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# A Theoretical Approach for Investigation of IL-17 Signalling Pathway in Psoriasis

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## Abstract

Cytokines play a substantial role in many biologic mechanisms of body organs. The mechanisms involved in production and receptor pathways of these important proteins are not completely understood. For more study about receptor and producing signaling of cytokines, we design a panel to investigate the mechanisms which interfere with this biologic process. For more detail explanation of our idea, we focused on IL-17 secretion from T helper 17 cells of healthy and psoriatic groups in both in vitro and in vivo panels. With operating this research panel, we would have better comprehension about mechanisms involved in releasing of IL-17 from T helper 17 cells of both healthy and psoriatic groups. We would also have better understanding around IL-17 receptor signaling pathways of both normal and psoriatic subsets. Along the way, we could realize changes of mentioned mechanisms in psoriasis which should consider as potential therapeutic targets. Moreover, this study encompassed the new onset patients of psoriasis for evaluation of mechanisms related to initiation of this disease. We concluded that this panel has the capability to be an effective method for assessment of signaling pathways of different secretory agents which release from various cells. Furthermore, this panel is capable to illustrate gene expression changes which occur in many processes such as aging, wound healing, inflammatory diseases, malignancies, etc.

## Keywords

Cytokines Signalling, IL-17, Gene Expression Pattern, Psoriasis, Inflammation, Speculation of IL-17 Generation Signalling

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## 1. Introduction

Cytokines are biological proteins secret from different immune cells such as neutrophils, macrophages, T and B cells, etc. Other cells which have essential role in immune responses like endothelial cells, epithelial cells and fibroblasts can also release cytokines. These proteins play a key role in interactive signalling among immune and other cells. Cytokines execute both inflammatory and anti-inflammatory performances in body tissues [1]. They react against pathogenic micro-organisms and make immune tolerance to gastrointestinal Microbiota as examples of inflammatory and anti-inflammatory actions, respectively [2, 3]. On the other hand, these immune agents exert their role in wound healing, aging, and other biologic processes [4, 5].

Through the pivotal role of cytokines in progression of different diseases such as malignancies, immune deficiencies, autoimmune disease, infectious disease and aging phenomenon, it's important to recognize the exact molecular pathways involved in stimulation and inhibition of cytokines generation [6-8]. Despite the crucial role of cytokines, stimulatory and inhibitory processes related to generation of them are unknown. For example, positive relationship among stimulation of sympathetic receptors (including α, β) and releasing of inflammatory cytokines such as IL-1, 6 and TNF- α has been demonstrated in medical literature [9, 10]. Also, positive correlation among inhibition of cyclooxygenase 2 (COX2) and decreased production of IL-6

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have been explained [11]. However, signalling pathways among sympathetic receptors and COX2 with secretion of noted cytokines are unrecognized. Also, it seems that the basic signalling which initiate the gene expression of cytokines in healthy individuals are unknown yet. On the other hand, the processes of cytokines signalling in above-mentioned clinical complications are probably changed [12].

With identifying the normal and pathologic signalling which interferes with generation of cytokines, we can detect the pathologic alterations in different disorders and this potential achievement would help us finding new therapeutic targets

### 1.1. Our Hypotheses

We proposed a theoretical panel for more detail assessment of the basic signalling related to generation of cytokines. We aimed to investigate the basic pattern of cytokines production through RNA sequence technique. For explanation of our idea, we decided to evaluate the signalling involved in the generation of interleukin 17 from T helper 17 cells in normal population and patients with psoriasis. *(The following panel is just for explanation of our idea about the gene expression pattern and the interpretation of it. Thus, we do not perform any experimental study about this idea).*

### 1.2. Expand This Panel (Our Hypothesis)

We suggest generalizing this research panel for other cytokines and biologic agents in different cells of immune system and other biologically active cells in both healthy and patient individuals. For example, assessment of TNF-α in macrophages and synovial cells of patient with rheumatoid arthritis and healthy individuals with the same method is fundamental study to find novel therapeutics for this autoimmune disease. We also propose to generalize this research panel for assessment of new onset form of systemic disease compared with chronic forms of them

## 2. Material and Methods

### 2.1. In Vitro

We employ three separated groups of 12 individuals (each group contains 4 participants) which include normal group, new onset patients with psoriasis and patients with psoriasis who afflicted with psoriasis for at least 2 years. Normal group are healthy individuals who aimed for evaluating the manner of genes expression in T helper 17 cells as the baseline pattern and after exposure to IL-17, anti-IL17, anti-IL17 receptor antibody in separated cell cultures taken from them. Second group are patients with new onset of psoriasis who should be assessed in terms of gene expression exactly like the normal group. Finally, third group are patients with psoriasis (for at least 2 years) who should be assessed in terms of gene expression exactly like other groups.

Baseline Assessment of Genes Expression:

We separate T helper 17 from all three groups through MACS (magnetic associated cell sorter) technique. Indeed, we have 12 separated cell lines, belong to each of 12 individuals (4 cell lines of normal group, 4 cell lines of new onset psoriasis and 4 cell lines of patient with at least two years of psoriasis), for assessment of genes expression without any intervention. Then, we assess a sample of T helper 17 cells of all groups with RNA sequencing. Hence, we have 12 numbers of RNA sequencing results as baseline genes expression.

