, anti-CD4, anti-CD8, anti-Vα7. 2 and anti-CD161 for 30 min. in 37ºC. After washing in cold fetal calf serum in phosphate buffered saline (FCS/PBS) (2%) the cells were fixed by 1% paraformaldehyde. To stain TNF-α intracellularly, anti-TNF-α-PE (eBiosciense) diluted at 1:200 using cold PBS containing 0.1% Saponin was added to the cells and incubated for overnight in 4ºC. All measurements were carried out in triplicate for each concentration of leptin.

**Flow cytometry analysis**

Half million stained cells were analyzed by BD FACSConto II flow cytometry (BD Biosciences, San Jose, CA, USA). To analyze the data, FlowJo (version 6) was used. The following antibodies for flow cytometry were used:

anti-CD3-FITC (eBiosciense), anti-CD161-PEcy7 (eBioscinese), anti-Vα7.2-PerCp/cy5.5 (Biolegend), anti-TNF-PE (eBiosciense). Isotype, which controls antibodies with same clone and color were used.

## Statistical analysis

GarphPad prism version 7 was used to analyze the data. Using Kolmogorov-Smirnov test, the normality of the data was checked. Mann–Whitney U test was used for comparing the mean of producing on MAIT cells, which was producing TNF-α in different dose of leptin simulation. A p-value less than 0.05 considered as significant.

# Results

Proliferation of MAIT cells after 5 days were measured by flow cytometry and staining for Vα7.2 and CD161. The results have shown in figure 1 that proliferation responses of MAIT cells in the different dose of leptin have not shown significant differences. On the other hand, in the dose of 800 ng/ml, the number of MAIT cells showed decrease, but statistically there were not significant ($p>0.05$).

Frequency of TNF-α producing cells has assessed intracellularly in the stimulated cells in different concentrations of leptin. The results are shown in Figure 2. We analyzed TNF-α production in CD3, CD3CD8 and CD3CD8Vα7.2CD161 by gating the cells according to the gating strategy, which shown in figure 2 (A). Based on the Mann–Whitney U test, the percent of TNF-α positive MAIT cells compared with different concentrations of leptin. Accordingly, in 250 and 400 ng/ml concentration of leptin, frequency of TNF-α producing MAIT cells were significantly higher than the other dose of leptin and isotype control. In addition, in 800 ng/ml concentration of leptin, production of TNF-α was significantly decreased when compared with 250, 800 ng/ml. Our analysis in case of CD8 positive MAIT cells did show a significant difference between different doses of leptin as well as CD3 positive cells.

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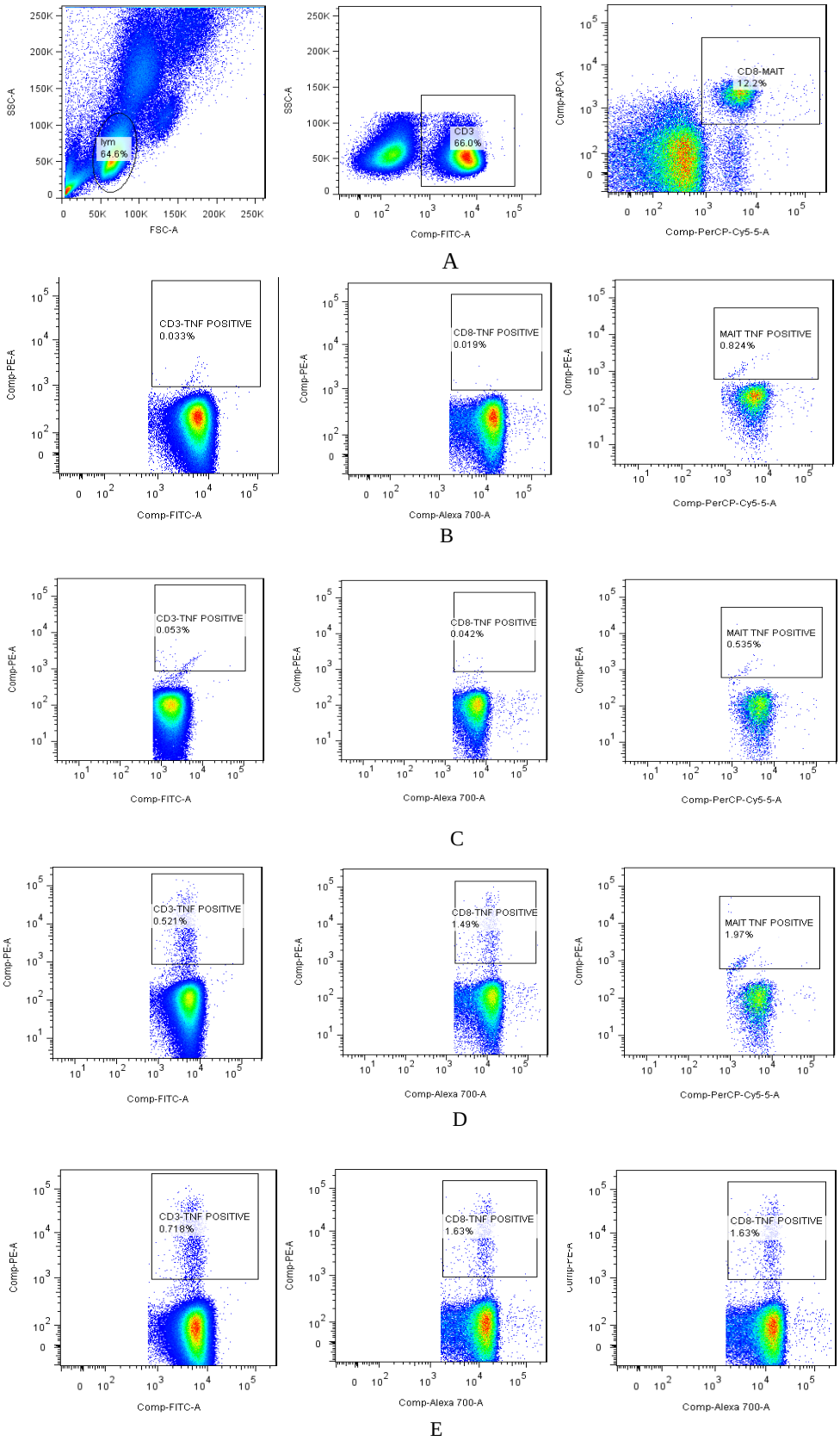



