The nuclear receptor PPARγ controls the expression of the short isoform of TSLP in the colon
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Introduction:
Peroxisome proliferator activated receptor gamma (PPARγ) plays a key role in gut homeostasis through anti-inflammatory properties. PPARγ expression by colonic epithelial cells (CEC) is decreased in patients with ulcerative colitis (UC). We hypothesized that PPARγ controls the expression of various factors for intestinal homeostasis. The thymic stromal lymphopoietin (TSLP) is an epithelial cytokine playing an important role during intestinal tolerance. Two isoforms of TSLP, TSLP1 and TSLP2, are described, but their distinct expression pattern and function are insufficiently investigated. The short-form TSLP (TSLP2) is synthesized constitutively in CEC and epithelial lung cells. This isoform may play an anti-inflammatory role. The long-form TSLP (TSLP1) is induced by stimulation of poly (I:C) (double strand RNA) in the epithelial lung cells. TSLP1 orients lymphocytes toward a Th2 inflammatory profile.

Aim: To investigate the relationship between the expression of TSLP and PPARγ in the colon.

Results:
A) TSLP expression is induced by PPARγ agonists in the colon
1) Colonic epithelial cell lines

Caco-2 cells

Figure 2: TSLP expression is highly induced by PPARγ agonists in Caco-2 cells. TSLP expression levels are evaluated by quantitative RT-PCR in Caco-2 cells in the absence or presence of PPARγ agonists: (A) GED 30 mM, 5-ASA 30 mM (n=6); (B) Pioglitazone 10 µM (n=6).

2) Mice’s colon

Figure 3: TSLP expression is highly induced by PPARγ agonists in T84 cells. TSLP expression levels are evaluated by quantitative RT-PCR in T84 cells in the absence or presence of PPARγ agonists: (A) GED 30 mM, 5-ASA 30 mM (n=6); (B) Pioglitazone 10 µM (n=6).

B) The short-form TSLP is mainly expressed in CEC

Figure 5: The TSLP2 expression is highly induced by PPARγ agonists in Caco-2 cells. Total TSLP (TSLP1+ TSLP2) and TSLP2 induction levels are the same. TSLP1 is not expressed in CEC and not induced by PPARγ agonists. TSLP expression levels are evaluated by quantitative RT-PCR in Caco-2 cells in the absence or presence of PPARγ agonists: (A) GED 30 mM, 5-ASA 30 mM (n=6); (B) Pioglitazone 10 µM (n=6).

Figure 6: The decrease of PPARγ expression is associated with a decrease of TSLP expression in caco-2 ShPPARγ. (A) PPARγ expression levels is evaluated by quantitative RT-PCR in ShLuc-caco-2 cells and ShPPARγ-caco-2. Confirmation of the deficit of PPARγ gene expression by quantitative RT-PCR and Western blot of the PPARγ protein in the ShPPARγ-caco-2 cell line compared to ShLuc-caco-2 cell line. (B) TSLP expression levels is evaluated by quantitative RT-PCR in ShLuc-caco-2 cells and ShPPARγ-caco-2 cells.

C) Defective PPARγ expression induces a defective TSLP expression

1) In vitro ShPPARγ Caco-2 cell line

Figure 7: Treatment of ShPPARγ-caco-2 cells with PPARγ agonists doesn’t achieve the level of expression of the gene encoding TSLP and TSLP2 compared to ShLuc-caco-2 cells. TSLP (A) and TSLP2 (B) expression levels are evaluated by quantitative RT-PCR in ShLuc-caco-2 cells and ShPPARγ-caco-2 cells in the absence or presence of PPARγ agonists: GED 30 mM, 5-ASA 30 mM (n=6).

2) Decrease of TSLP expression is correlated with impairment of PPARγ in the CEC of UC patients.

Figure 8: A decrease of TSLP and TSLP2 expression is observed in the colon of UC patients. The decrease of TSLP and TSLP2 expression is correlated with the decrease of PPARγ expression. TSLP expression levels is evaluated by quantitative RT-PCR on healthy and inflammatory mucosa of UC patients (control patients: n = 18; UC patients: healthy colon mucosa: n = 9, injured colon mucosa: n = 21).

TSLP 2 is the major form of TSLP in the colon and its expression is regulated by PPARγ. These results support the hypothesis that, in UC, the impaired expression of PPARγ in CEC could play a role in the loss of intestinal tolerance though a decreased TSLP 2 expression.