



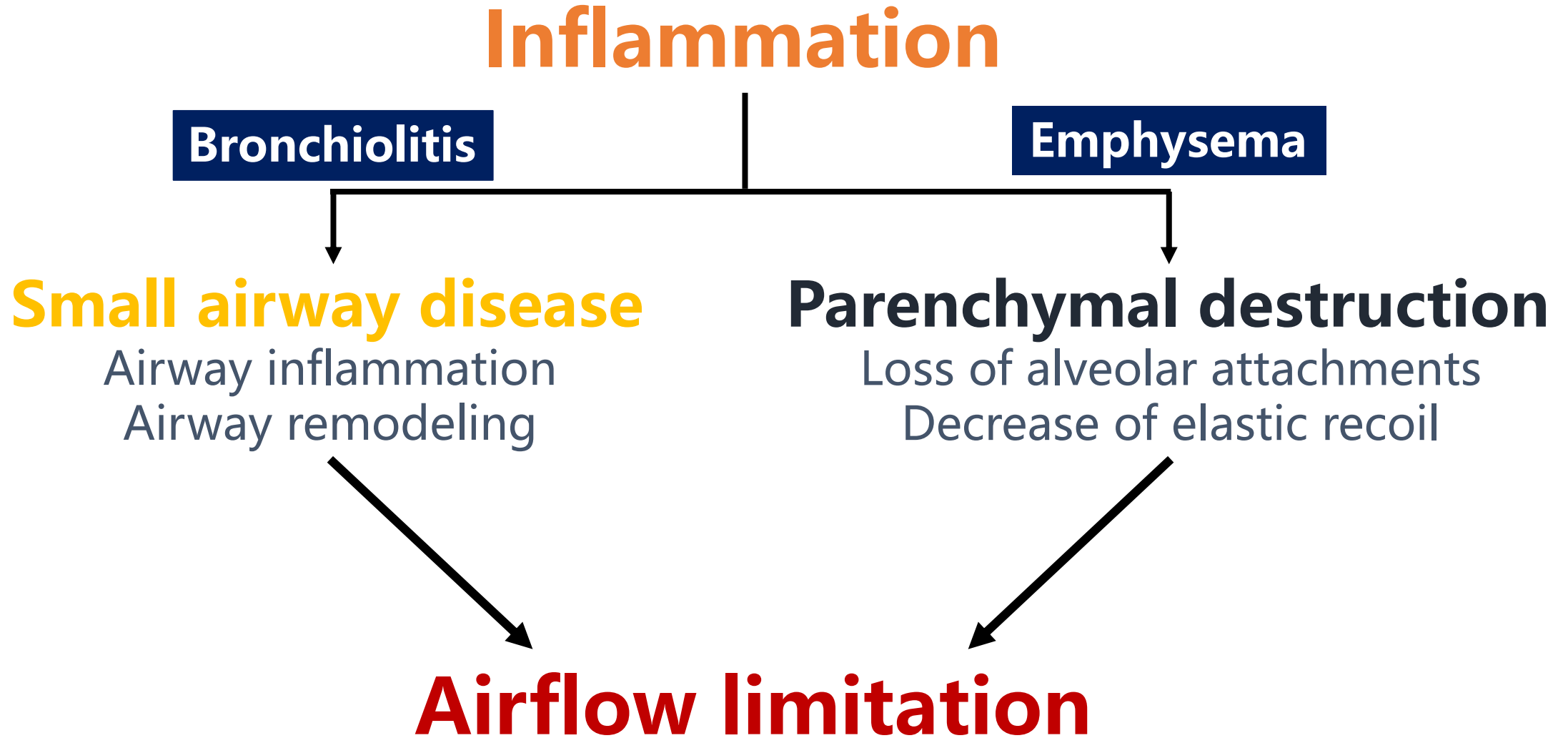
2019台灣胸腔暨重症加護醫學會

2019 Taiwan Society of Pulmonary and Critical Care Medicine

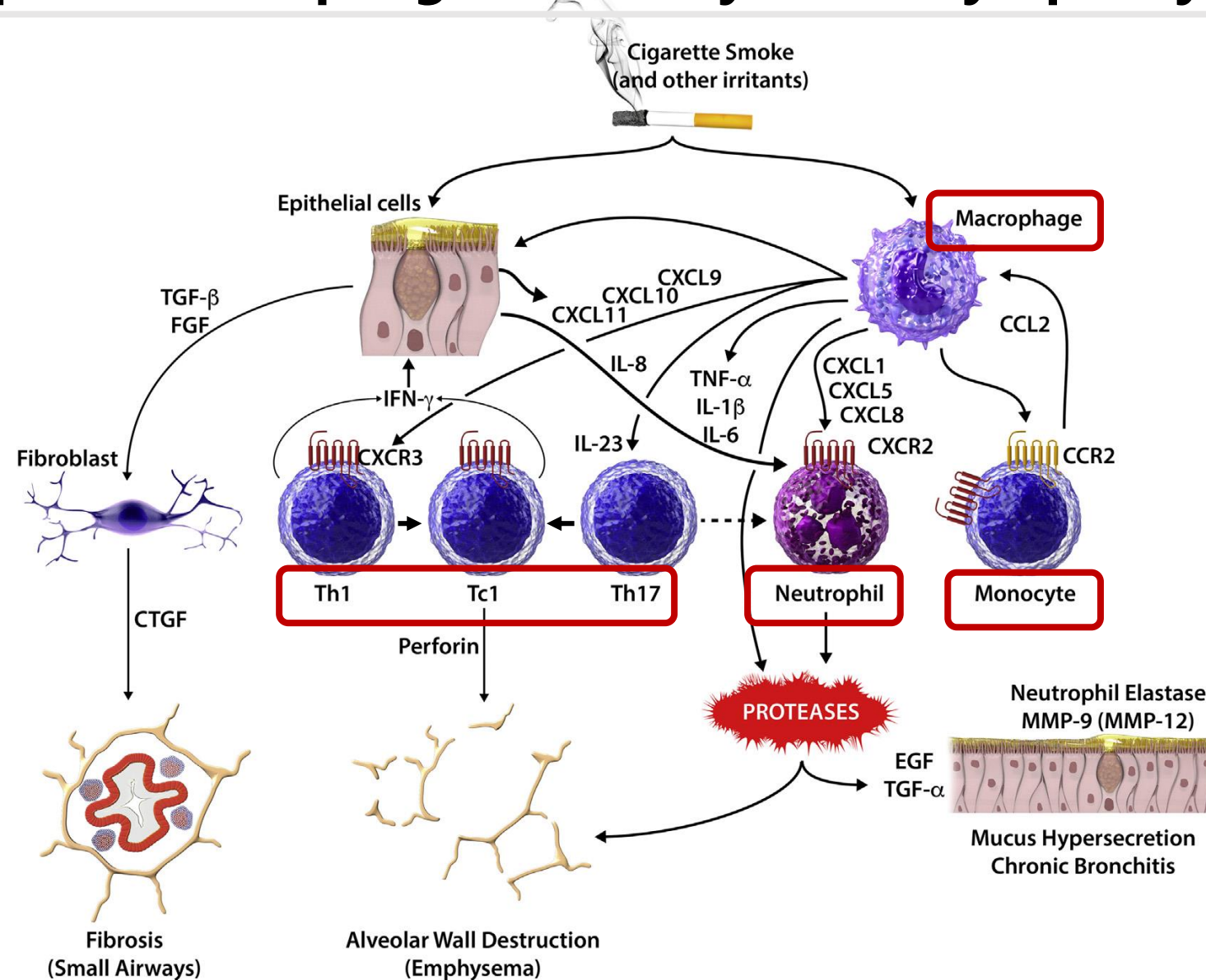
NOTCH signaling & T cell differentiation in COPD

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- 日期：108年12月7日
- 地點：高雄展覽館3樓 301B

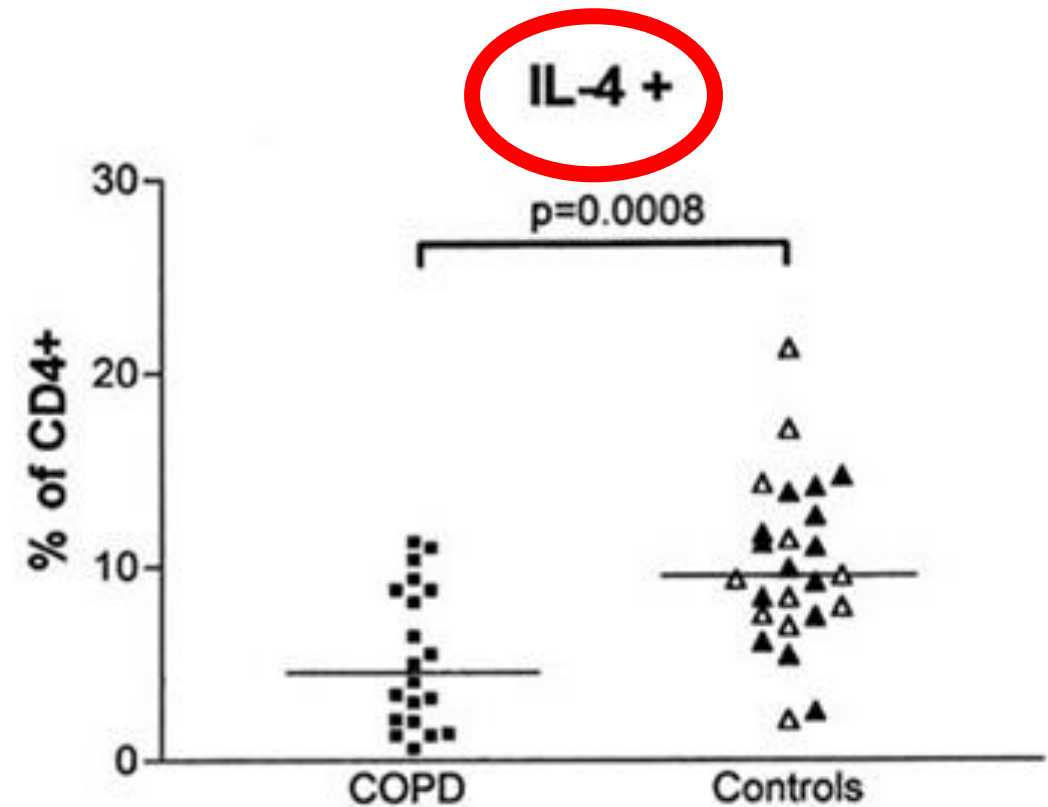
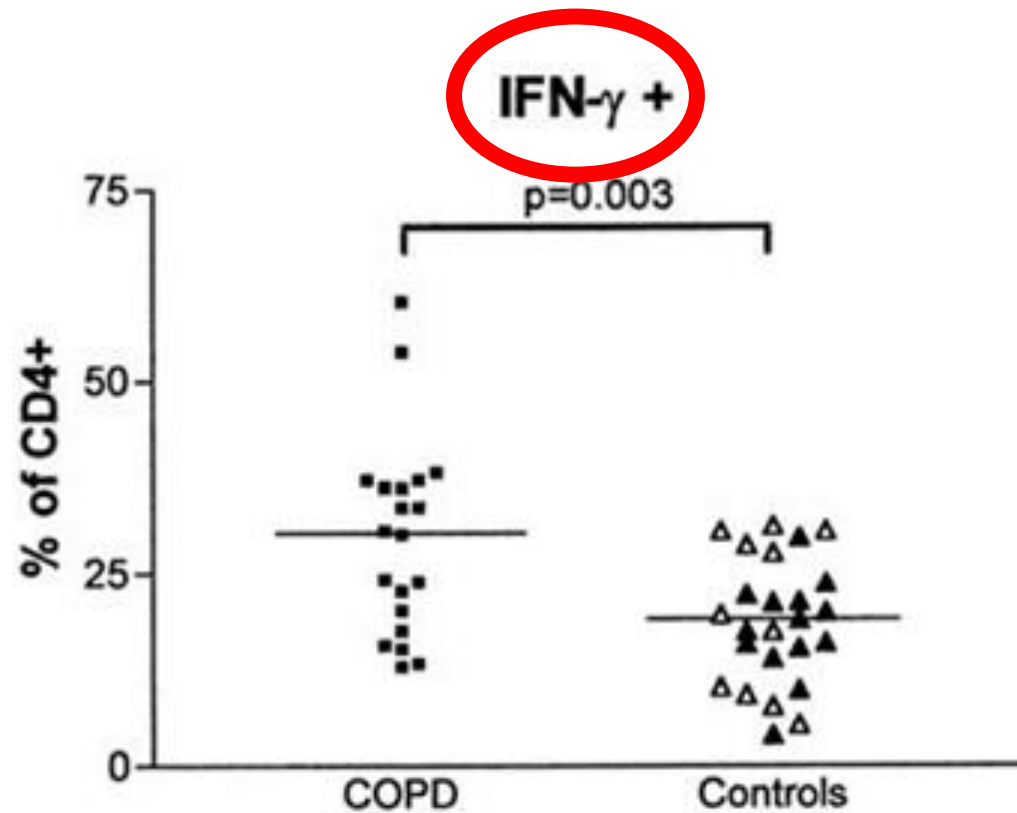
Inflammation is central for the development of COPD