**Fig. 1.** Flow cytometry analysis of MAIT cells in PBMCs population. A: gating strategy for determining of CD3CD8Vα7.2CD161. Isotype controls were used for analyzing of stimulated cells (B). Stimulation of PBMCs was done based on different concentrations of leptin, which are shown in following section including 50 ng/ml (C), 250 ng/ml (D) and 800 ng/ml (E) respectively.

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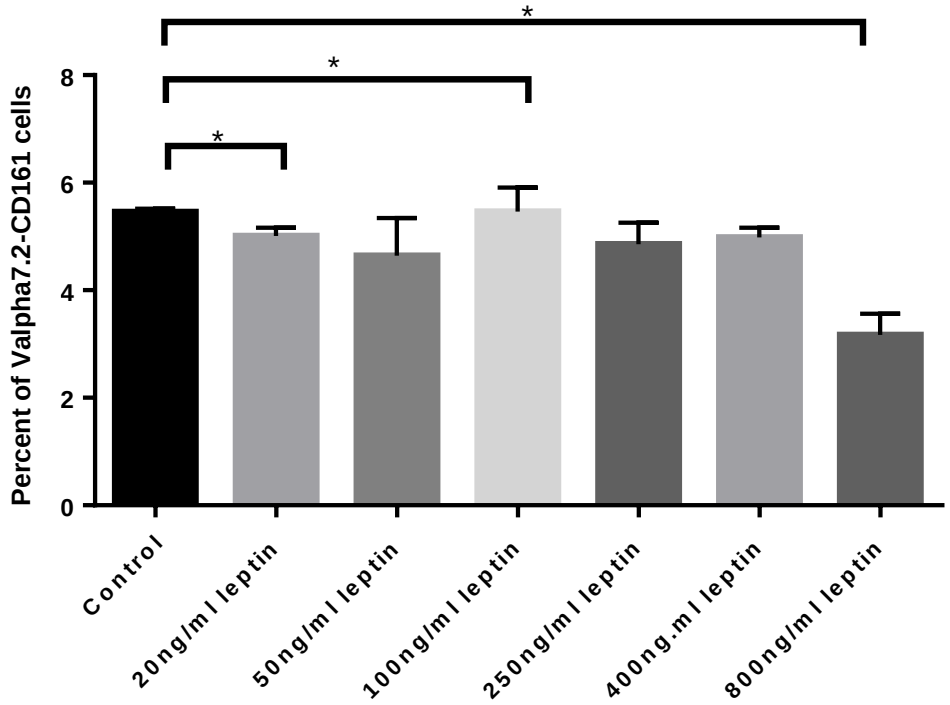



**Fig. 2.** Frequency of MAIT cells in response to leptin stimulation. PBMCs were cultured in the presence of different doses of leptin for 5 days and frequency of positive cells for CD3CD161Vα7.2 were determined and compared with unstimulated cells. Statistical analysis did not show significant differences between the different groups ($p>0.05$). *shows no significant differences.

