



**HAL**  
open science

## **Mucosal IL-7 response in the gut during HIV/SIV acute infection**

Carolina Moraes-Cabe, Magali Rancez, Bénédicte Charmeteau-De-Muylder, Suzanne Figueiredo-Morgado, Magali Mas, Rémi Cheynier, Anne Couëdel-Courteille

### ► To cite this version:

Carolina Moraes-Cabe, Magali Rancez, Bénédicte Charmeteau-De-Muylder, Suzanne Figueiredo-Morgado, Magali Mas, et al.. Mucosal IL-7 response in the gut during HIV/SIV acute infection. 22nd International AIDS Conference (AIDS 2018), Jul 2018, Amsterdam, Netherlands. 2018. hal-03000417

**HAL Id: hal-03000417**

**<https://hal.science/hal-03000417>**

Submitted on 11 Nov 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Mucosal IL-7 response in the gut during HIV/SIV acute infection

Carolina Moraes-Cabe<sup>1,2,3</sup>, Magali Rancez<sup>1,2,3</sup>, Angelina Mimoun<sup>1,2,3,4</sup>, Bénédicte Charmeteau-de-Muylder<sup>1,2,3</sup>, Suzanne Figueiredo<sup>1,2,3</sup>, Magali Mas<sup>1,2,3</sup>, Rémi Cheyrier<sup>1,2,3</sup>, Anne Couëdel-Courteille<sup>1,2,3,4</sup>

<sup>1</sup>INSERM, U1016, Institut Cochin, Paris 75014, France; <sup>2</sup>CNRS, UMR8104, Paris 75014, France; <sup>3</sup>Université Paris Descartes, Sorbonne Paris Cité, Paris 75014, France; <sup>4</sup>Université Paris Diderot, Paris 75013, France

## Introduction

Interleukin-7 (IL-7) is an essential cytokine for the development and homeostasis of T lymphocytes. This cytokine has long been described as constitutively produced by stromal cells of lymphoid and non-lymphoid organs. Homeostatic production of IL-7 is independent of extrinsic stimuli, plasma IL-7 levels being regulated by its consumption by T-cells (Fry and Mackall 2005, Mazzucchelli and Durum 2007). However, IL-7 production by stromal cells can be regulated by the microbiota as well as by bacterial and viral infections (Shalapur et al., 2010).

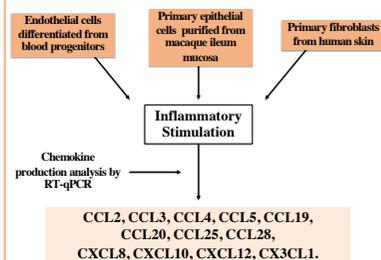
We recently demonstrated that IL-7 production is transiently increased in the gut of acutely SIV-infected rhesus macaques (Ponte et al., 2017), suggesting a regulation by inflammatory cytokines. This increase leads to local expression of several chemokines and immune cell homing into the gut, with a possible consequence on both the initiation of the antiviral immune response and the establishment of viral reservoirs (Ponte et al., 2017).

## Aims

This work aims at deciphering the implication of intestinal mucosal cells on IL-7 production and IL-7-dependent chemokine expressions observed in the gut of acutely SIV-infected macaques.

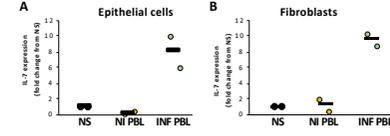
## Methodology

Primary epithelial cells and fibroblasts purified from healthy tissue and endothelial cells differentiated from blood progenitors were cultured in the presence of HIV/SIV-infected PBMCs supernatants or inflammatory cytokines (TNF $\alpha$ , IFN $\alpha$ , IFN $\beta$  or IFN $\gamma$ , IL-7, IL-7Ra) and chemokine expressions were quantified by RT-qPCR.



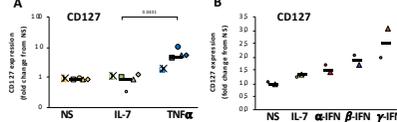
## Results

### HIV infection promotes IL-7 overexpression by stromal cells.



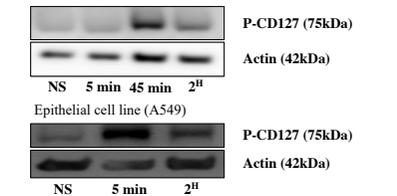
**Fig 1. Mucosal cells overexpress IL-7 when stimulated with the supernatant of HIV-infected PBL.** IL-7 mRNAs expressed by simian primary intestinal epithelial cells (A) and human primary fibroblasts (B) were quantified by RT-qPCR and normalized to HPRT mRNA. At each culture condition, each symbol represents one sample/donor. Results are presented as fold changes over non-stimulated cells values. Medians are shown as horizontal bars. NS: non-stimulated; NI PBL: supernatant of non-infected PBL; INF PBL: supernatant of HIV/SIV-infected PBL.