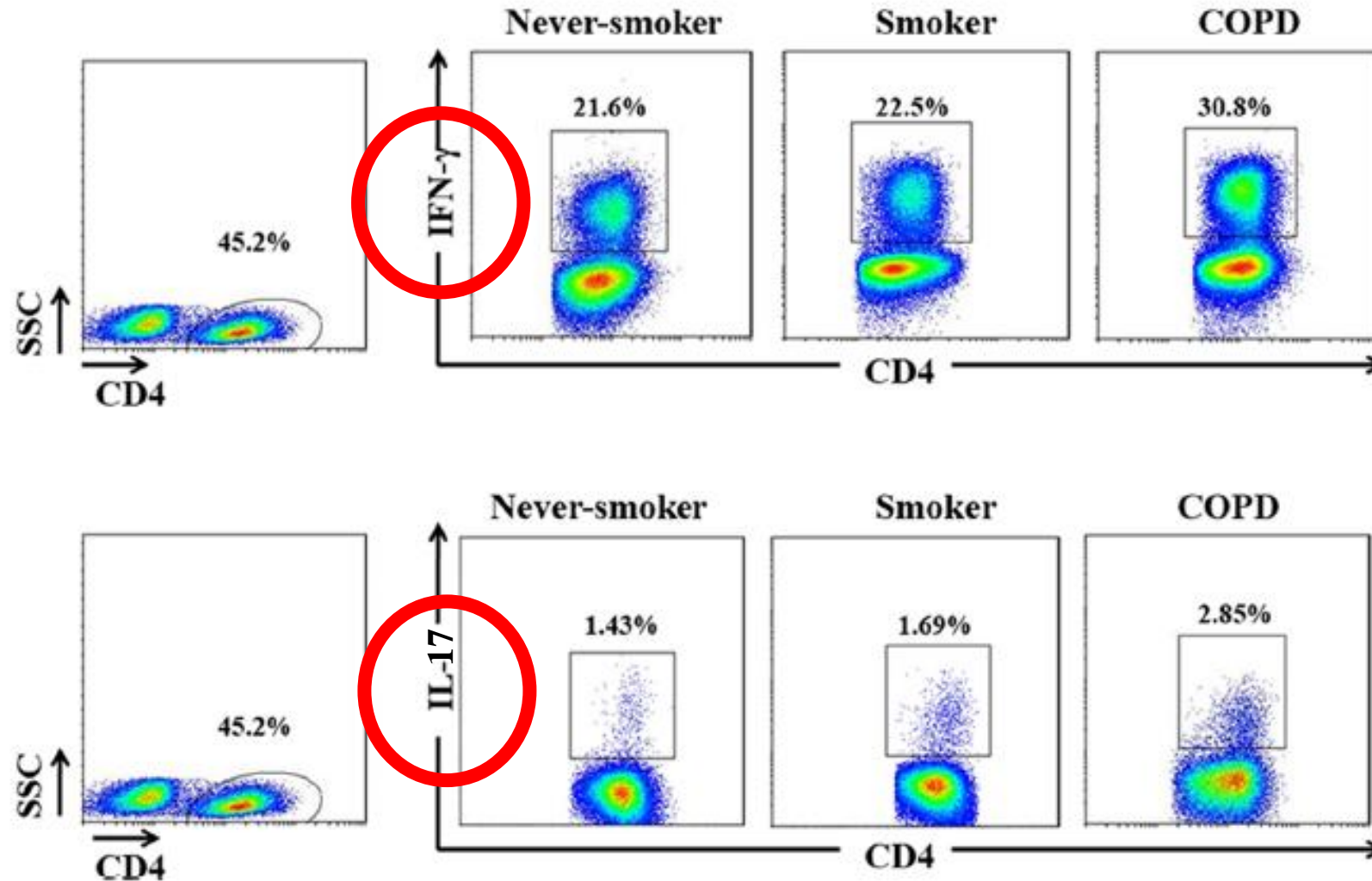
Chronic inflammation in COPD mainly involves the infiltration of neutrophils, macrophages, monocyte, and lymphocytes



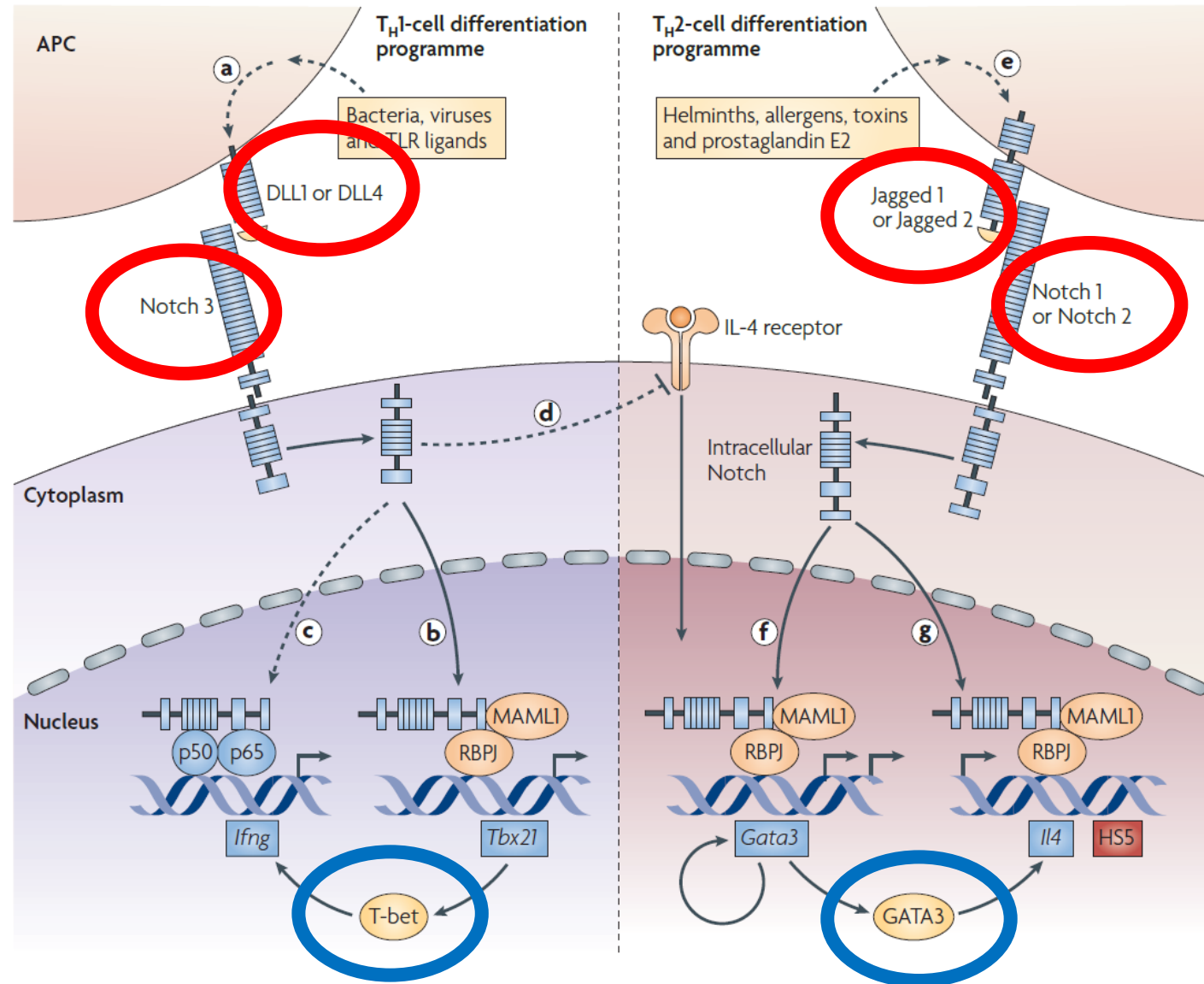
Th1 dominate response of peripheral blood CD4+ T cells in patients with COPD whose capacity for IFN- γ expression was significantly increased



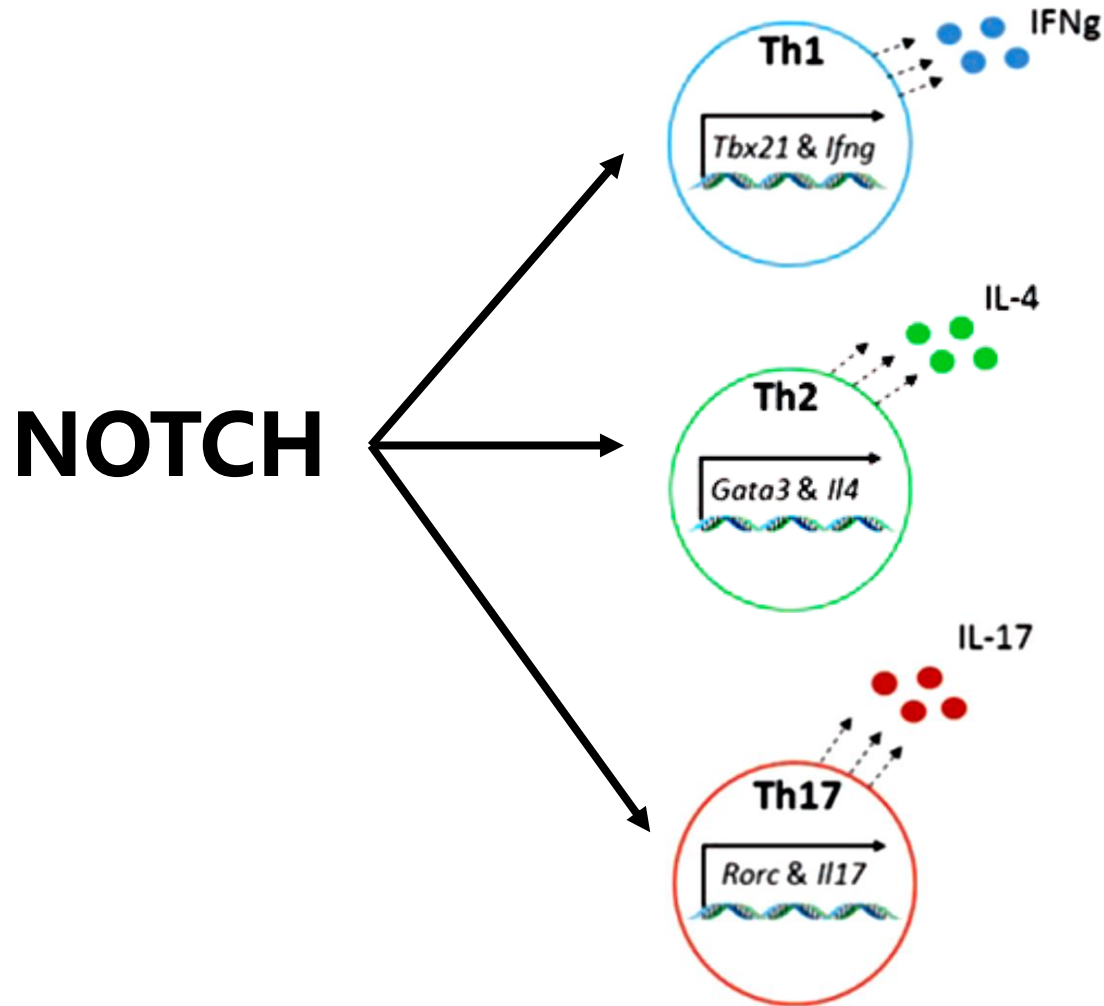
Proportions of Th1 and Th17 cells were significantly increased in patients with COPD compared with never-smokers and smokers



The different faces of Notch in T-helper-cell differentiation



Mechanisms Used by Notch to Induce T cell Differentiation



- ❑ Notch enables T helper cell differentiation into Th1, Th2, and Th17 lineages by directly inducing expression of lineage defining transcription factors and cytokines.
- ❑ In preclinical models of multiple-sclerosis, arthritis, and asthma, targeting Notch via antibodies to its ligands or chemical inhibitors results in decreased T cell mediated pathology. In mouse models of cancer, deliberate activation of Notch promotes antitumor T cell responses.