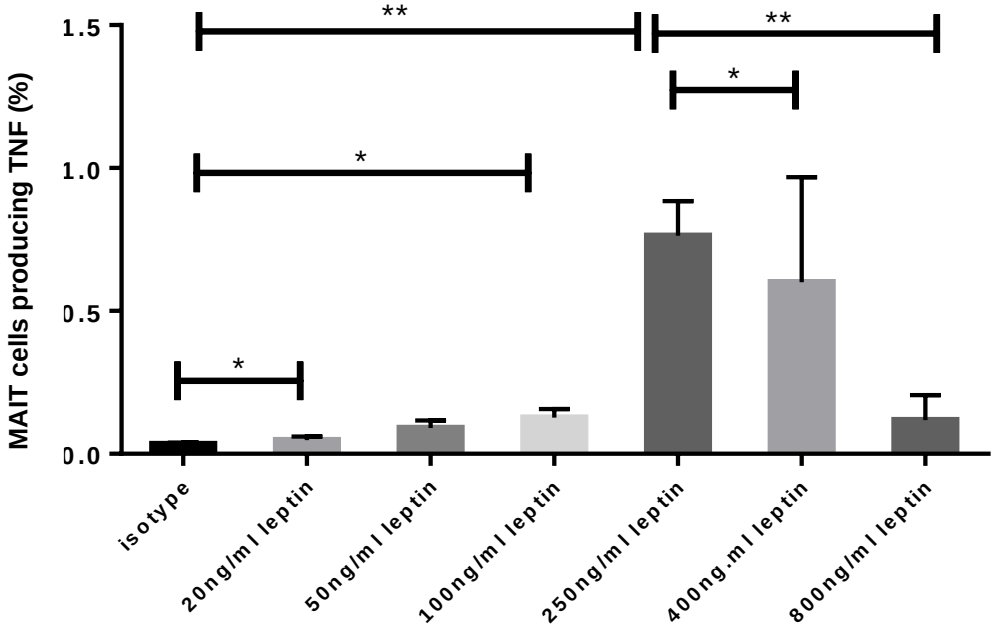



**Fig. 3.** Frequency of intracellular TNF-α positive MAIT cells stimulating with different doses of human recombinant leptin. As the graph shows, in 250 ng/ml of leptin, frequency of TNF-α producing MAIT cells are higher than unstimulated cells and other doses of leptin. Production of TNF-α by MAIT cells was not dose dependent and with 800 ng/ml of leptin, TNF-α positive MAIT cells declined significantly when compared with 250 and 400 ng/ml of leptin. *shows no significant and ** shows significant differences.

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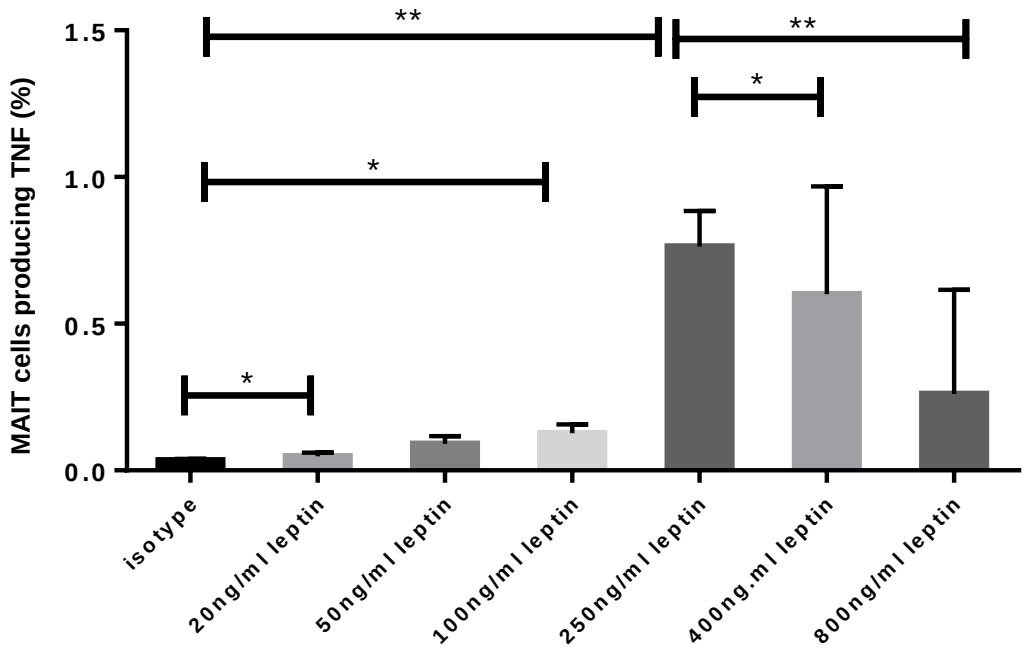