### IL-7Ra (CD127) is expressed on endothelial cells and fibroblasts and up-regulated upon stimulation



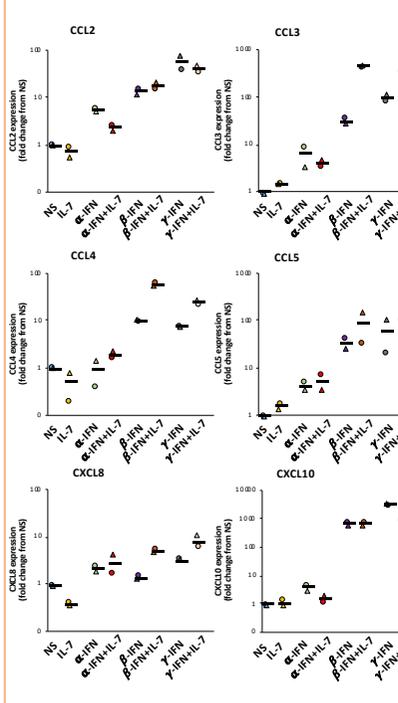
**Fig 2. IL-7Ra (CD127) is overexpressed in stimulated mucosal cells.** CD127 mRNAs in TNF $\alpha$ -stimulated human primary endothelial cells (A) and interferons-stimulated primary fibroblasts (B) were quantified by RT-qPCR and normalized to HPRT mRNA. At each culture condition, each symbol represents one sample/donor. Results are presented as fold changes over non-stimulated cells values. Medians are shown as horizontal bars. Statistical differences are shown (Wilcoxon signed rank test).

### IL-7Ra (CD127) phosphorylation upon IL-7 stimulation



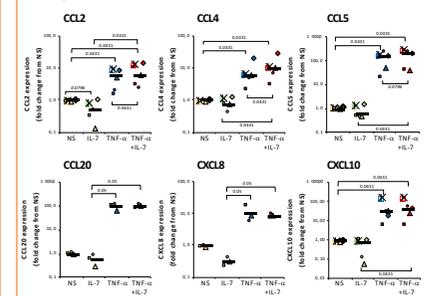
**Fig 3. IL-7 stimulation phosphorylates IL-7Ra on mucosal cells.** Phosphorylation of CD127 was verified by Western Blot in IL-7-stimulated fibroblasts (top) and epithelial cells (bottom). Specific p-CD127 antibody was used to detect phosphorylated CD127. Actin was used as internal control. Blots are representative of 2 independent experiments.

### IL-7 potentiates the effect of inflammatory cytokines for the expression of some chemokines in human fibroblasts



**Fig 4. Chemokines transcription is up-regulated in stimulated fibroblasts.** mRNAs coding for CCL2, CCL3, CCL4, CCL5, CXCL8 and CXCL10 in non-stimulated and overnight stimulated fibroblasts were quantified by RT-qPCR.

### IL-7 potentiates the effect of inflammatory cytokines for the expression of some chemokines in human endothelial cells



**Fig 5. Chemokines transcription is up-regulated in stimulated endothelial cells.** mRNAs coding for CCL2, CCL4, CCL5, CCL20, CXCL8 and CXCL10 in non-stimulated and 4h stimulated human EC were quantified by RT-qPCR.

## Conclusions

- The supernatant of HIV-infected PBLs triggers IL-7 production by epithelial cells and fibroblasts, contrarily to the supernatant of non-infected PBLs.
- Endothelial cells and fibroblasts are able to overexpress CD127 expression upon inflammatory stimulation.
- In combination with TNF $\alpha$ , IL-7 triggers increased mRNA expression of CCL2, CCL4 and CCL5 in human endothelial cells. IL-7 also increases the mRNA expression of CCL2, CCL3, CCL4, CXCL8 in primary fibroblasts in combination with type I and type II interferons ( $\alpha$ -IFN,  $\beta$ -IFN and  $\gamma$ -IFN).
- During the acute phase of SIV-infection, as a result of the inflammatory environment and IL-7 production, epithelial cells, endothelial cells and fibroblasts are likely to participate to the increase of chemokine production that leads to immune cell recruitment into infected tissues.

## Acknowledgment

This work was supported by the ANRS, SIDACTION, INSERM, CNRS and Université Paris Descartes. Thank you to IDMIT animal caretakers and veterinaries, to core facilities (Cybio and Genom'IC platforms at Cochin Institute) and other collaborators for additional support.