Providing Cell Lines for More Gene Expression Assessment in Exposure with IL-17, Anti-IL17 and Anti-IL17 Receptor:

After noted baseline investigation, we divide each of cell lines of T helper 17 samples into three cell cultures (Thus, we have 3 numbers of cell samples for every participant in order to incubation of each of them with IL-17, anti-IL17 antibody and anti-IL17 Receptor antibody in separated lines). In fact, for each of three groups, we have 12 numbers of separated cell cultures. We have 36 numbers of separated cell cultures, totally.

#### 2.1.1. Normal Group Study

1) We incubate the cells of normal group (4 separated cell lines) with IL-17 (with concentration of 27.3 ± 9.5 mcg/mL) (FDA approved subcutaneous dose of 300mg Secukinumab [7], in order to achieve 27.3 ± 9.5 mcg/mL plasma concentration of this human anti-IL17 monoclonal antibody for management of psoriasis. Hence, we decided to provide this concentration of IL-17 and anti-IL17, Secukinumab, for our human cell culture) and take samples from the cell culture used for RNA sequencing every 12 hours up to six times (72 hours). (Total numbers of RNA sequencing in this part are 24 times).
2) We incubate the cells of normal group (4 separated cell lines) with anti-IL17 (with concentration of 27.3 ± 9.5 mcg/mL) (FDA approved subcutaneous dose of 300mg Secukinumab [13], in order to achieve 27.3 ± 9.5 mcg/mL plasma concentration of this human anti-IL17 monoclonal antibody for management of psoriasis. Hence, we decided to provide this concentration of IL-17 and anti-IL17, Secukinumab, for our human cell culture) and take samples from the cell culture used for RNA sequencing every 12 hours up to six times (72 hours). (Total numbers of RNA sequencing in this part are 24 times).
3) We incubate the cells of normal group (4 separated cell lines) with Brodalumab, a human anti-IL17 receptor antibody, with concentration of 13.4mcg/mL. (According to Medscape explanation, the peak plasma concentration of

Brodalumab is 13.4μgr/ml) [8]. Thus, we use this concentration for our human cell cultures) and take samples from the cell culture used for RNA sequencing every 12 hours up to six times (72 hours). (Total numbers of RNA sequencing in this part are 24 times).

