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Evaluation of innate lymphoid cells, mucosal-associated invariant T cells and helper T cells in human autoimmune uveitis

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INTRODUCTION AND OBJECTIVE

Up to 50 % of uveitis are classified as « idiopathics ». Uveitis association with Th1 and Th17-mediated systemic inflammatory disorders - such as IBD and spondylarthritis - and immunosuppressive agents efficacy suggest underlying autoimmune mechanisms. Specific T cell responses to retinal antigens (IRBP and S-arrestin) have been identified in patients with idiopathic uveitis. A transgenic murine model of spontaneous autoimmune uveitis recently showed that specific retinal antigen T cells were initially activated in the intestine by microbiota extracts before they migrated and entered into the eye (1).

Innate lymphoid cells (ILC) and **mucosal-associated invariant T cells (MAIT)** are innate immune cells recently discovered and particularly represented in mucosal tissues. These cells have never been evaluated in human uveitis.

Objective → To study **circulating ILC, MAIT and T lymphocytes** in **human autoimmune uveitis**

Functional evaluation of T cells: polyclonal stimulation and identification of S-arrestin specific T cells

FLOW CYTOMETRY

ICS

PBMC stimulation
(1x10⁶ cells)

PMA/ionomycin

or

S-arrestin peptides

Conditions:

- Negative control
- Overnight incubation (14-16h)
- 37 °C, 5% CO₂



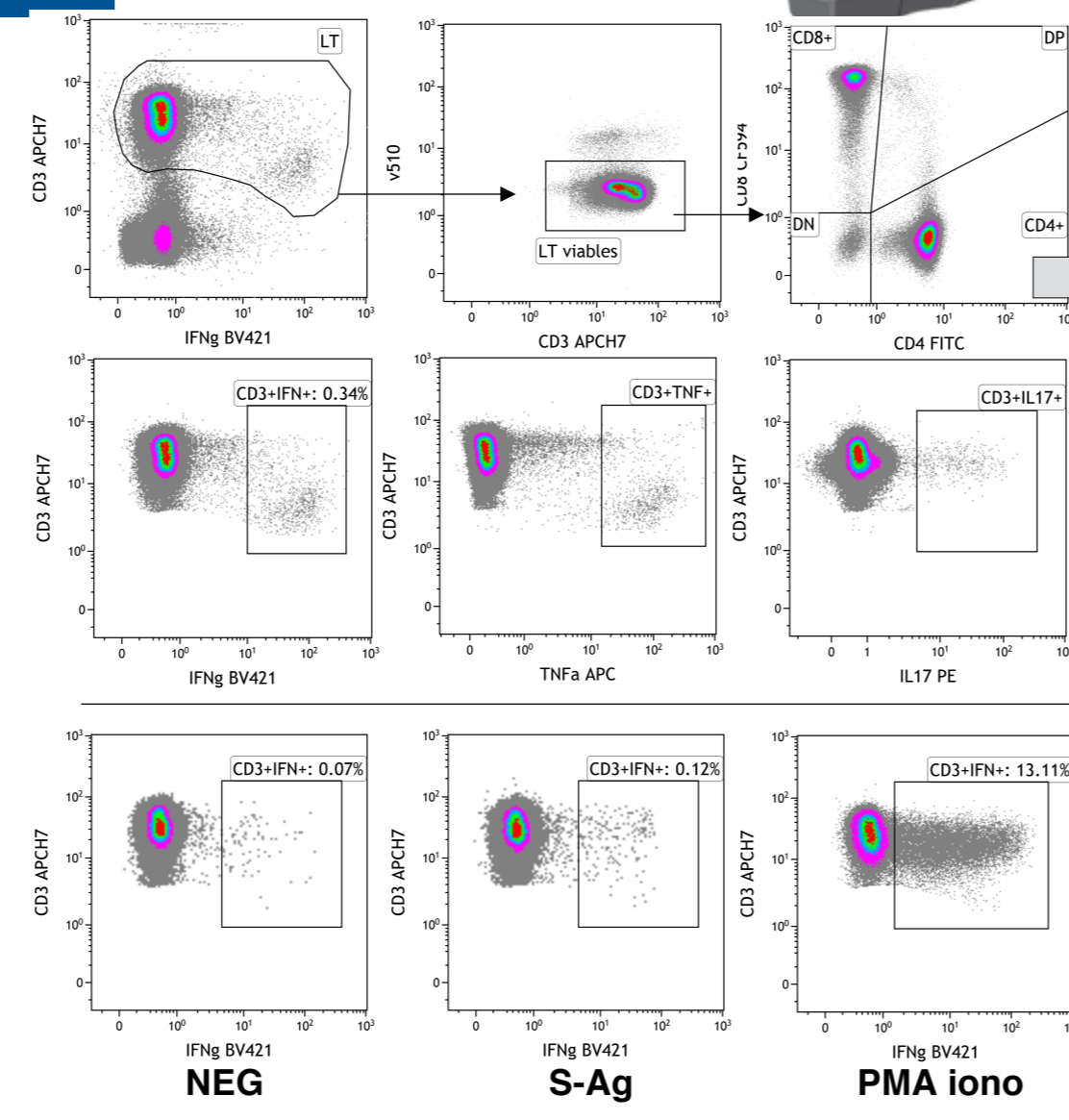
IFN-γ

TNF-α

IL-17

Gating:

- lymphoid cells (SS/FS)
- singlets
- CD3 +
- viability stain 510 -



PROLIFERATION

CFSE-labeled PBMC stimulation
(2x10⁵ cells)