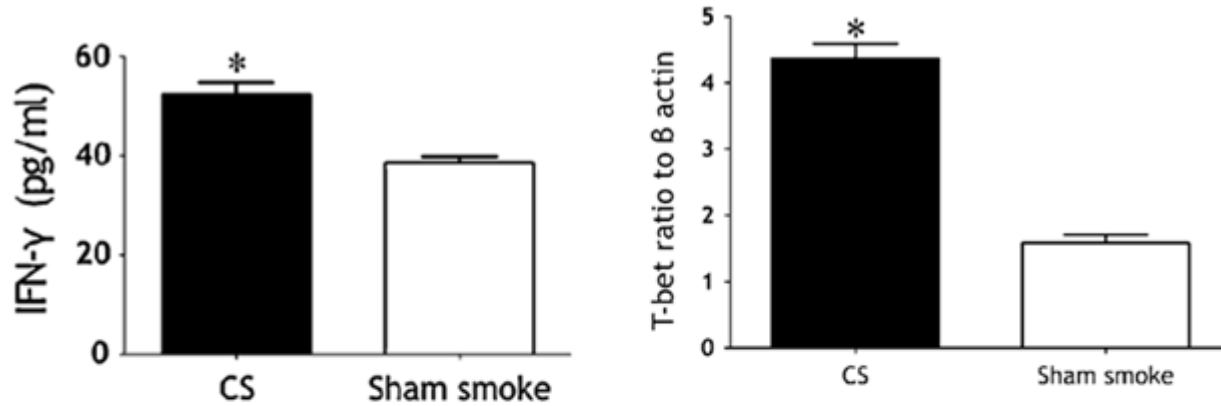
Involvement of Notch1/Notch3 in COPD

| Reference | Specimen Source | Change of Notch1/Notch3 | Biological function |
|--------------------------------|---|-------------------------|--|
| Guseh et al. [2009] | Lung tissue from Rosa-Notch ICIRES-GFP mice | Notch1↑ | Increased mucous cells, decreased ciliated cells in the airway and prevented the differentiation of alveolar cell types |
| Boucherat et al. [2012] | Lung tissue from Hoxa5-/- mice | Notch1↑ | Induced goblet-cell differentiation and mucus overproduction |
| Tsao et al. [2011] | Lung tissue from Pofut1cTb3 mice | Notch1↓ | Increased goblet cells and ciliated cells, decreased Clara cell number |
| Tilley et al. [2009] | Lung tissue from COPD patient | Notch3↓ | Notch3 downregulated in airway epithelium |
| Dang et al. [2003] | Lung tissue from SP-C-N3IC transgenic mice | Notch3↑ | Inhibited type I pneumocyte differentiation, induced abnormalities of lung morphogenesis and perinatal lethality |

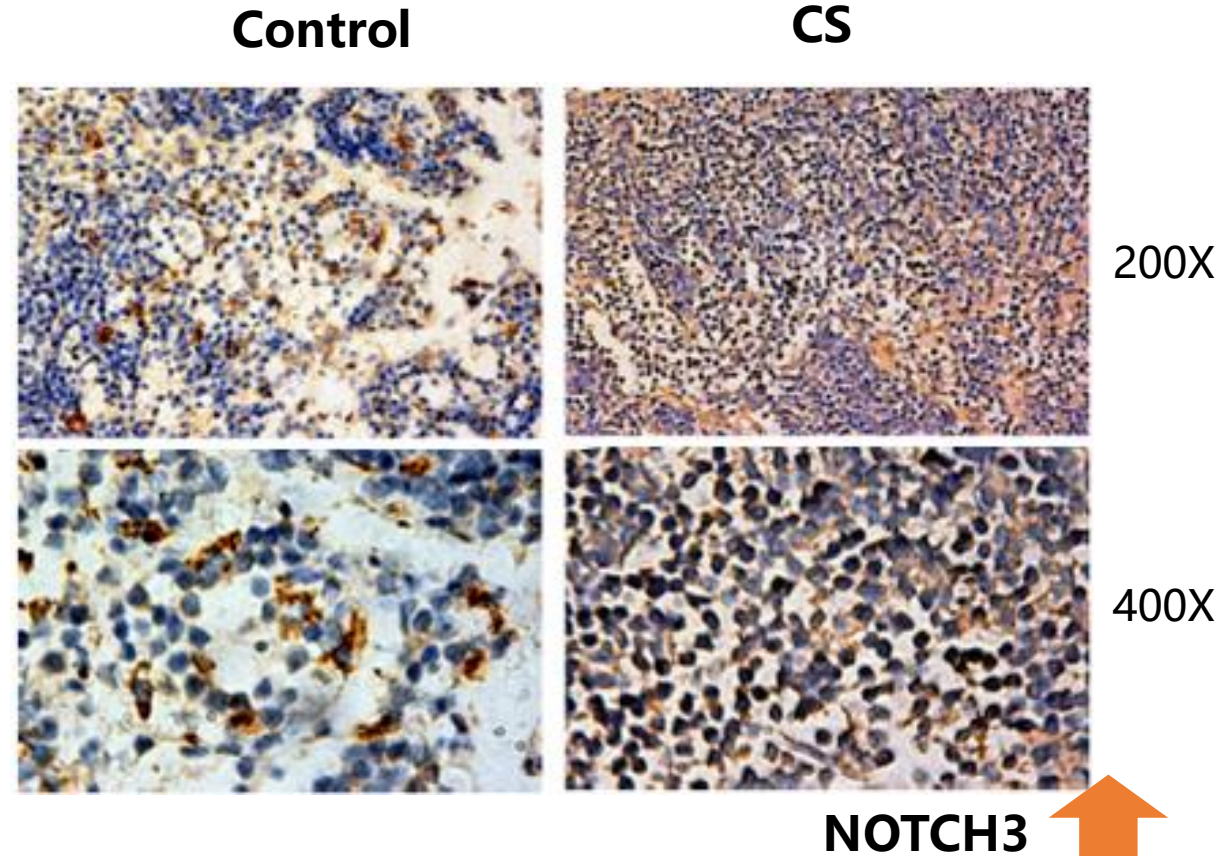
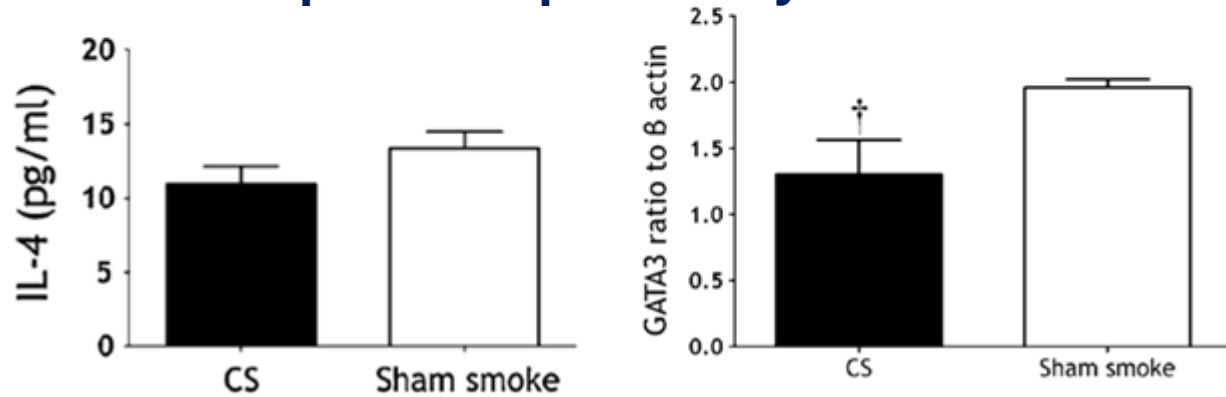
COPD, chronic obstructive pulmonary disease.

Notch signaling in lymphoid tissue of the lung, which is likely relevant to the pathogenesis of pulmonary emphysema

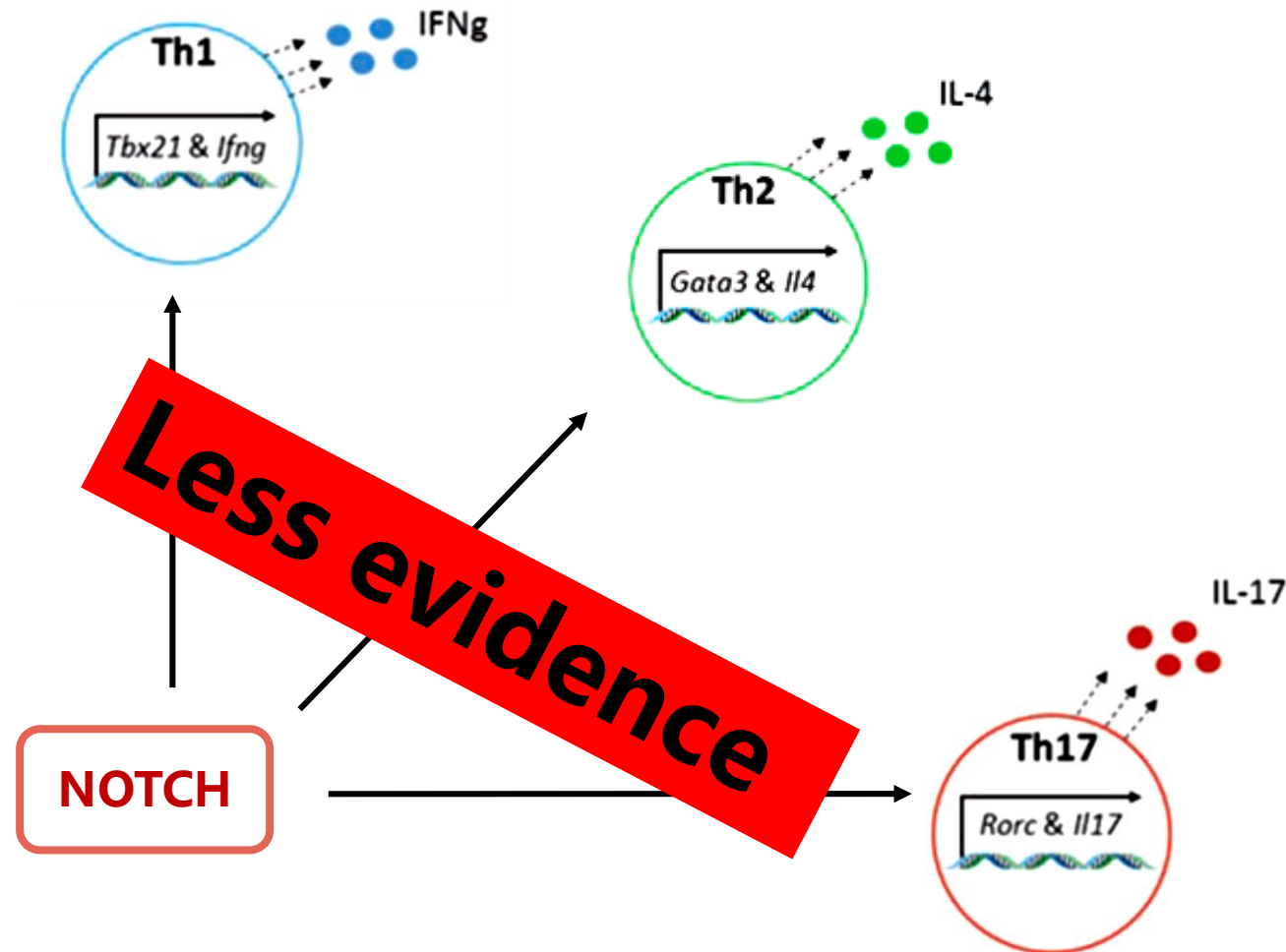
Th1-polarized pulmonary inflammation



Th2-polarized pulmonary inflammation



What is the association between NOTCH signaling and cell differentiation in COPD inflammation

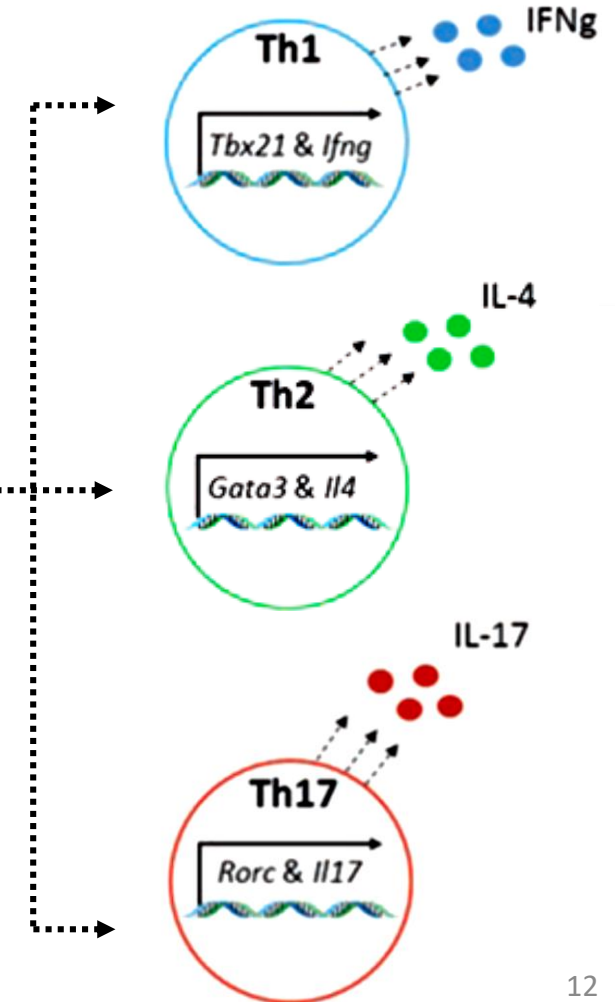
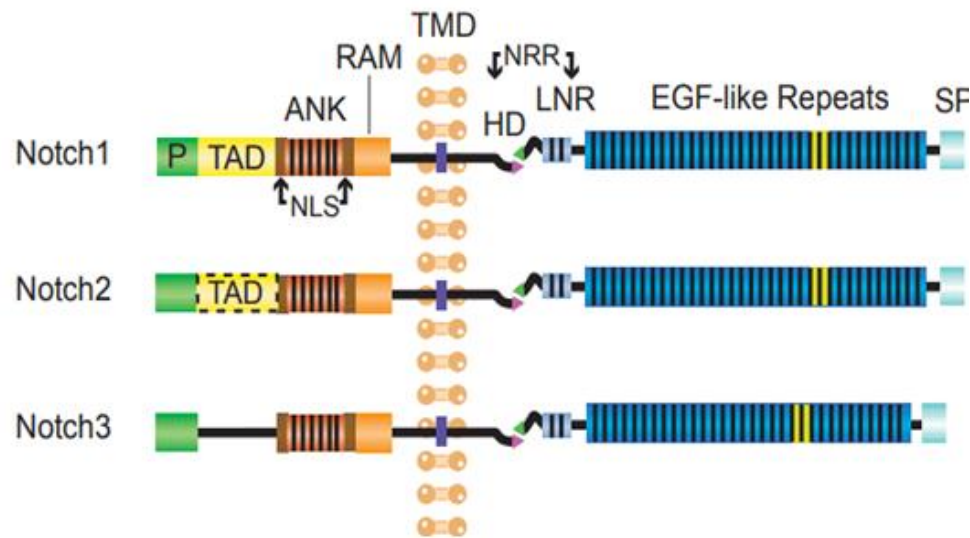