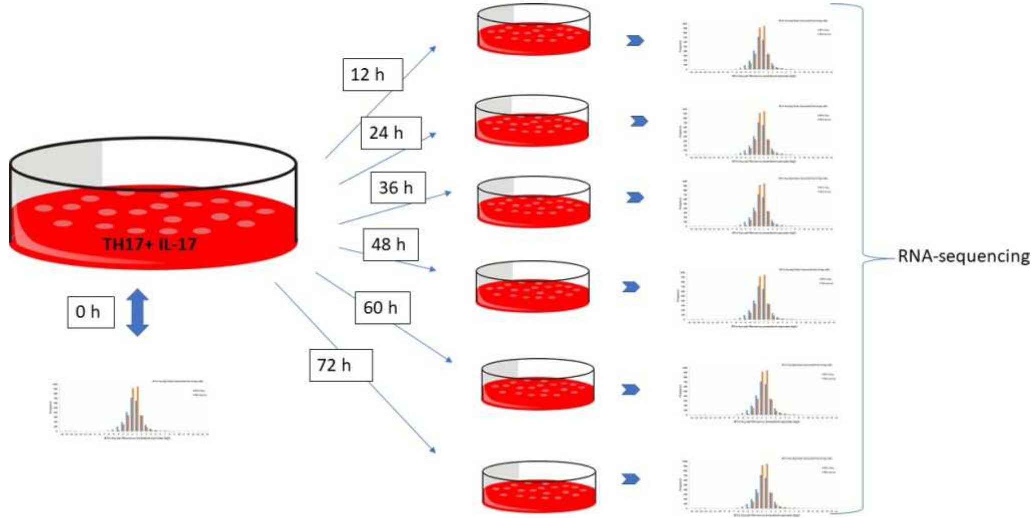


**Figure 1.** We incubate the cells of normal group (4 separated cell lines) with IL-17.

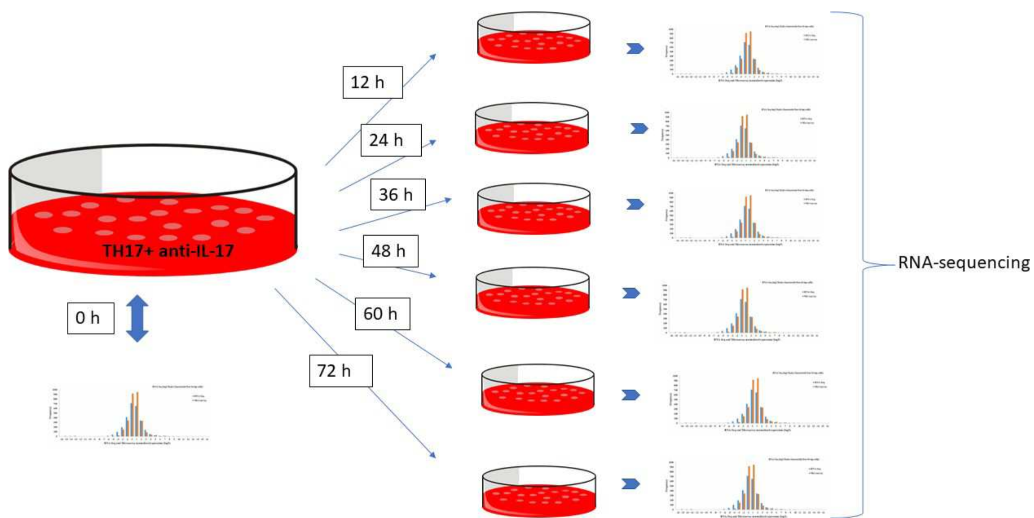


**Figure 2.** We incubate the cells of normal group (4 separated cell lines) with IL-17.

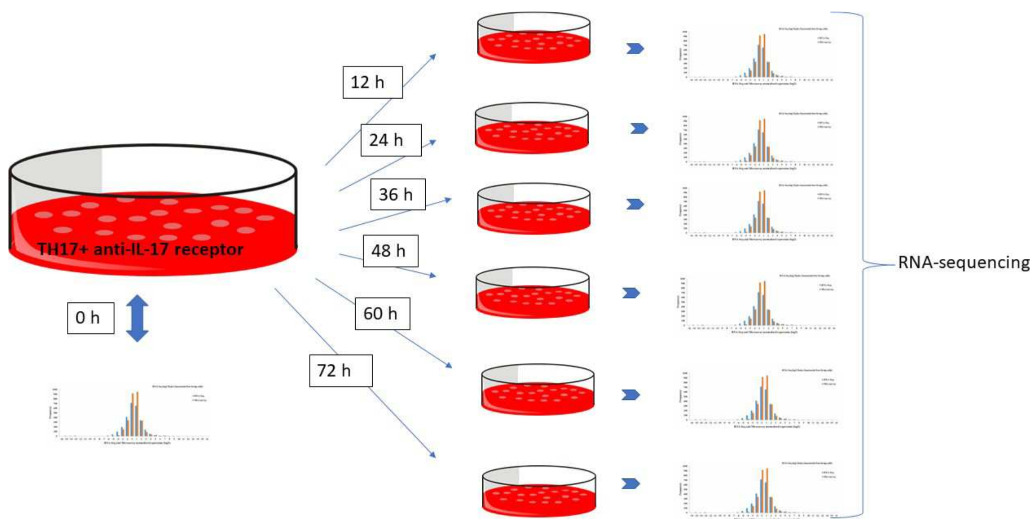


**Figure 3.** We incubate the cells of normal group (4 separated cell lines) with Brodalumab, a human anti-IL17 receptor antibody.

### 2.1.2. New Onset Patient with Psoriasis Study

4) We incubate the cells of new onset patient group (4 separated cell lines) with IL-17 (with concentration of 27.3 ± 9.5 mcg/mL) and take samples from the cell culture used for RNA sequencing every 12 hours up to six times (72 hours). (Total numbers of RNA sequencing in this part are 24 times)
5) We incubate the cells of new onset patient group (4 separated cell lines) with anti-IL17 (with concentration of 27.3 ± 9.5 mcg/mL) and take samples from the cell culture used for RNA sequencing every 12 hours up to six times (72 hours). (Total numbers of RNA sequencing in this part are 24 times)
6) We incubate the cells of new onset patient group (4 separated cell lines) with Brodalumab, a human anti-IL17 receptor antibody, (with concentration of 13.4 mcg/mL) and take samples from the cell culture used for RNA sequencing every 12 hours up to six times (72 hours). (Total numbers of RNA sequencing in this part are 24 times)

### 2.1.3. Study of Patients with at Least 2 Years of Psoriasis

7) We incubate the cells of patients with at least 2 years of psoriasis (4 separated cell lines), with IL-17 (with concentration of 27.3 ± 9.5 mcg/mL) and take samples from the cell culture used for RNA sequencing every 12 hours up to six times (72 hours). (Total numbers of RNA sequencing in this part are 24 times)
8) We incubate the cells of patients with at least 2 years of psoriasis (4 separated cell lines), with anti-IL-17 (with concentration of 27.3 ± 9.5 mcg/mL) and take samples from the cell culture used for RNA sequencing every 12 hours up to six times (72 hours). (Total numbers of RNA sequencing in this part are 24 times)
9) We incubate the cells of patients with at least 2 years of psoriasis (4 separated cell lines) with Brodalumab, a human anti-IL17 receptor antibody, (with concentration of 13.4 mcg/mL) and take samples from the cell culture used for RNA sequencing every 12 hours up to six times (72 hours). (Total numbers of RNA sequencing in this part are 24 times)

We would take 12 numbers of results of RNA sequencing as baseline investigation of whole genes expression. Also, we would take 216 numbers of results of RNA sequencing from all three groups after exposure to IL-17, anti-IL17 and anti-IL17 receptor antibody in 12 hours intervals. Thus, the total numbers of RNA sequencing in in vitro part of this study is 228 times of RNA sequencing.

## 2.2. In Vivo

In animal study, we propose to investigate the role of IL-17 in T helper 17 cells of mice. In order to perform this investigation, we should utilize 12 numbers of mice in four separated groups (each group contains 3 numbers of mice), including two group of normal mice (first group for IL-17, second group for anti-IL17) and two groups of psoriatic mice model (first group for IL-17, second group for anti-IL17).

Most studies which assessed the effects of IL-17 Receptor signalling in psoriatic mice are carried out it through deletion of IL-17 Receptor gene. Hence, through the lack of evidence about administration of IL17 Receptor antibody in psoriatic mice, we cannot propose injection of this antibody in in vivo part of this study.