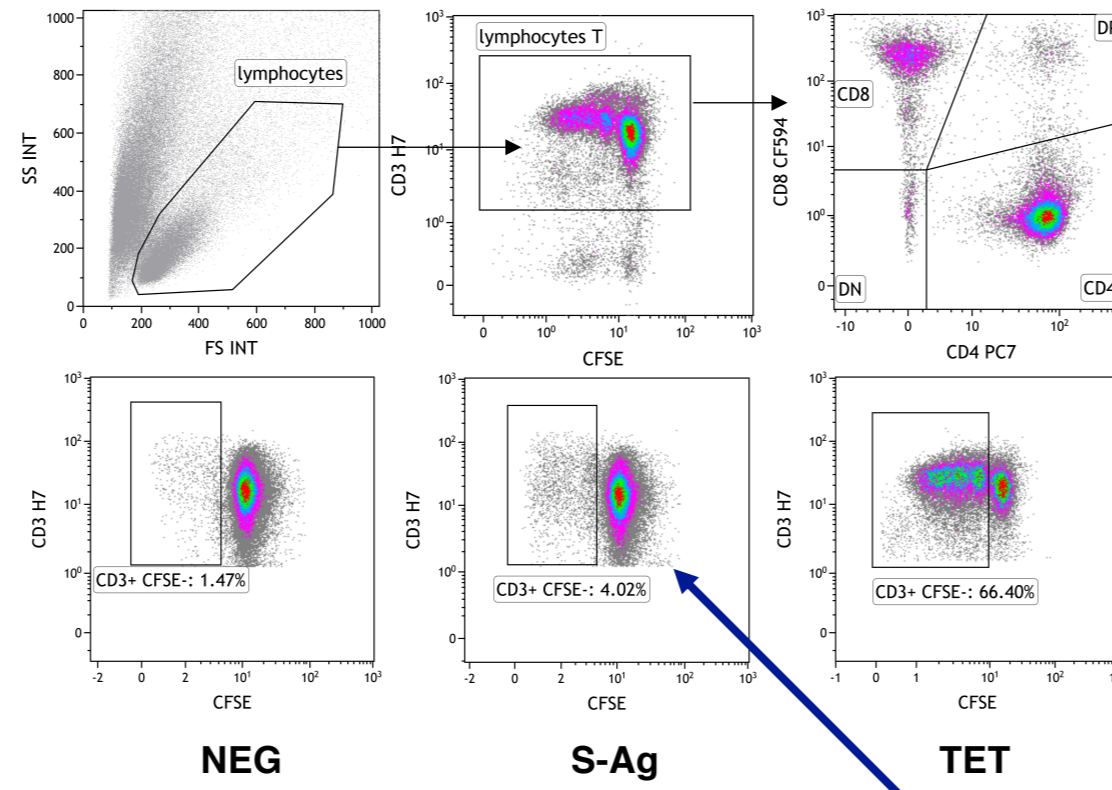
S-arrestin peptides

or

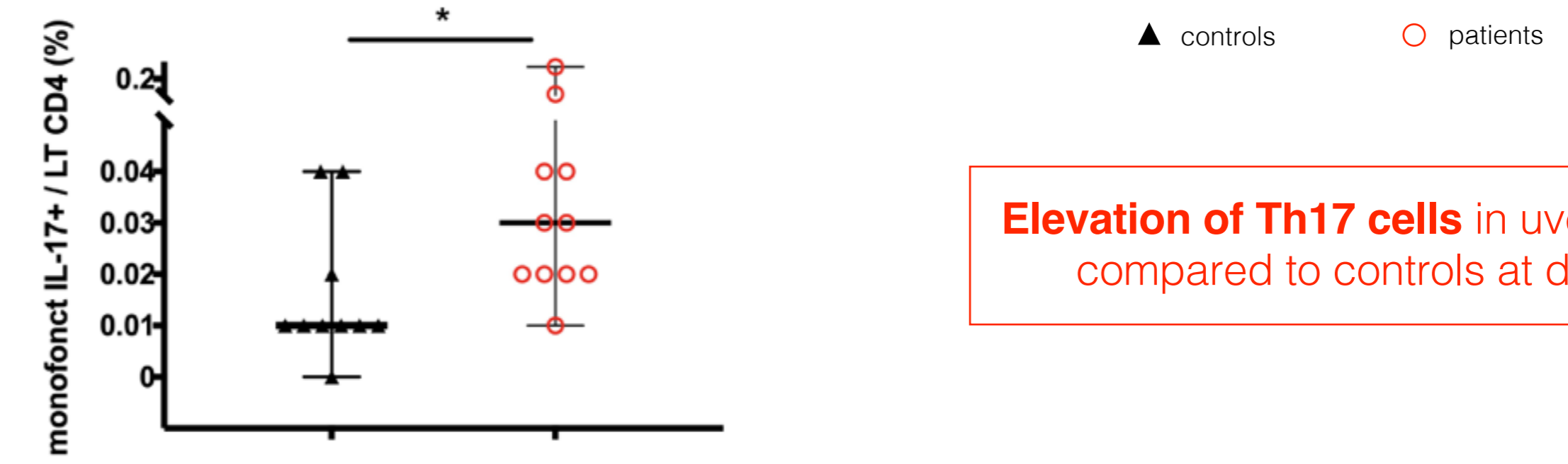
Tetanus anatoxin

Conditions:

- Negative control
- 7 days incubation
- 37 °C, 5% CO₂



Proportions of circulating monofunctional IL-17+ CD4+ T cells and S-arrestin specific T cells