Aim



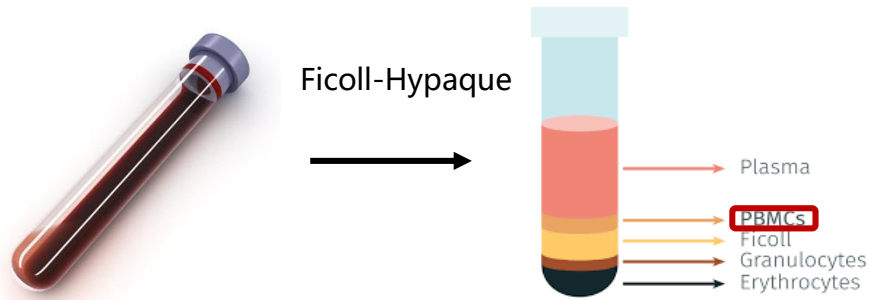
To evaluate the correlation between Notch signaling and T cell differentiation in COPD

Experimental Design



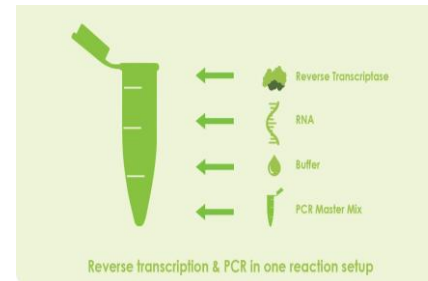
Material & Method

PBMCs isolation

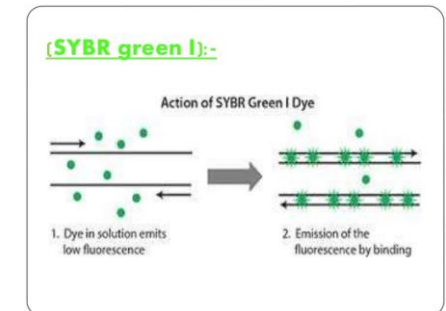


Lymphocyte were involved in PBMC

RT-PCR



Real-time PCR (qPCR)



Primer

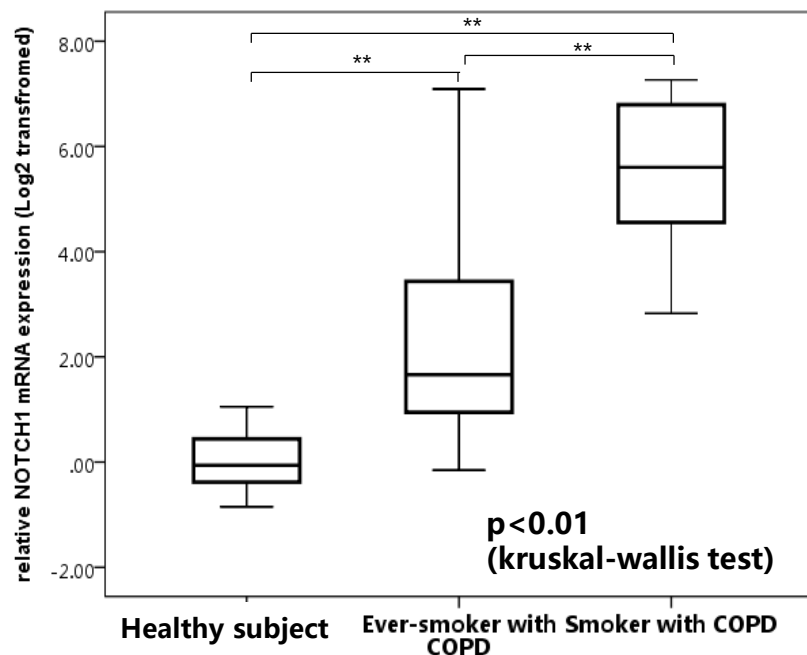
| | |
|--------------|-------------------------------------|
| NOTCH | NOTCH1, NOTCH2, NOTCH3 |
| Th1 | T-bet, IFN— γ , STAT1, STAT4 |
| Th2 | GATA-3, IL-4 |
| Th17 | ROR- γ t, IL-17 |

Result

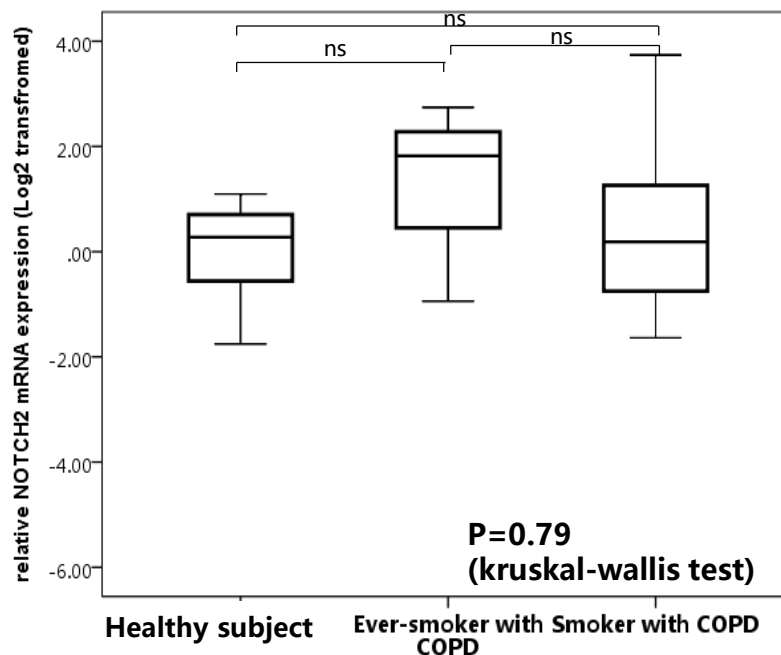


NOTCH expression in PBMC of COPD patients and healthy subject

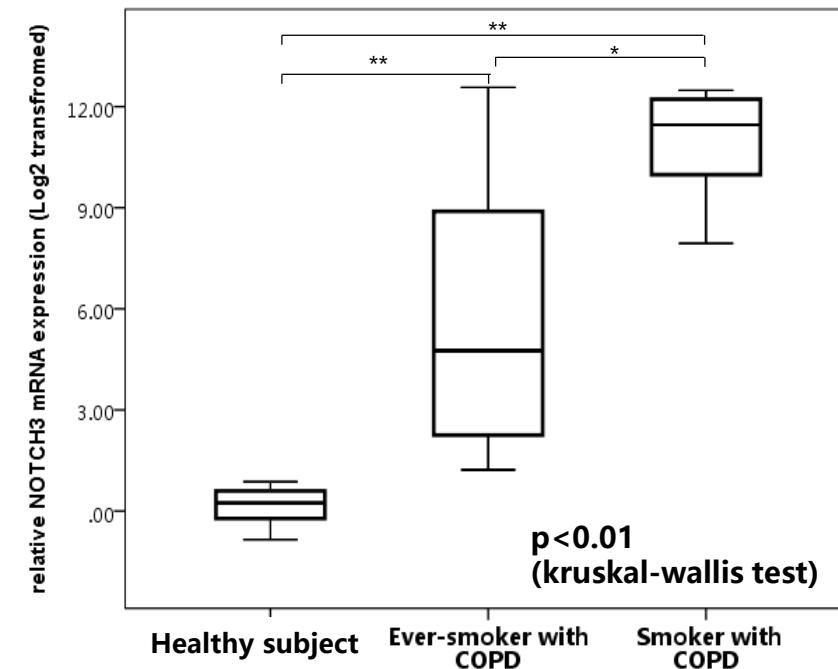
NOTCH1



NOTCH2



NOTCH3

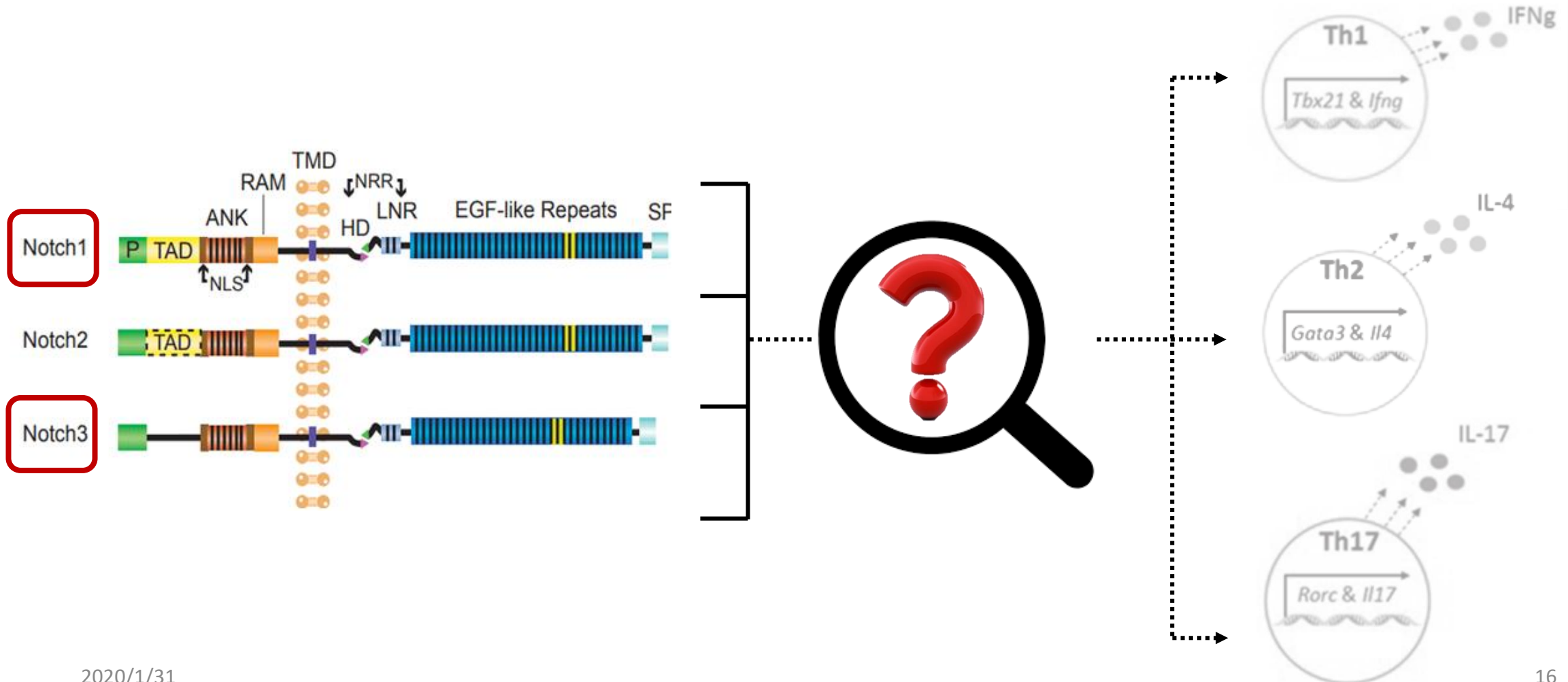


NOTCH1 and NOTCH3 mRNA expression was significantly increased in smoker with COPD