### 2.2.1. Normal Group Assessment IL17

In normal mice, we should separate T helper 17 cells from them (with MACS) and perform RNA sequencing as a baseline investigation. Then, we inject a proper dose of IL-17 (500 µgr per mouse [15]), (Despite lack of any in vivo experiment about confirmed dose of IL-17, according to Kimiko Nakajima et al., mouse model of psoriasis study who utilized this dose of anti-IL17 for controlling of this disease, we presume to administer this dose of the cytokine for our panel.) through intravenous administration. After 72 hours, we repeat RNA sequencing from T helper 17 cells with the same method. Hence, we have 6 times of RNA sequencing in this part of study.

### 2.2.2. Anti-IL17

We also should evaluate the role of anti-IL17 in T helper cells in normal mice. We separate T helper 17 cells from them (with MACS) and perform RNA sequencing as a baseline investigation. Then, we inject a proper dose of ani-IL17 (500 µgr per mouse [13]), (Despite lack of any in vivo experiment about confirmed dose of IL-17, according to Kimiko Nakajima et al., mouse model of psoriasis study who utilized this dose of anti-IL17 for controlling of this disease, we presume to administer this dose of this cytokine for our panel.) through intravenous administration. After 72 hours, we repeat RNA sequencing from T helper 17 cells with the same method. Therefore, we have 6 times of RNA sequencing in this part of study.

### 2.2.3. Psoriatic Group Assessment IL17

In psoriatic study, we should separate T helper 17 cells from 3 numbers of mice (with MACS) and perform RNA sequencing as a baseline investigation. Then, we inject a

proper dose of IL- 17 (500 μgr per mouse), through intravenous administration. After 72 hours, we repeat RNA sequencing from T helper 17 with the same method. Hence, we have 6 times of RNA sequencing in this part of study.

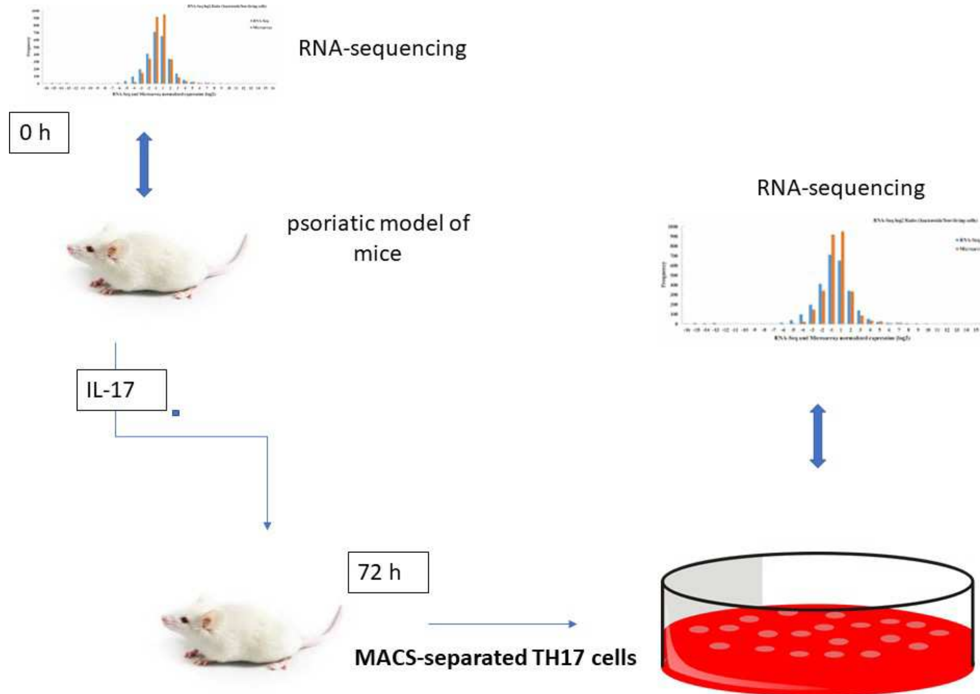


**Figure 4.** In psoriatic study, we should separate T helper 17 cells from 3 numbers of mice (withMACS).

### 2.2.4. Anti-IL17

We also should assess the role of anti-IL17 in T helper cells of 3 separated psoriatic mice. We should separate T helper 17 cells from mice (with MACS) and perform RNA sequencing as a baseline investigation. Then, we inject a proper dose of anti-IL17 (500 μgr per mouse), through intravenous administration in psoriatic mice. After 72 hours, we repeat RNA sequencing from T helper 17 with the same method. Hence, we have 6 times of RNA sequencing in this part of study.