**Fig. 4.** Frequency of TNF-α positive MAIT cells, which stimulated by human recombinant leptin were evaluated by flow cytometry using CD3CD161Vα7.2 markers. The stimulated cells were assessed intracellularly after 48 hours and as the graph shows, in 250 and 400 ng/ml of leptin, frequency of TNF-α producing MAIT cells are higher than unstimulated cells and other doses of leptin. *shows no significant and **shows significant differences between groups.

## Discussion

Although Leptin's effects on conventional T cells and regulatory T cells have investigated in recent years, in case of MAIT cells, very limited studies have been conducted [29]. In our study, it was shown for the first time that leptin in concentrations of 250 and 400 ng/ml affects TNF-α production intracellularly. In our study, MAIT cells were cultured in medium supplemented with 5% human AB serum (0.5–1 ng/ml) because FCS or fetal bovine serum contains 10–20 ng/ml leptin in RPMI 10% FCS. In the present study frequency of MAIT cells after 5 days of stimulation with leptin in different doses were evaluated. Our results showed a decreased frequency of MIAT cells in dose of 800 ng/ml, whereas in other concentrations proliferation did not show a significant difference. Based on these results, leptin did not affect on the proliferation ability in MAIT cells in physiologic concentration while in high concentration of the hormone proliferation of the cells decreased substantially. Such high concentration might exist only in lipid tissues. According to the other studies, leptin has substantial suppressive effects on regulatory T cells proliferation at 250 ng/ml. Interestingly, anti-leptin antibody has been suggested as a method for recovery expansion ability of the cells in human. Other researches also indicated

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that leptin neutralization could induce IL-2 secretion by regulatory T cells. Other related studies approved that the efficiency of anti-leptin antibody in inducing proliferation of regulatory T cells is better than recombinant IL-2. Conversely, addition of increasing doses of recombinant leptin to the cell cultures has not affected the IL-2-mediated proliferation. In case of human MAIT cells, it is strongly suggested that the role of IL-2, IL-12 and IL-18 in proliferation of the cells investigate.

Human MAIT cells in response to the certain stimulants have ability to produce inflammatory cytokines [30, 31]. Involvement of the cells in effective immune responses especially against extracellular bacterial has been approved. Recent studies also have shown that there is an interesting cooperation between the cells and Th17 cells exists [32, 33]. MAIT cells are mainly activated the bacteria's vitamin B12 derivatives [34]. According to the new researches, it has been cleared that IL-12 and IL-18 stimulation simultaneously activates the cells independent of T cell receptor engagement [35, 36]. Effects of leptin on cytokines production by MIAT cell has not investigated yet. In case of our study, MAIT cell responded to 250 and 400 ng/ml of leptin hormone by inducing TNF-α intracellularly. We have not investigated the likelihood activation mechanisms of MAIT cells by leptin while it is important to find out the mechanisms of MAIT activation because leptin as important protein in lipid metabolism besides its presence in blood (10-30 ng/ml in human) in the lipid tissue it seems is more concentrated comparing to blood, which may affect MAIT cells behaviors. Therefore, leptin can in cooperation with IL-6 and using very similar receptor induces inflammatory responses [37]. Based on the new findings in human regulatory T cells (CD3CD25FOXP3+) have ability to produce leptin and express high amounts of leptin receptor (ObR) on their surfaces [38, 39]. Interestingly, leptin causes persistent anergic state in regulatory T [40]. Additionally, T cells are able to express leptin receptors on their surface [35, 41-43]. In case of MAIT cells this issue, neither has nor cleared so far. We have done the study in different concentrations of leptin, including physiologic concentration 20 and 50 ng/ml (obese serum levels) and high dose of leptin, which our results confirmed in the physiologic levels leptin has not induced TNF-α in the MAIT cells of course in protein level. However, our results showed in high dose of leptin, MAIT cells are affected by increasing TNF-α production. Although, the leptin's dose that was used in the study has not seen in serum of subjects, but in lipid tissues, the condition might be created.

## Conclusion

MAIT cells as an important population of T cells are affected by leptin hormone in human functionally. Some inflammatory condition in obese people may be mediated by this protein. Very similar receptors for leptin and IL-6 show that synergistic effects may exert between leptin and other inflammatory cytokine in inducing acute phase proteins especially C-reactive protein.

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## Conflict of interest

The authors expressed no conflicting financial interests.

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