**** $p < 0.01$
* $p < 0.05$**

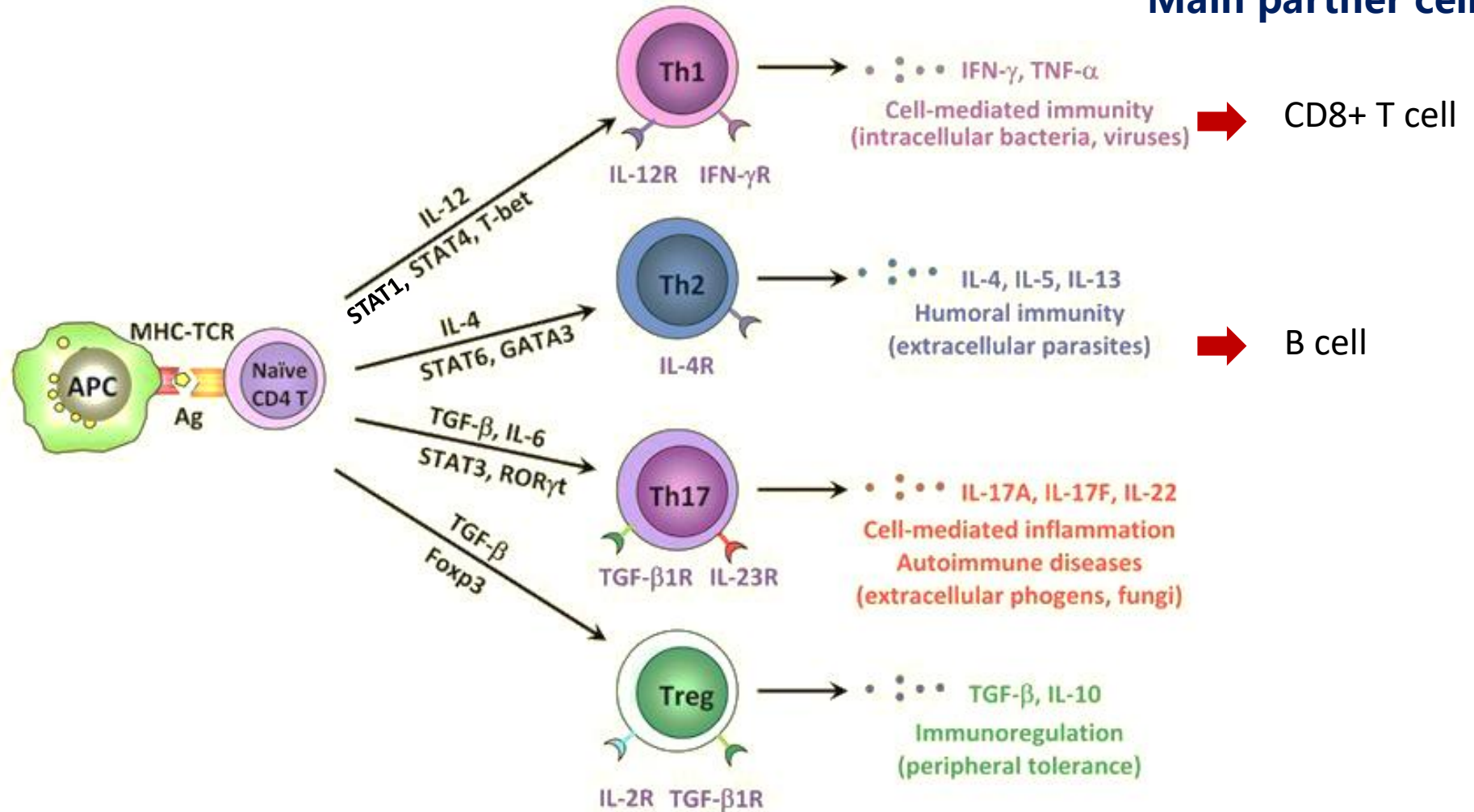


NOTCH1 and NOTCH3 mRNA high expression were observed in patients with COPD



Th cell differentiation from naive CD4+ T cells

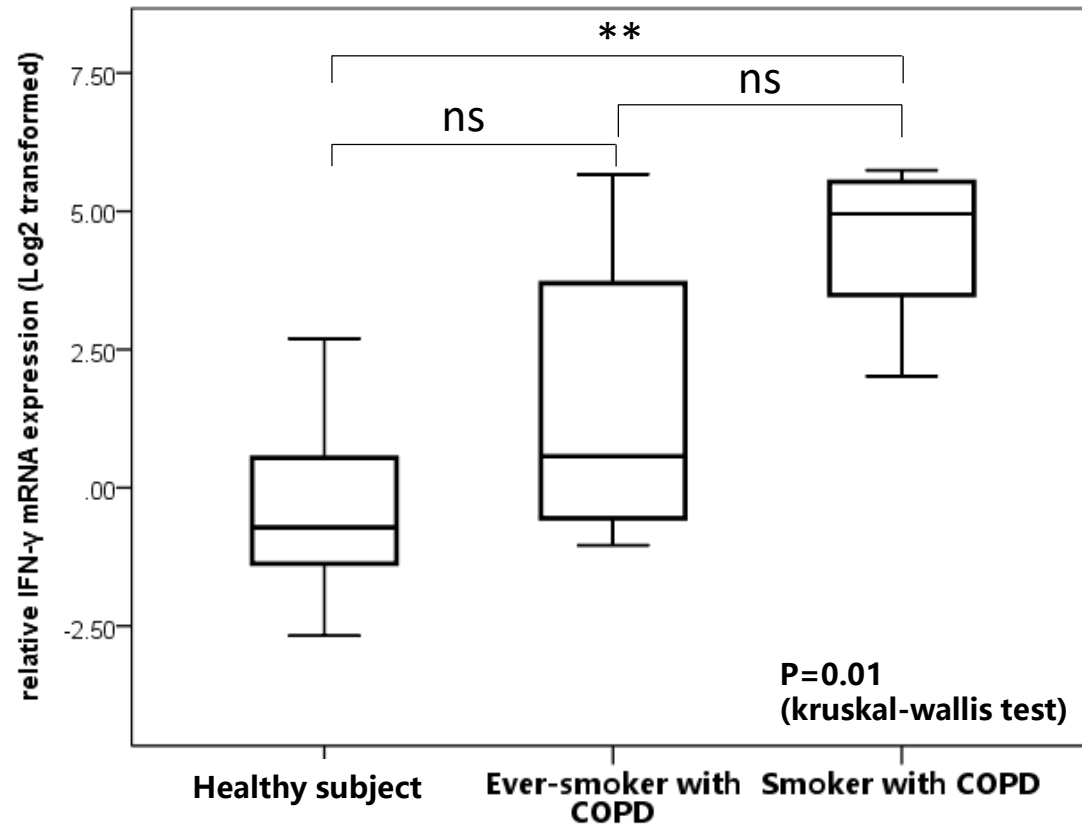
Main partner cell type



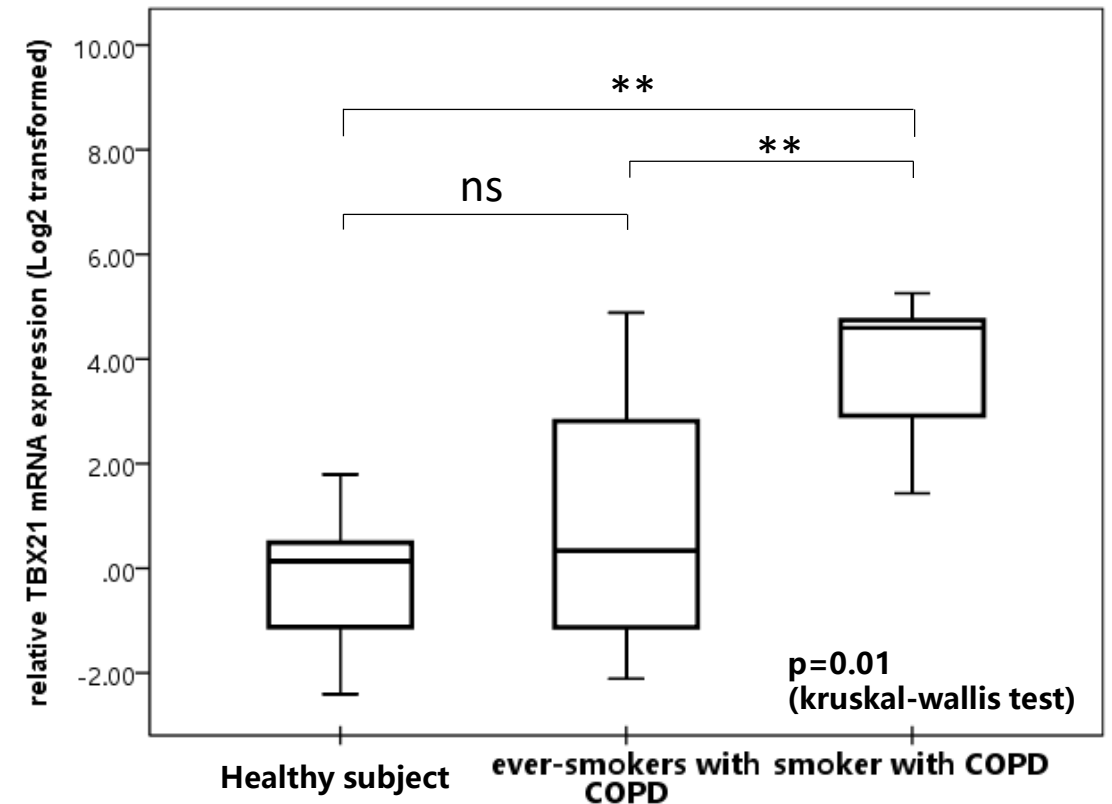


Th1 response in COPD patients and healthy subject

IFN- γ



T-bet



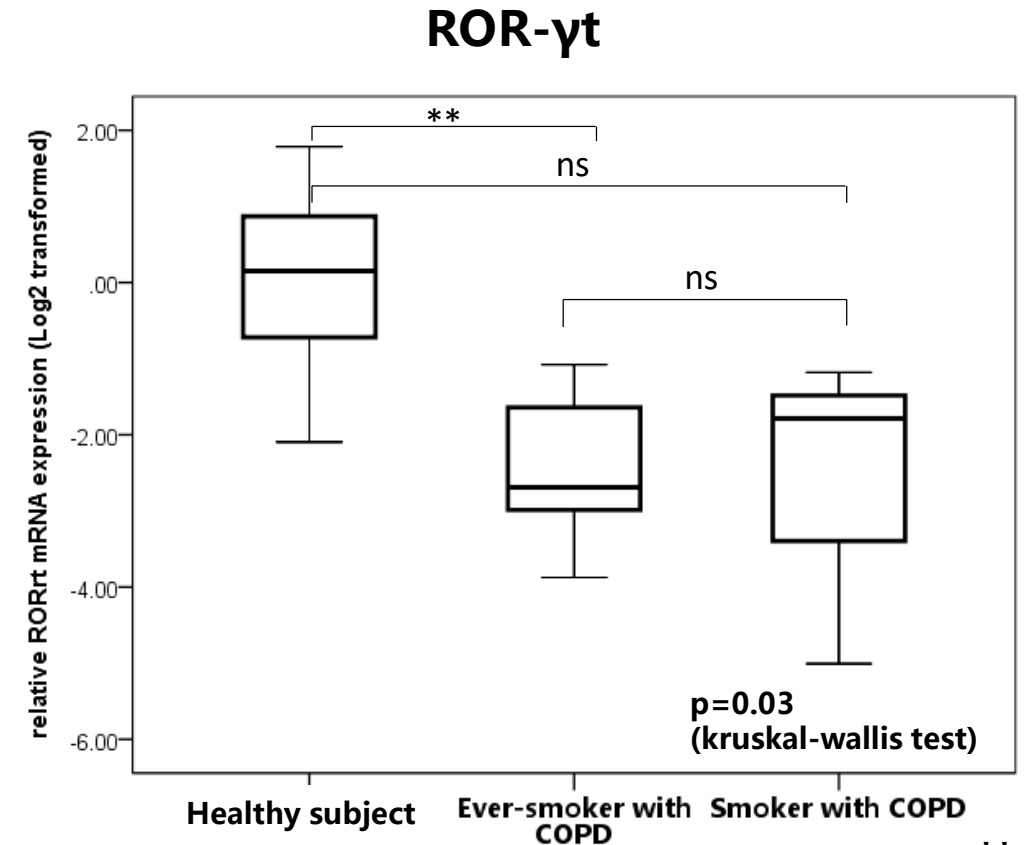
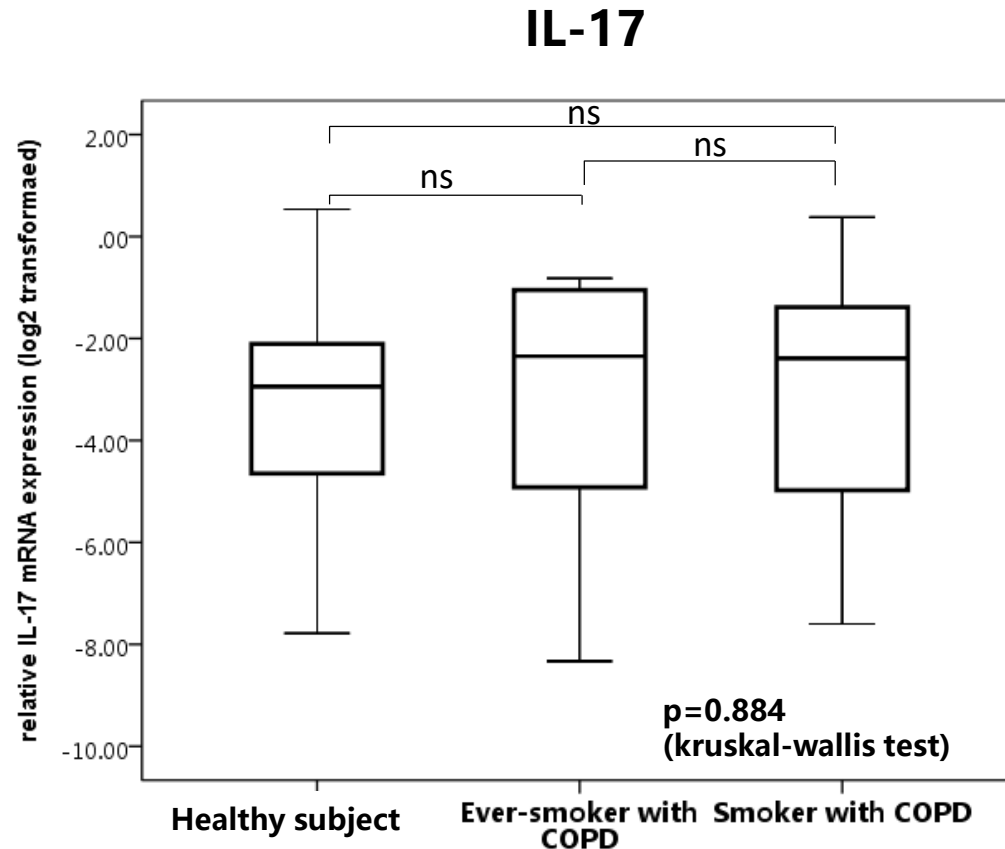
T-bet and IFN- γ mRNA expression was significantly increased in smoker with COPD