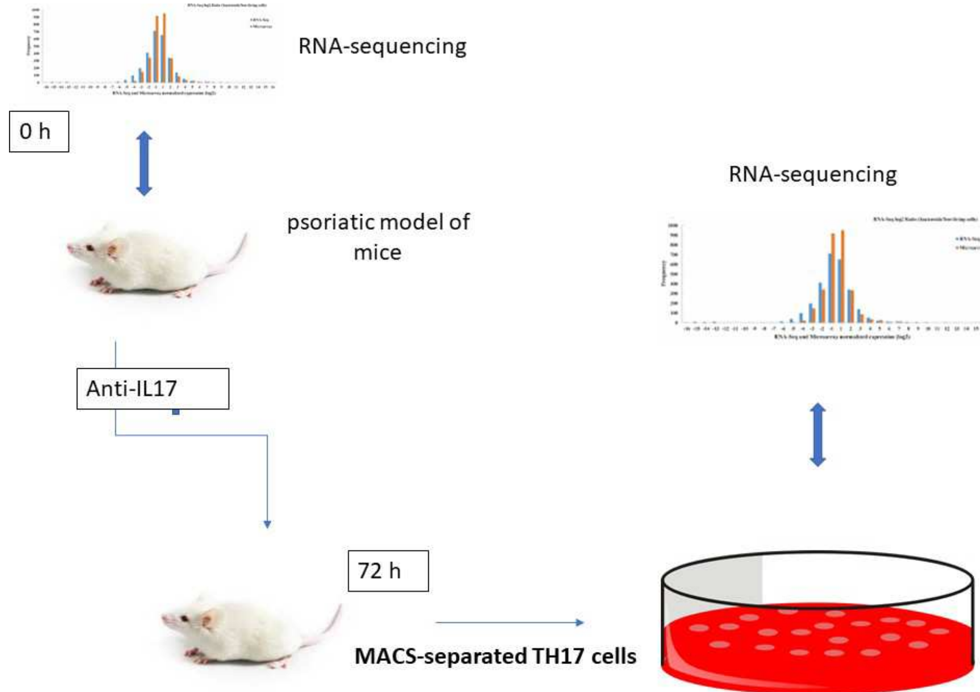


**Figure 5.** We also should assess the role of anti-IL17 in T helper cells of 3 separated psoriatic mice. We should separate T helper 17 cells from mice (with MACS).

Along the way, total numbers of RNA sequencing in in vivo part of this study is 24 times.

Collectively, we have 252 times of RNA sequencing in this study.

# 3. Discussion and Results

RNA sequencing technique analyses 21000 genes expression approximately. Results of RNA sequencing are scales which demonstrate the amounts of m-RNAs related to each of gene expression [14].

Due to unknown mechanisms involved in production of IL-17 in healthy and patient individuals, analyse differences between these groups is complicated. However, we want to elucidate the essential interpretations which are necessary for this study.

## 3.1. Potential Consequences of Normal Group Study (in Vivo and in Vitro)

Through unknown pattern which regulate the production of cytokines, we designed a panel to illustrate whole genes expression of T helper 17 cells in separated steps. With analysing the results of RNA sequencings in normal group and studying the manner of expression of any specific gene (with IL-17, anti-IL17 and anti-IL17 receptor in vivo and in vitro results), we can speculate the signalling pattern related to generation of IL-17. The same interpretation should carry out in patient groups with psoriasis (with IL-17, anti-IL17 and anti-IL17 receptor in vivo and in vitro results).

To proper interpretation of consequences, we should adjust all animal (in vivo) studies results of RNA sequencings with human cell cultures (in vitro) results of RNA sequencings.

After adjustment of gene expression results in normal groups of in vivo and in vitro study (with exception of patients with new onset of psoriasis in in vitro part of study), we should detect genes with the most expression changes. Probably the proteins belonged to the mentioned genes have key roles in signalling pathways of IL-17. Hence, this panel can help us to detect more signalling pathways which interfere with IL-17 production in normal individuals. Based on understanding physiologic signals interfere with IL-17 generation from T helper 17 cells, we can have better insight into the process of this polypeptide production.

We assumed that we have 4 separated groups of genes which can interfere with receptor signalling and generation signalling of IL-17 in Normal T helper 17 cells including:

A) Group A of genes which demonstrate increased expression when IL-17 receptors stimulate. It means that expression of these genes is related to IL-17 receptor and stimulation of IL-17 receptor has stimulatory influences on these genes.

B) Group B of genes which show decreased expression when IL-17 receptors stimulate. It means that expression of these genes is related to IL-17 receptor and also stimulation of IL-17 receptor has inhibitory influences on these genes.

C) Group C of genes which have stimulatory effect on IL-17 production. It means that raised expression of these genes lead to increased production of IL-17.

D) Group D of genes which have inhibitory effect on IL-17 production. It means that raised expression of these genes lead to decreased production of IL-17.

Based on mentioned A, B, C and D groups of genes, what kind of genes expression behaviour can we expect about each of them?

To answer this question, we should assume that negative feedback (which regulates releasing of hormones) plays an important role in production of IL-17 from T helper 17 cells [15]. We should also assume that biological signalling (sensors) which detect high levels of IL- 17 are different from the sensors which detect low levels of IL-17 in T helper 17 cells.

Based on these assumptions (and after adjustment of animal study with human cell culture), we want to expect gene expression manner in each cell line of normal groups:

*Group A:*

With respect to our explanation, group A of genes shows additive manner of expression after stimulation of IL-17 receptor. In other words, IL-17 receptors stimulate genes expression of group A. Therefore, these are a category of genes which have most growth (ascending slope) in terms of gene expression after exposure of IL-17 to T helper 17 cells. Also, these genes demonstrate most declines (descending slope) in terms of gene expression after exposure of anti-IL17 receptor antibody to T helper 17 cells. Finally, this group of genes reveal decreased manner in terms of gene expression after exposure to anti-IL17 antibody. The rate of decreasing of gene expression after exposure to anti-IL17 antibody is possibly less compared with anti- IL17 receptor antibody exposure.

We know that anti-IL17 receptor antibody can completely block IL-17 receptor. On the other hand, after exposure of normal T helper 17 cells to anti IL-17 antibody: 1) it is possible that all

IL-17 polypeptides would not completely neutralize. Thus, exceedingly small amounts of IL-17 are sufficient for minimal activity of IL-17 receptors. 2) Even if we assume

that all IL-17 proteins have been neutralized, it is possible that IL-17 receptors could be slightly stimulated by other inflammatory cytokines. Due to partial blockade of IL-17 receptors in normal cell cultures which have been exposed to anti-IL17 antibody, these receptors can continue their function with minimal activity. Hence, the rate of decreasing of gene expression after exposure to anti- IL17 antibody is maybe less than anti-IL17 receptor antibody exposure.