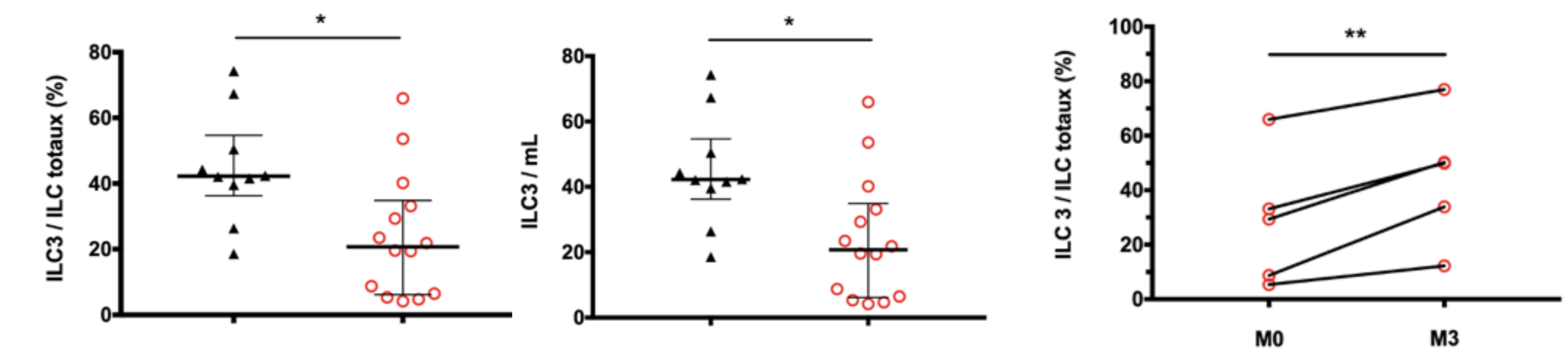


Elevation of Th17 cells in uveitis patients compared to controls at diagnosis

Detection of **S-arrestin specific lymphocyte responses** (IFN-γ production and/or proliferation) in 4/15 patients

	ICS	ICS	ICS	CFSE	CFSE	CFSE
	Δ CD3 IFN-γ+ (ratio)	Δ CD4 IFN-γ+ (ratio)	Δ CD8 IFN-γ+ (ratio)	Δ CD3+ (index)	Δ CD4+ (index)	Δ CD8+ (index)
#4	0,05 % (1,71)	0,04 % (2)	0,03 % (1,75)	1,8 %	2,7 % (2,26)	0,03 %
#5	0 %	0 %	0 %	0,3 %	0,5 % (2,01)	0 %
#9	0,03 % (1,67)	0,03 % (4)	0,01 %	0 %	0 %	0 %
#15	0 %	0 %	0,01 %	2,7 % (1,77)	3,7 % (1,82)	1,8 (0,75)

Proportions and absolute numbers of circulating ILC and MAIT cells



Diminution of ILC 3 in uveitis patients compared to controls at diagnosis
Elevation of ILC 3 after 3 months of corticosteroids in uveitis patients (no clinical activity detected)