****p<0.01**

***<0.05**



Th17 response in COPD patients and healthy subject

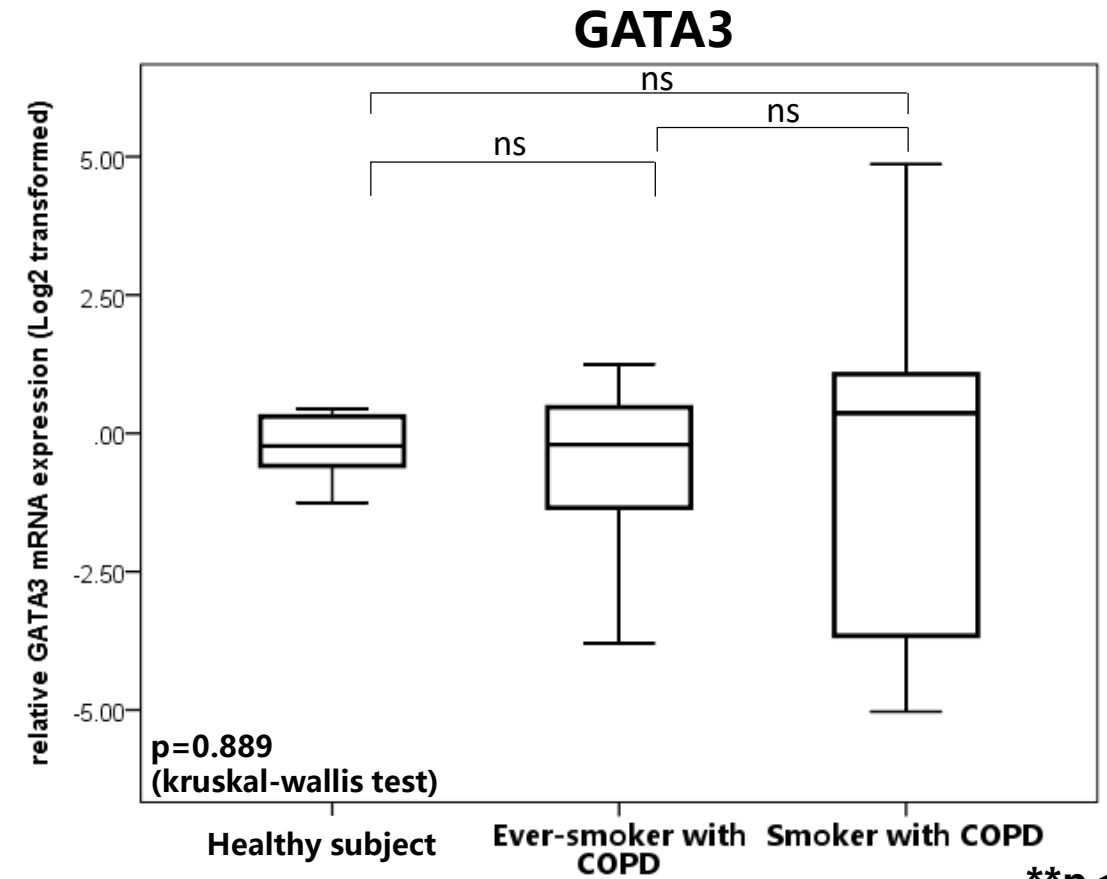
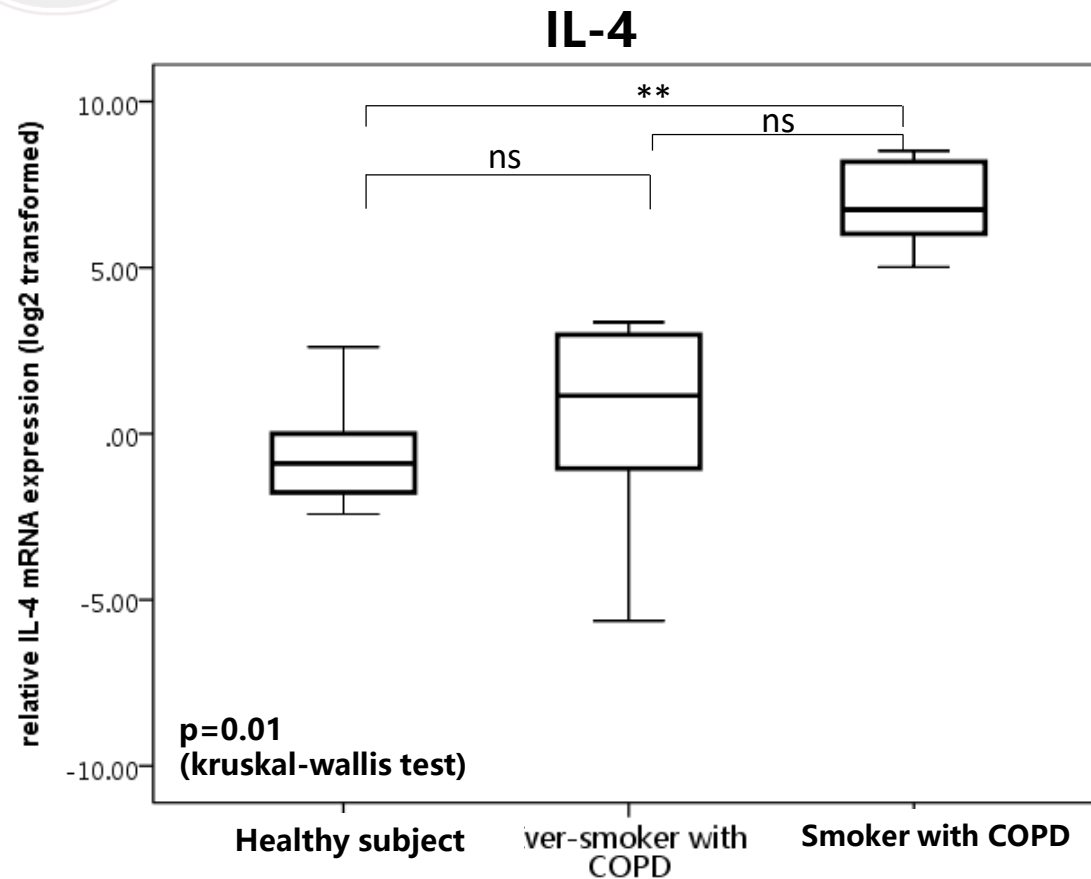


**p<0.01
*<0.05

IL-17 mRNA expression is no significant difference between each other, whereas ROR-γt mRNA expression was decrease in patients with COPD



Th2 response in COPD patients and healthy subject

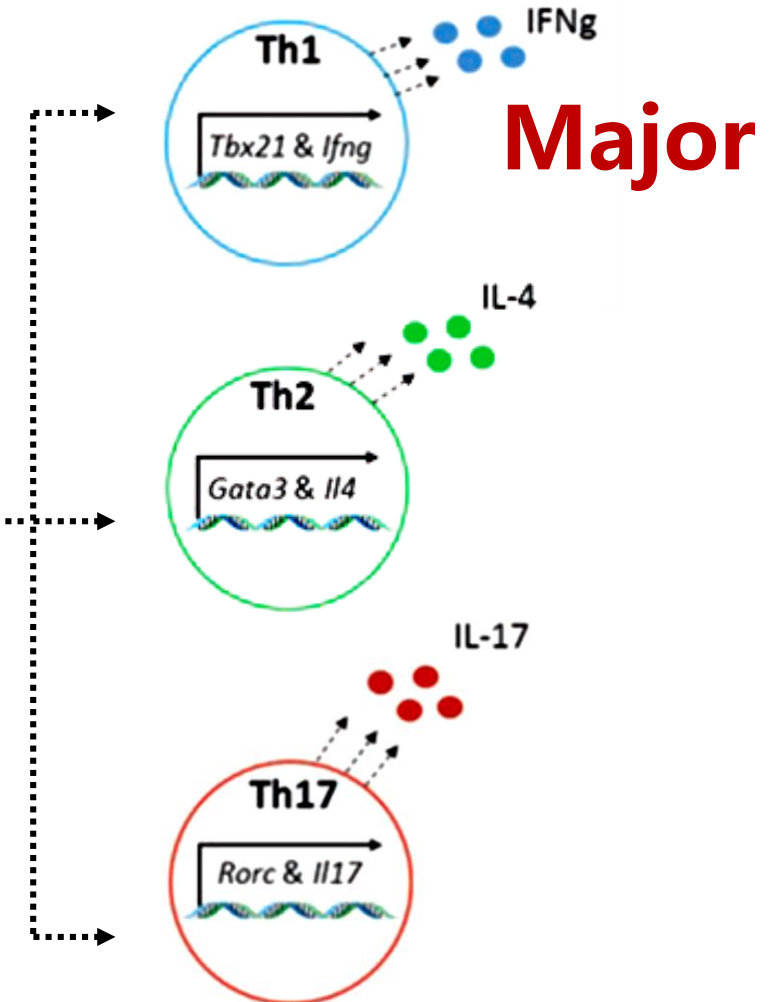
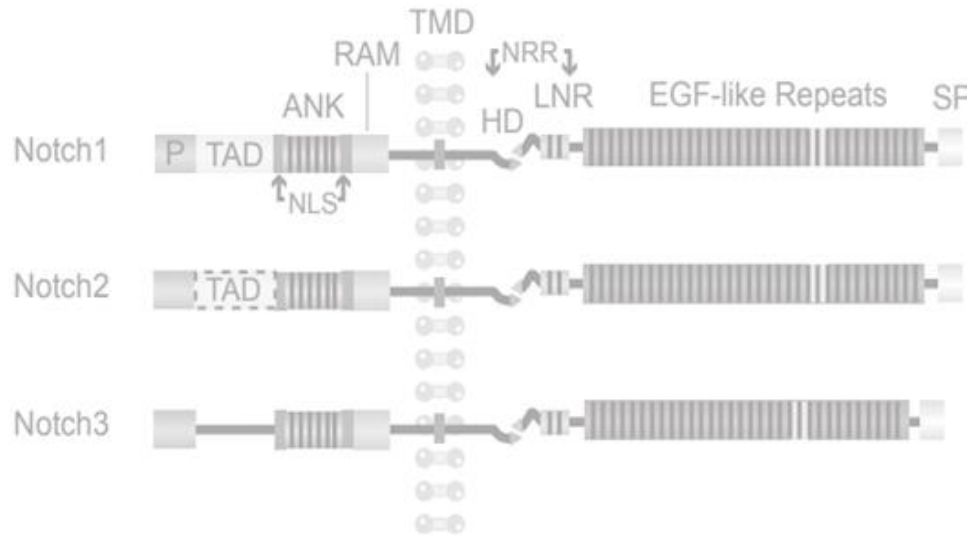


**p<0.01
*p<0.05

IL-4 mRNA expression was increased, whereas GATA3 mRNA expression is no difference between each.