Diagram 1 (Group A)

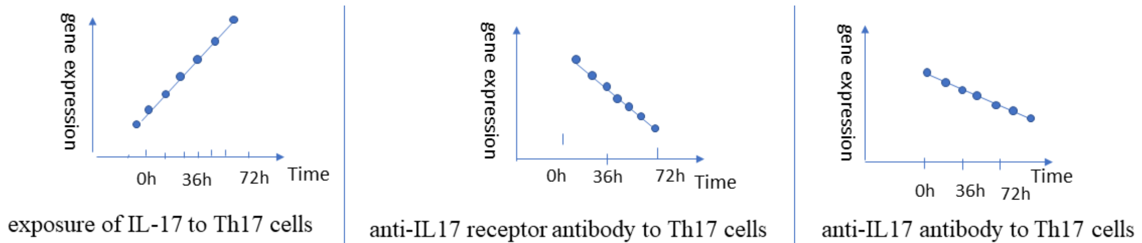


**Figure 6.** Group A of genes shows additive manner of expression after stimulation of IL-17 receptor.

*Group B:*

Based on our explanation, group B of genes shows declining manner of expression after stimulation of IL-17 receptor. In other words, IL-17 receptors inhibit genes expression of group B. Therefore, these are a category of genes which have most growth (ascending slope) in terms of gene expression after exposure of anti-IL17 receptor antibody to T helper 17 cells. Also, these genes demonstrate most declines (descending slope) in terms of gene expression after exposure of IL17 to T helper 17 cells. Finally, this group of genes exhibit decreased manner in terms of gene expression after exposure to anti-IL17 antibody. Because of noted reason, the rate of increasing of gene expression after exposure to anti-IL17 antibody is possibly less compared with exposure to anti-IL17 receptor antibody.

*Diagram 2 (Group B)*

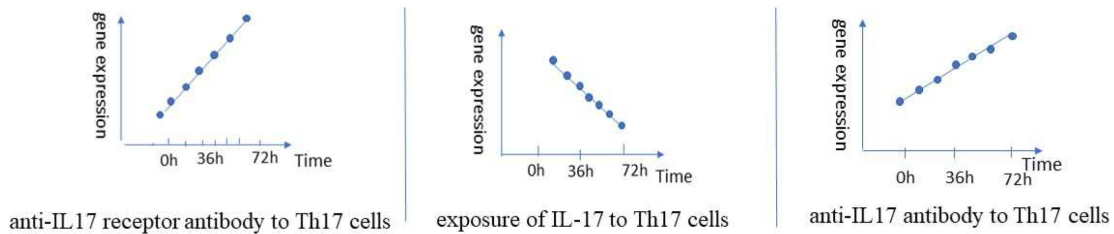


**Figure 7.** Group B of genes shows declining manner of expression after stimulation of IL-17 receptor.

*Group C:*

According to our definition, group C of genes have stimulatory performance in producing of IL-17. Based on our assumptions, we can expect that this category of genes has most growth (ascending slope) in terms of gene expression after exposure of anti-IL17 to T helper 17 cells. In a setting of negative feedback, exposure of anti-IL17 to normal T helper 17 cells lead to neutralization of IL-17 peptides and subsequent stimulating of expression of these genes. Also, these genes illustrate most declines (descending slope) in terms of gene expression after exposure of IL17 to T helper 17 cells (due to negative feedback). Finally, this group of genes show steady manner in terms of gene expression after exposure to anti-IL17 receptor antibody (Since this group of genes is not related to IL-17 Receptor signalling).

*Diagram 3 (Group C)*

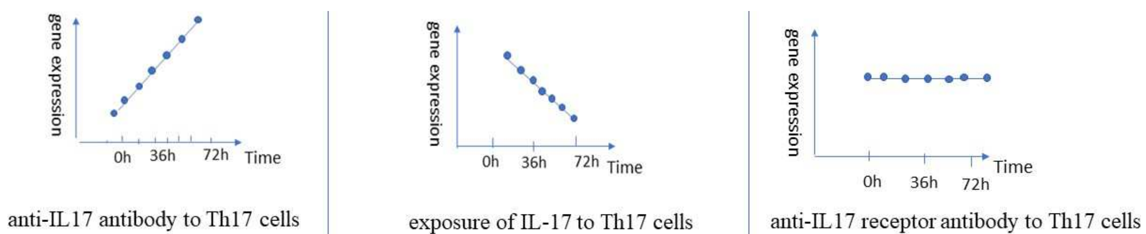


**Figure 8.** Group C of genes have stimulatory performance in producing of IL-17.

*Group D:*

According to our description, group D of genes have inhibitory effects on production of IL-17. Based on our assumptions, we can speculate that this category of genes has most growth (ascending slope) in terms of gene expression

after exposure of IL17 to normal T helper 17 cells. In a setting of negative feedback, exposure of IL17 to normal T helper 17 cells result in reduced production of IL-17 peptides and subsequent stimulating of expression of these genes. Also, these genes illustrate most declines (descending slope) in terms of gene expression after exposure of anti-IL17 to T helper 17 cells (due to negative feedback). Finally, this group of genes show steady manner in terms of gene expression after exposure to anti-IL17 receptor antibody (Since this group of genes is not related to IL-17 receptor signaling).