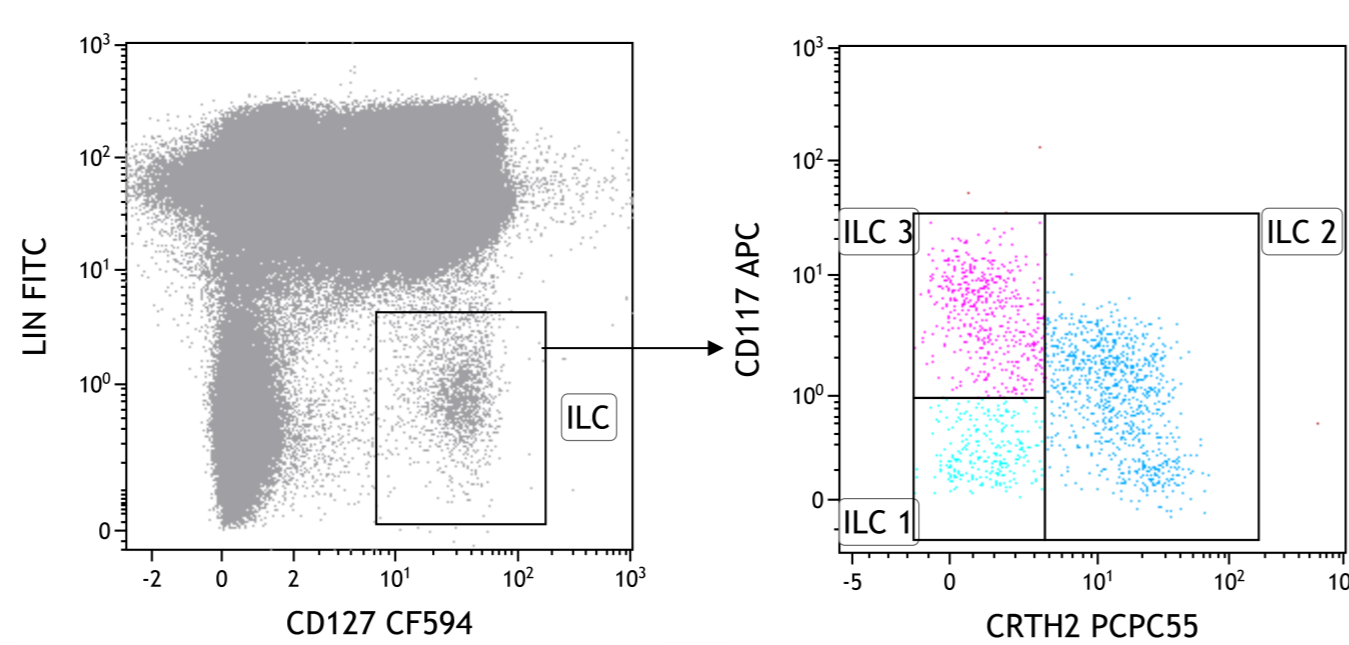
ILC and MAIT identification

FLOW CYTOMETRY

ILC

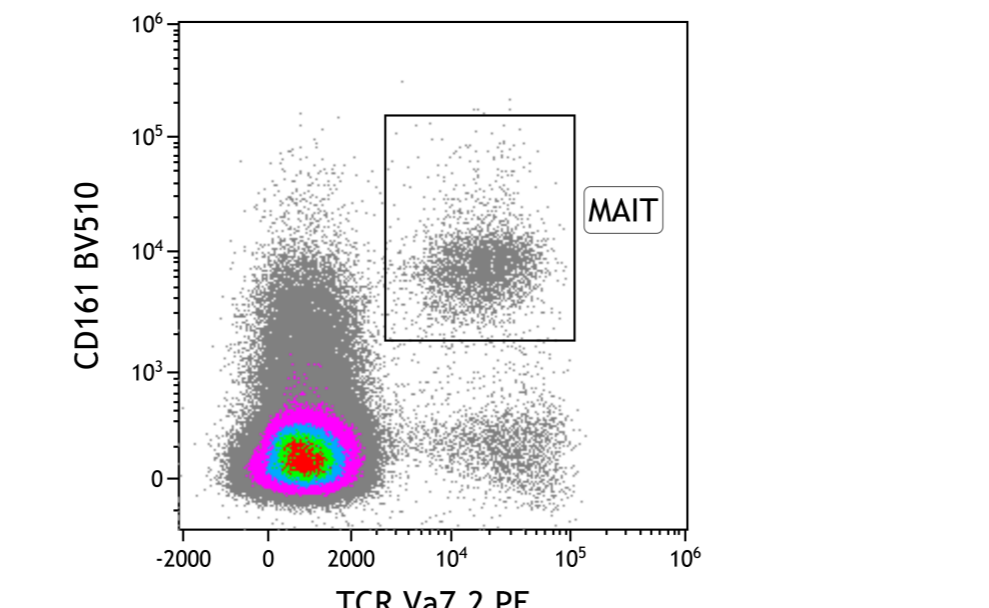
Pool lineage:
CD2 - CD19
CD3 - CD20
CD8 - CD33
CD14 - CD34
CD15 - CD56
CD16 - CD123