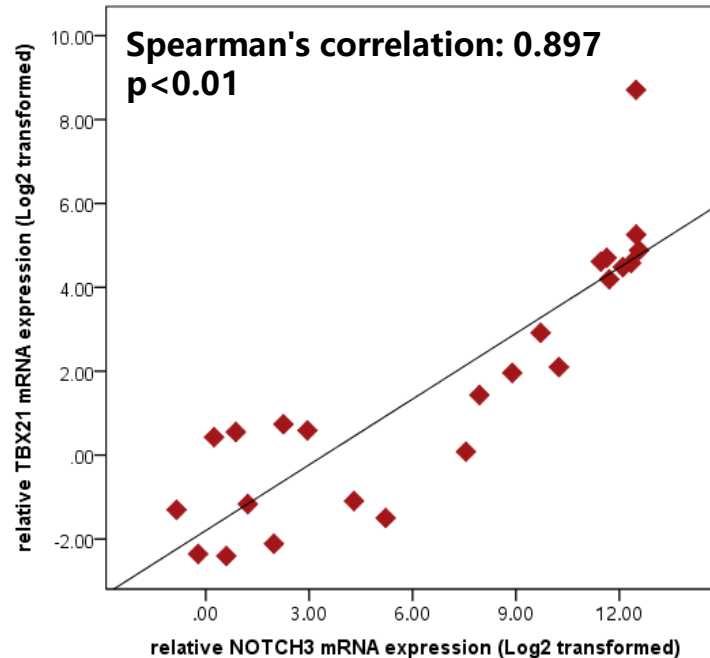
Th1 response was observed in COPD patients



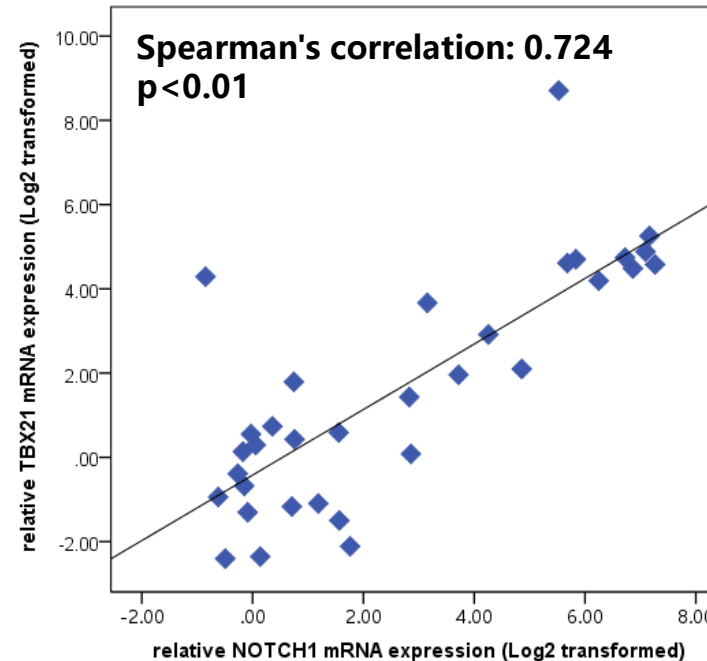


The correlation between T-bet and NOTCH signaling

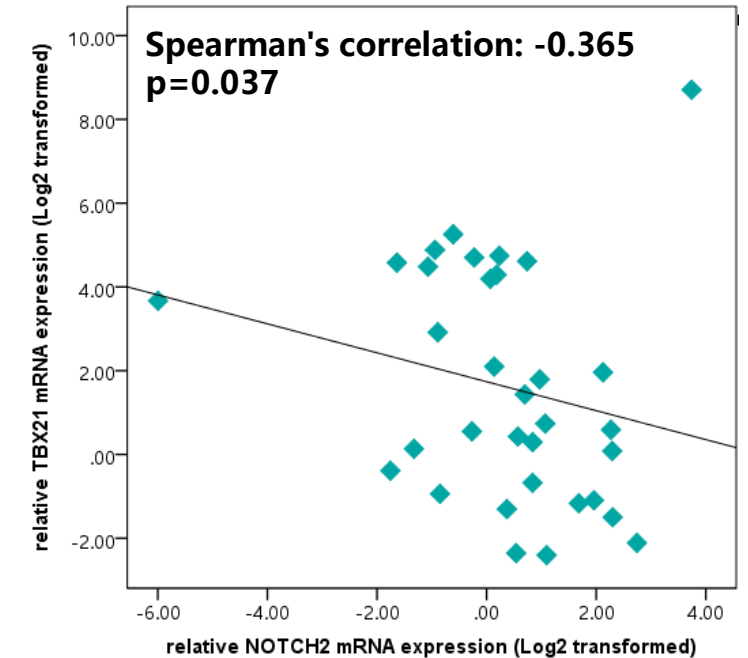
NOTCH3



NOTCH1



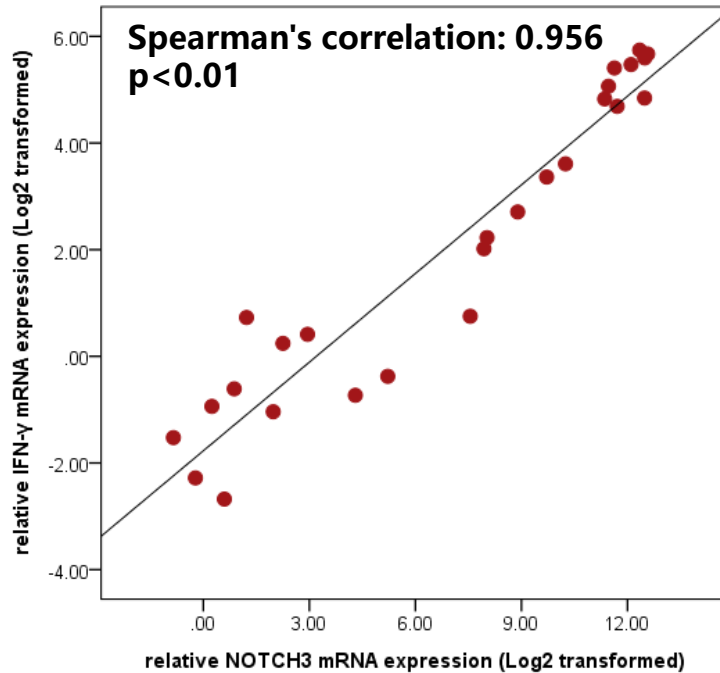
NOTCH2



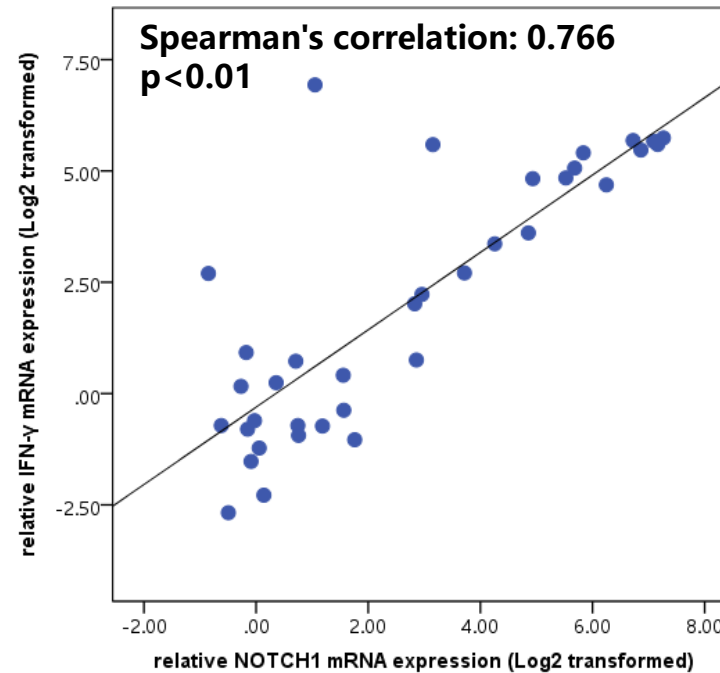
T-bet expression was significantly positively correlated with NOTCH1 and NOTCH3