*Diagram 4 (Group D)*

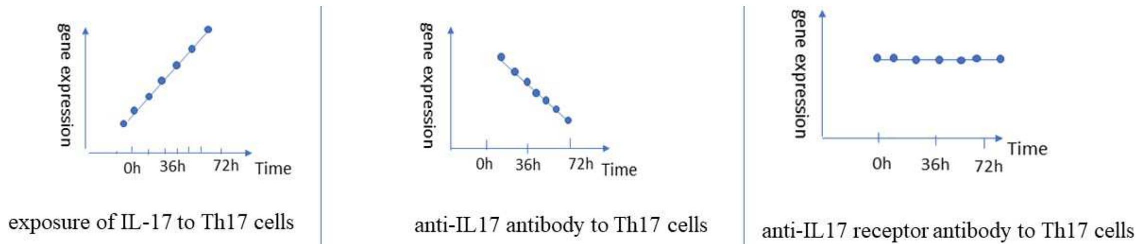


**Figure 9.** Group D of genes have inhibitory effects on production of IL-17.

## 3.2. Potential Consequences of Psoriatic Group Study (in Vivo and in Vitro)

After adjustment of gene expression results in psoriatic groups of in vivo and in vitro study, we should identify genes with the most expression changes. Probably the proteins belonged to the mentioned genes have key roles in signalling pathways of IL-17 generation. Hence, this panel can help us to detect more signalling pathways which interfere with IL-17 production in psoriasis. Based on understanding pathologic signals interfere with IL-17 production from T helper 17 cells, we can have better understanding about the process of this polypeptide production.

We assumed that we have 2 separated groups of genes which can interfere with receptor signalling of IL-17 in psoriatic T helper 17 cells including:

A) Group E of genes which demonstrate increased expression when IL-17 receptors stimulate. It means that expression of these genes is related to IL-17 receptor and stimulation of IL-17 receptor has stimulatory influences on these genes (in pathologic setting of psoriasis).

B) Group F of genes which show decreased expression when IL-17 receptors stimulate. It means that expression of these genes is related to IL-17 receptor and stimulation of IL-17 receptor has inhibitory influences on these genes (in psoriasis).

Due to pathologic changes in production of IL-17 balance in Psoriasis, the negative feedback (which regulates releasing of hormones) may not play fundamental role in production of IL-17 from T helper 17 cells. Thus, we cannot detect groups of genes (like C and D in normal group) which interfere with production of IL-17 in T helper 17 cells of psoriatic group based on negative feedback.

What kind of genes expression behaviour can we expect about each of E and F groups?

Based on these assumptions (and after adjustment of animal study with human cell culture), we want to expect gene expression manner in each cell line of normal groups:

*Group E:*

Regarding to the explanation, group E of genes shows additive manner of expression after stimulation of IL-17 receptor. Therefore, these are a category of genes which have most growth (ascending slope) in terms of gene expression after exposure of IL-17 to T helper 17 cells. Also, these genes demonstrate most declines (descending slope) in terms of gene expression after exposure of anti-IL17 receptor antibody to T helper 17 cells. Finally, this group of genes reveal decreased manner in terms of gene expression after exposure to anti-IL17 antibody. Based on noted reason, the rate of reducing of gene expression after exposure to anti-IL17 antibody is possibly less compared with anti-IL17 receptor antibody exposure.

*Diagram 5 (Group E)*

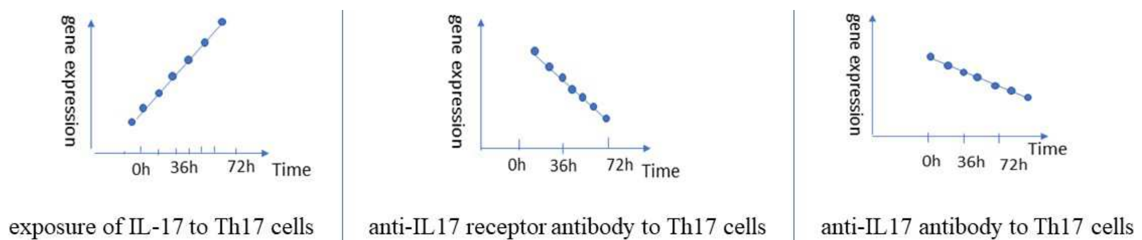


**Figure 10.** Group E of genes shows additive manner of expression after stimulation of IL-17 receptor.

*Group F:*

Based on our explanation, group F of genes shows declining manner of expression after stimulation of IL-17 receptor. Therefore, these are a category of genes which have most growth (ascending slope) in terms of gene expression after exposure of anti-IL17 receptor antibody to T helper 17 cells in psoriatic group. Also, these genes demonstrate most declines (descending slope) in terms of gene expression after exposure of IL17 to T helper 17 cells. Finally, this group of genes exhibit decreased manner in terms of gene expression after exposure to anti- IL17 antibody. Because of noted reason, the rate of increasing of gene expression after exposure to anti-IL17 antibody is possibly less compared with anti-IL17 receptor antibody exposure.