Gating:
• lymphoid cells (SS/FS)
• singlets



MAIT

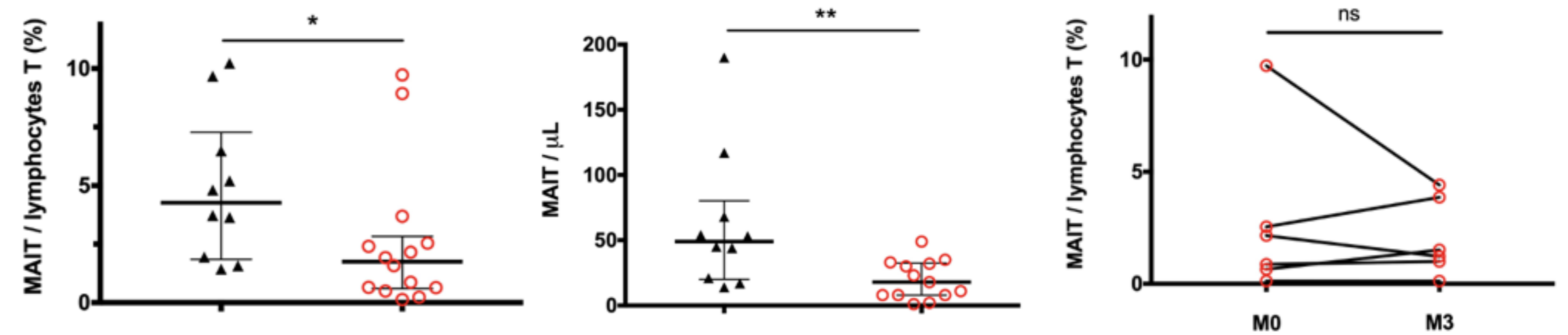
Gating:
• lymphoid cells (SS/FS)
• singlets
• CD3 +



RESULTS

Elevation of CCR6+ ILC 3 proportions in uveitis patients at diagnosis

Total ILC were negatively correlated with clinical activity in uveitis patients



Diminution of MAIT in uveitis patients compared to controls at diagnosis

* p < 0,05, ** p < 0,01, **** p < 0,0001, ns: not significant

Patients characteristics

	Healthy volunteers (n=10)	Uveitis patients (n=15)	p-value
Age, years	54 [33-60]	47 [42-69]	0,53
Sex ratio (F/M)	5/5	9/6	0,7
Bilateral uveitis, n (%)		8/15 (53 %)	
Localization, n (%)			
Anterior		2/15 (13 %)	
Posterior		5/15 (33 %)	
Panuveitis		8/15 (53 %)	
Anterior chamber cells (RE/LE)		0 [0-1]/0 [0-1]	
Vitreous haze (RE/LE)		0 [0-1]/0 [0-1]	
Papillitis, n (%)		8/15 (53 %)	
Retinal and/or chorioidal lesions, n (%)		1/15 (7 %)	
Retinal vasculitis, n (%)		5/15 (33 %)	
Macular edema, n (%)		5/15 (33 %)	
Visual acuity (RE/LE)			
Monoyer		5 [2-10]/9 [4-10]	
Parinaud		2 [2-3,5]/2 [2-5,5]	
UVEDA score		2,77 [0,38-3,75]	
Leucocytes, nb/mm ³	5,85 [4,96-6,34]	7,07 [5,99-8,5]	0,03
Lymphocytes, nb/mm ³	1,78 [1,69-1,88]	1,94 [1,61-2,3]	0,8
Neutrophils, nb/mm ³	3,27 [2,91-3,47]	4,1 [3,27-5,73]	0,08
C-reactiv protein (CRP), mg/l		1,1 [0,1-5,9]	
Oral corticosteroid regimen, n (%)		12/15 (80 %)	

RE: right eye, LE: left eye

DISCUSSION

- Confirmation of global Th17 cellular responses in human autoimmune uveitis
- In 4/15 patients, retinal antigen-specific lymphocyte responses were detected at the time of diagnosis
- This is the first description of an **altered distribution of circulating ILC and MAIT correlated with clinical activity** in human uveitis
 - implication of ILC and MAIT in uveitis pathogenesis ?
- Intestinal recruitment of CCR6+ ILC (LTI? ILCP?) could putatively participate in Th1- and Th17-specific retinal antigens responses initiation or maintenance
- Our results need to be confirmed in a larger cohort and further investigations are needed to study **ILC and MAIT interactions with T cells** and determine whether they could represent **new therapeutic targets** in the future