The correlation between IFN- γ and NOTCH signaling

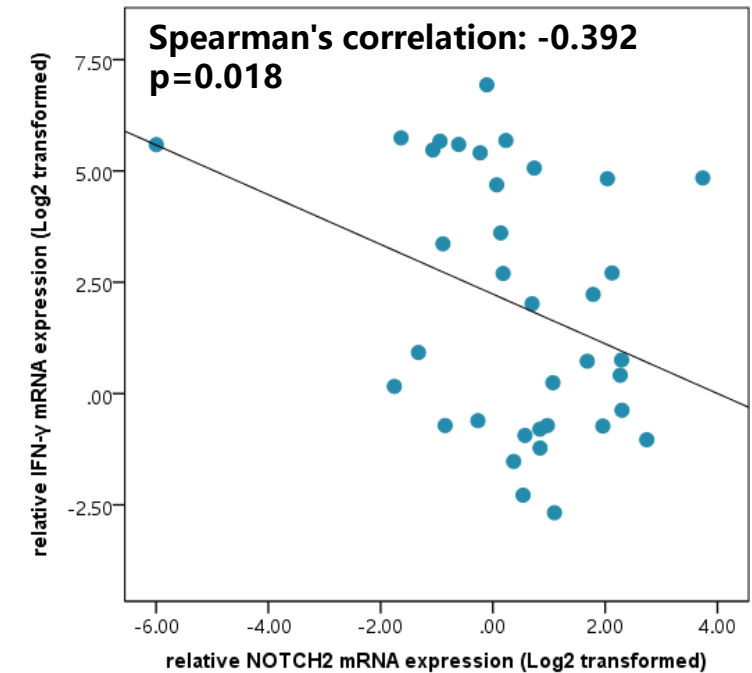
NOTCH3



NOTCH1



NOTCH2

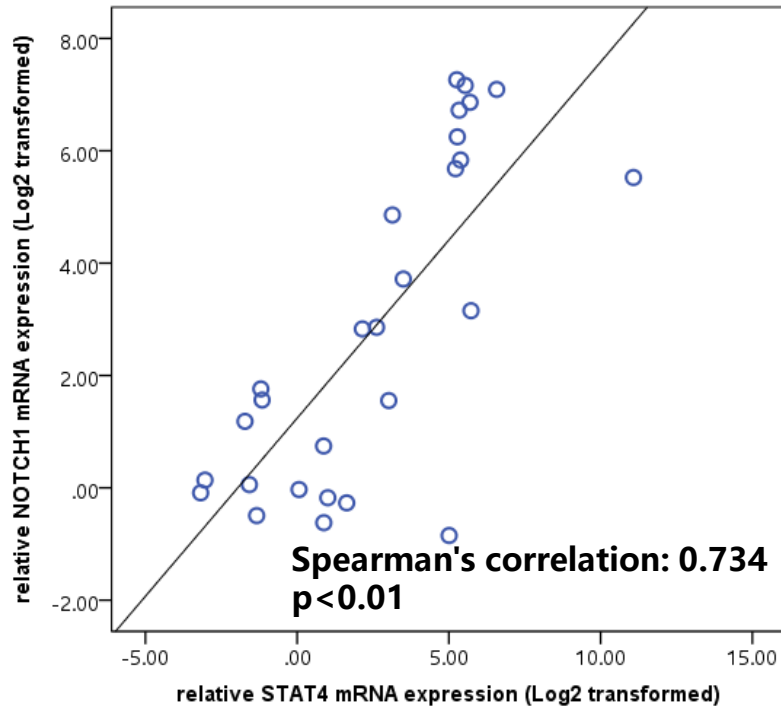


IFN- γ expression was significantly positively correlated with NOTCH1 and NOTCH3

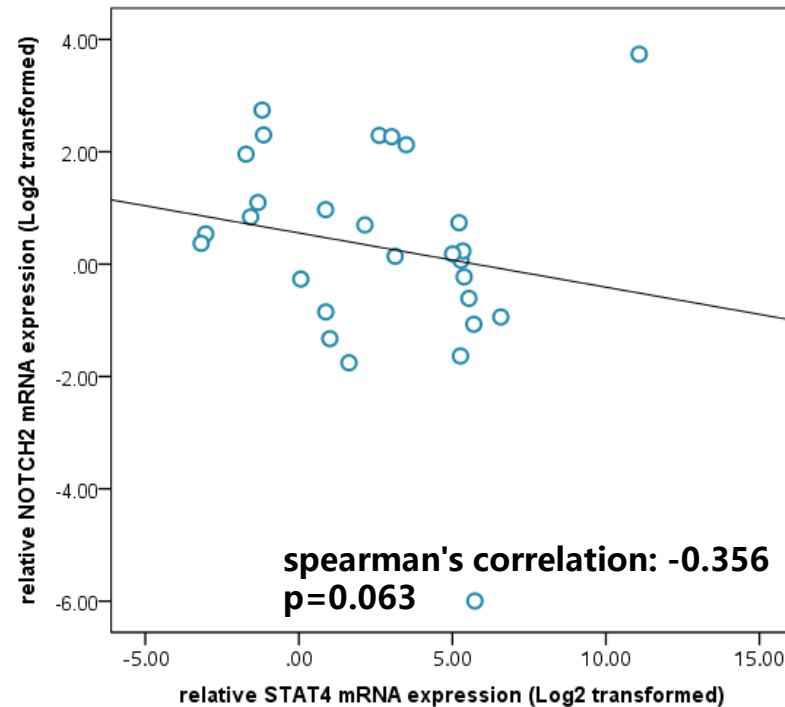


The correlation between STAT4 and NOTCH signaling

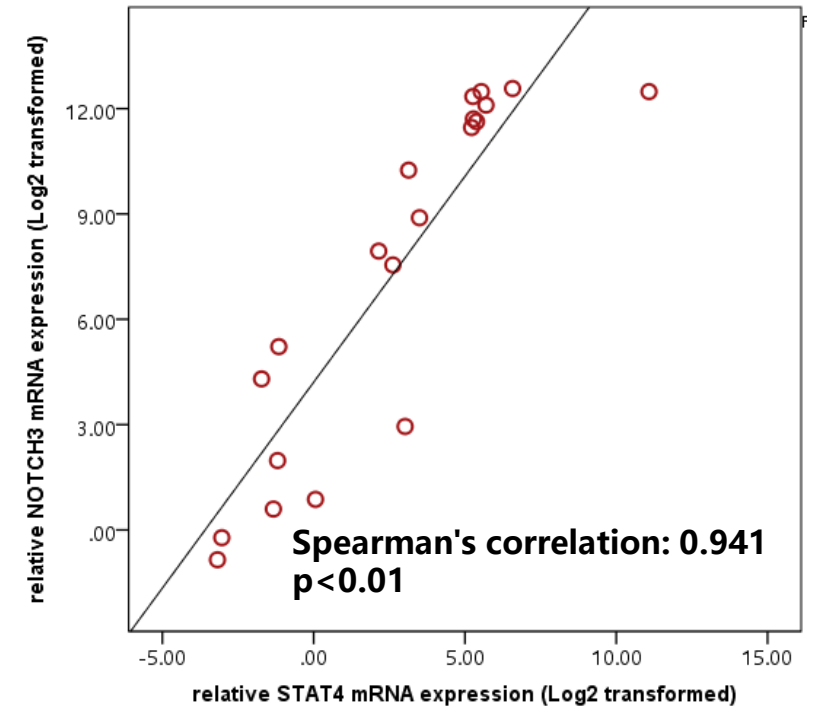
NOTCH1



NOTCH2



NOTCH3

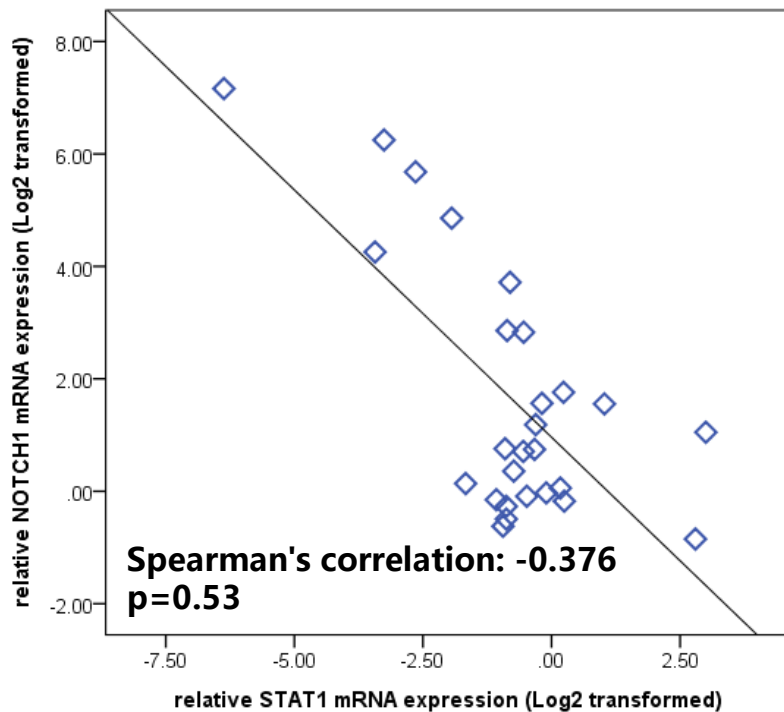


Notch1 and Notch3 was significantly positively correlated with STAT4

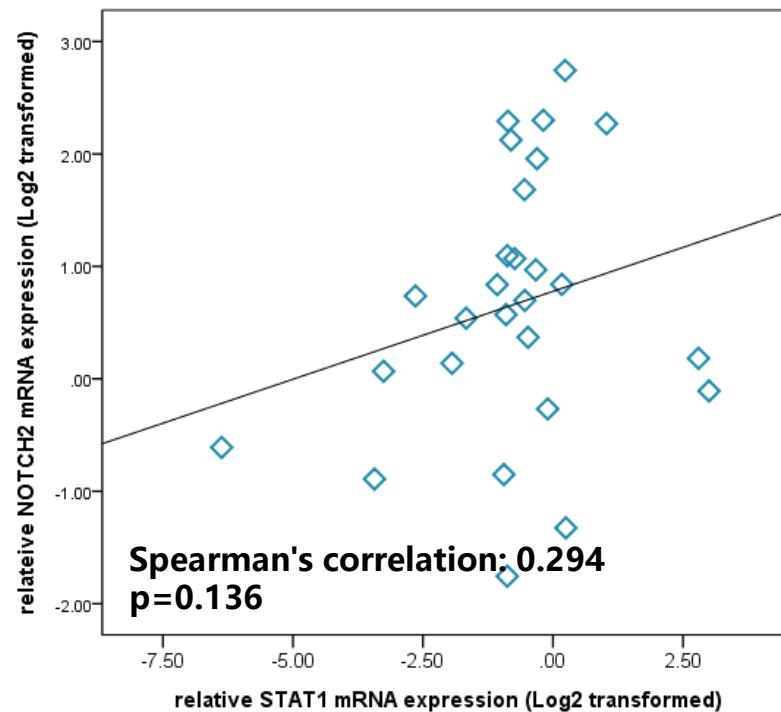


The correlation between STAT1 and NOTCH signaling

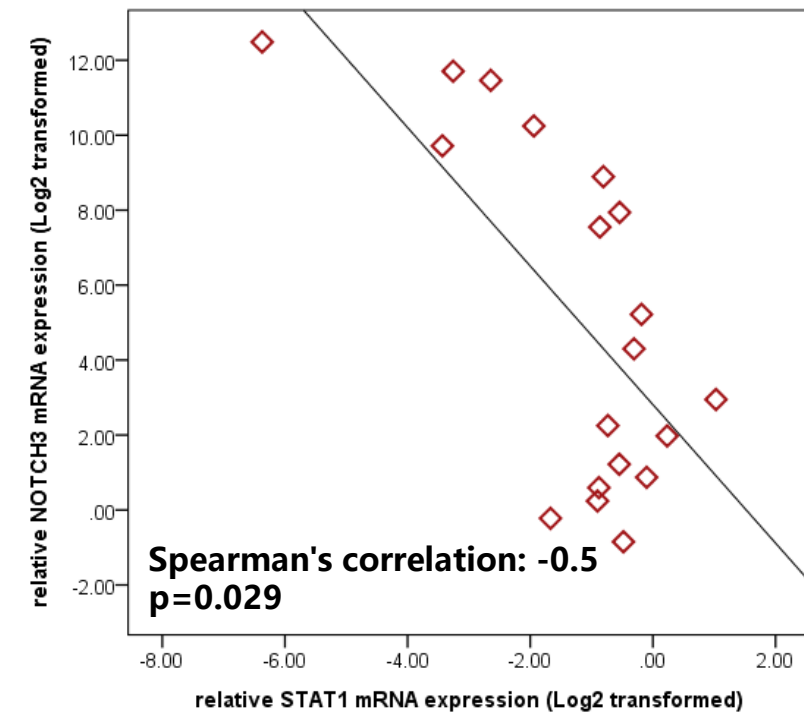
NOTCH1



NOTCH2



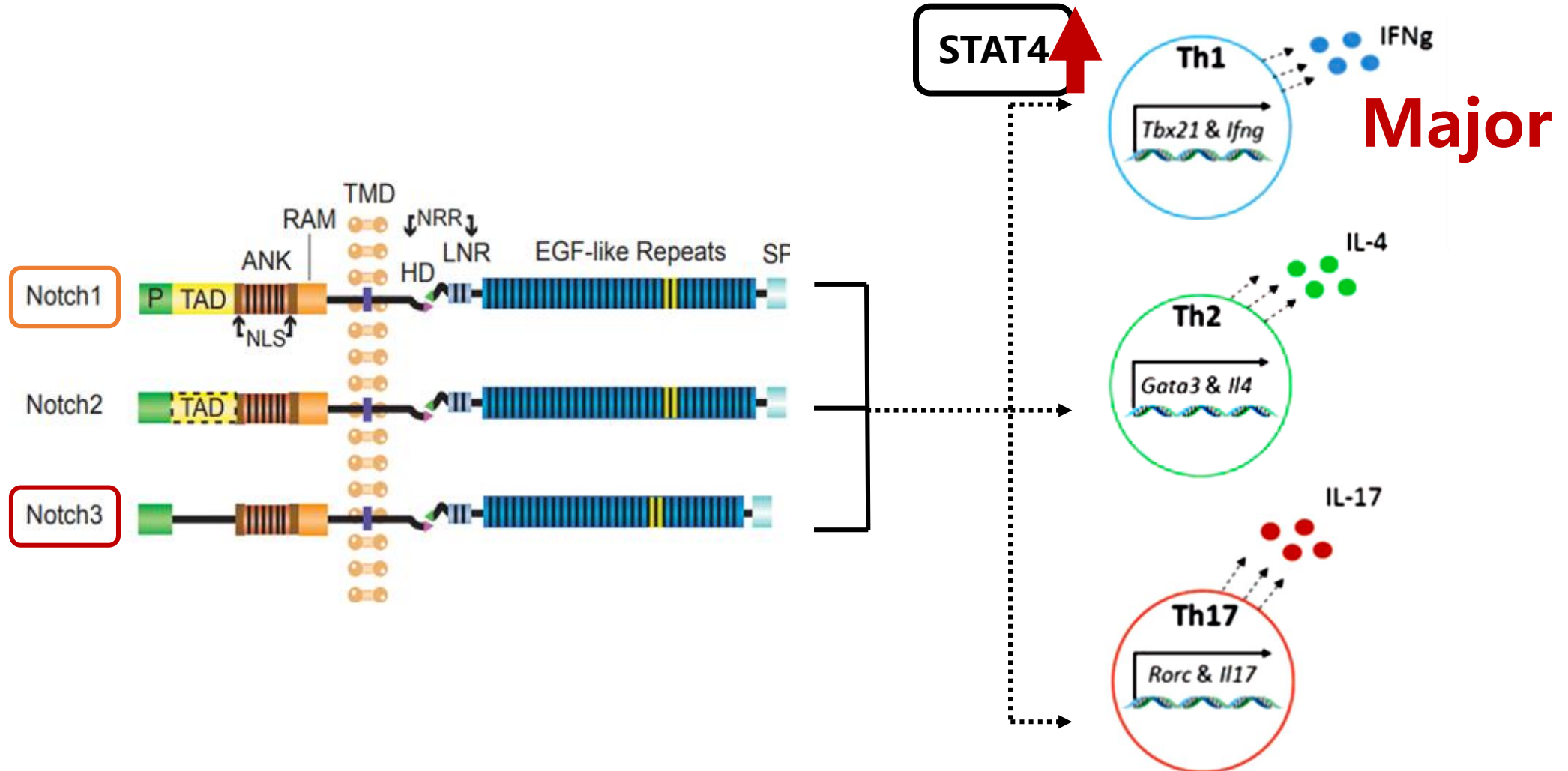
NOTCH3



Notch1, Notch2, and Notch3 were negatively correlation with STAT1

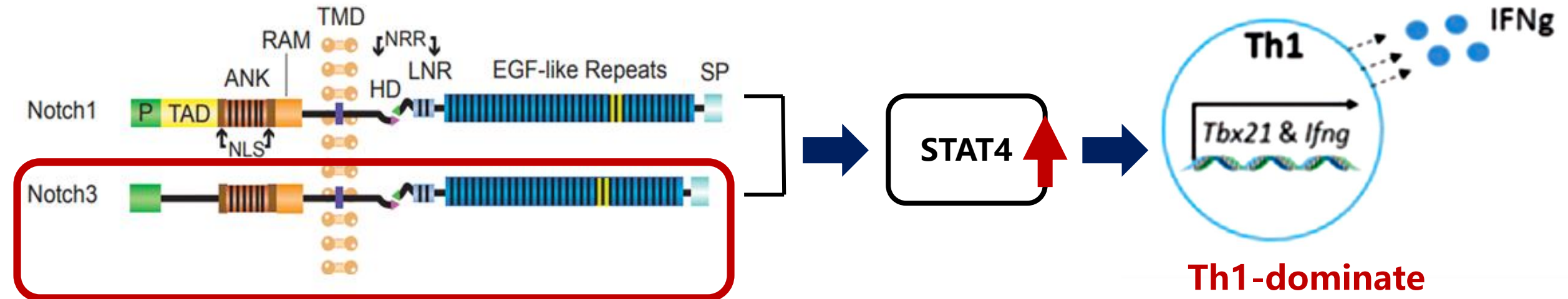


Positive correlations were observed between Th1 responses, Notch1, and Notch3



Conclusion

1. Th1 response increased were observe in patient with COPD
2. NOTCH1 and NOTCH3 mRNA expression were significantly increased in patient with COPD
3. NOTCH 1 and NOTCH3 were strongly correlated to Th1 response, including T-bet, IFN- γ , STAT-4



Acknowledgement

彰化基督教醫院 胸腔醫學研究室團隊



中興大學生物醫學所
特聘教授
林季干 老師



彰化基督教醫院
內科部研究中心執行長
許秋婷 研究員

Thank You