*Diagram 6 (Group F)*

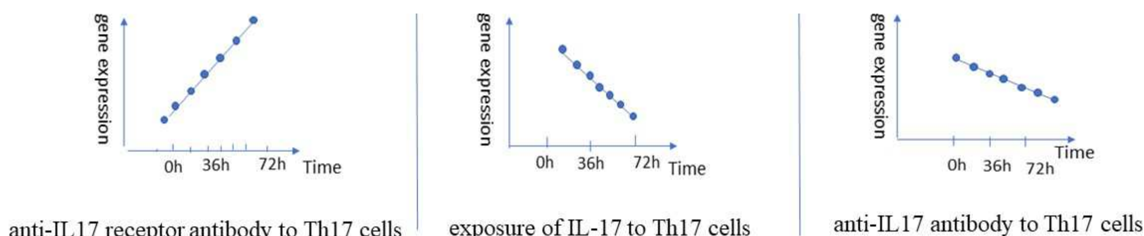


**Figure 11.** Group F of genes shows declining manner of expression after stimulation of IL-17 receptor.

The points which showed in the diagrams demonstrated the levels of gene expression in 12 hours intervals. The 1st up to 6th diagrams are represented the trend of gene expression in T helper 17 cells during exposure to IL-17, anti-IL17 and anti-IL17 receptor.

### 3.3. Details About Data Analyse

Detecting of every specific gene in A, B, C and D subsets would help us to have better imagination about function of this gene in signalling process of IL-17 in T helper 17 cells of normal individuals. Along the way, assessment of each specific gene in E and F subsets could help us achieving better insight around mechanisms interfere with post-IL17 receptor signalling of T helper 17 cells in psoriasis.

Following the manner of genes expression of A, B, C and D groups (which interfere with physiologic receptor and production signalling of IL-17) in psoriasis:

We should investigate the manner of expression of every gene (which is a subset of one of the A, B, C, D) in psoriatic group in order to better understanding of gene expression changes (related to IL-17 signalling pathways) in psoriasis. Therefore, it is possible to assess gene expression alteration related to each specific gene in psoriatic group compared with normal group. Hence, we can realize pathologic changes in terms of gene expression related to IL-17 in T helper 17 cells of psoriasis.

### 3.4. Transformation of Psoriatic Pattern into Physiologic Pattern as a Therapeutic Goal

Comparison of mentioned genes expression patterns between normal and patient groups may give us more aspects to discover more therapeutic goals in terms of transformation of psoriatic patterns into physiologic condition. Along the way, Bioinformatics can help us in predicting of possible potential treatments for psoriasis. Eventually, it seems that understanding the whole signalling pathways of inflammatory cytokines from different cells (including generation of IL-

17 from T helper 17) is inevitable for detection of novel therapeutic targets for better management of this disease.

#### 3.4.1. Post-IL17 Receptor Signalling Study

Genes of A and B groups should investigate as biologic factors affected with physiologic signalling of IL-17 receptor in T helper 17 cells. On the other hand, genes of E and F groups should consider as biologic factors affected with pathologic (psoriatic) condition of signalling of IL-17 receptor in T helper 17 cells. Group A and E of genes (which stimulate with IL-17 receptor in physiologic and pathologic condition, respectively) should be compared with each other to recognize the differences between physiologic and pathologic gene expression mechanisms. Also, group B and F of genes (which inhibit with IL-17 receptor in physiologic and pathologic condition, respectively) should be compared with each other for exploring the differences between physiologic and pathologic gene expression pathways.

#### 3.4.2. Signalling Related to IL-17 Production

About lacking negative feedback in psoriatic group, we cannot detect genes related to production of IL-17 (in both stimulatory and inhibitory pathways) in T helper 17 cells of psoriasis. So, we should assess just the normal group based on negative feedback. We should follow expression pattern of each gene of C and D groups (as genes which have stimulatory and inhibitory actions in physiologic setting, respectively) in psoriasis.

### 3.5. Analyse of Gene Expression Pattern in New onset of Psoriasis

We should evaluate the differences in manner of gene expression (related to each gene of A, B, C, D, E and F subsets) among T helper 17 cells of normal individuals, new onset of psoriasis and patients with psoriasis for at least 2 years in in vitro study. Hence, it's conceivable to identify the gene expression pattern in new onset form of psoriasis in order to better assessment of molecular mechanisms interfere with initiation of this disease.

We can also detect the group of genes which affected (in both stimulatory and inhibitory mechanisms) with IL-17 receptor in cell lines of new onset psoriasis (G and H groups respectively). Then, we can compare group E with G and group F with H of genes in terms of gene expression behaviour and differences in members (genes) of each paired group. Therefore, we would have better insight about molecular pathways involved in IL-17 receptor signalling in new onset of psoriasis.

## 4. Conclusion

Due to essential role of IL-17 in psoriasis, it's necessary to identify the exact biologic pathways of production and receptor signalling of this inflammatory cytokine. This observation can help us for detecting of potential therapeutic targets (related to IL-17) in patients with psoriasis. In addition, this study may have helpful results around physiologic details of IL-17 signalling in order to management of other inflammatory disorders. Moreover, in order to more detail detection of pathologic alterations of inflammatory pathways in psoriasis, this study has the capability to generalize to other inflammatory cells and cytokines in this disease.

We suggest generalizing this research panel for other cytokines and biologic agents in different cells of immune system and other biologically active cells in both healthy and patient individuals. For example, assessment of TNF-α in macrophages and synovial cells of patient with rheumatoid arthritis and healthy individuals with the same method is fundamental study to find novel therapeutics for this autoimmune disease. We also propose to generalize this research panel for assessment of new onset form of systemic disease compared with chronic forms of them.

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