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IL-7-dependent chemokine production by intestinal endothelial cells during acute HIV/SIV infection

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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 (Shalapur *et al.*, 2010).

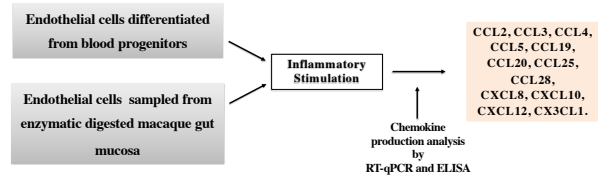
Moreover, *in vivo*, we recently showed that IL-7 production is transiently increased in the gut of acutely SIV-infected rhesus macaques (Ponte *et al.*, 2017), suggesting a regulation by inflammatory cytokines. This increase leads to local expression of several chemokines and immune cell homing into 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).

Among all cells that compose the gut mucosa, endothelial cells play a key role in immune cell migration into tissues. These cells support transmigration, express chemokines upon stimulation (Nakano *et al.*, 2012, Lo HM *et al.*, 2014) and can produce IL-7 (Iolyeva *et al.*, 2013). However, their role in IL-7 dependent T-cell homing during the acute phase of HIV/SIV infection remains to be addressed.

AIMS

This work aims at deciphering the implication of endothelial cells (EC) in the IL-7-dependent chemokine expression observed in the gut of acutely SIV-infected macaques.

METHODOLOGY



RESULTS

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

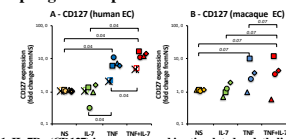


Fig 1. IL-7 α (CD127) is overexpressed in stimulated endothelial cells
CD127 mRNAs expression in human (A) and macaque (B) EC was quantified by RT-qPCR in non-stimulated and 4^h or overnight stimulated (B) cells.

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

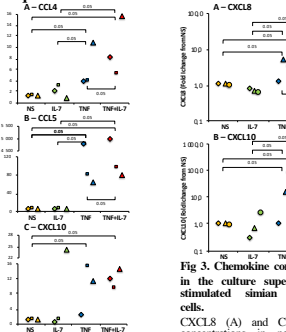


Fig 2. Chemokines transcription is up-regulated in stimulated simian endothelial cells
mRNAs coding for CCL4 (A), CCL5 (B) and CXCL10 (C) in non-stimulated and overnight stimulated simian EC were quantified by RT-qPCR.

Chemokine concentrations in the culture supernatants of stimulated simian endothelial cells

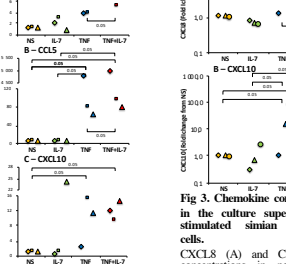


Fig 3. Chemokine concentrations in the culture supernatants of stimulated simian endothelial cells.
CXCL8 (A) and CXCL10 (B) concentrations in non-stimulated and overnight stimulated simian EC culture supernatants were assessed by ELISA (MSD).

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

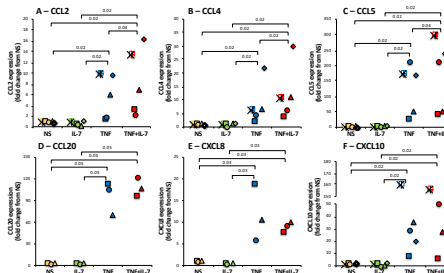


Fig 4. Chemokines transcription is up-regulated in stimulated endothelial cells
mRNAs coding for CCL2 (A), CCL4 (B), CCL5 (C), CCL20 (D), CXCL8 (E) and CXCL10 (F) in non-stimulated and 4^h stimulated human EC were quantified by RT-qPCR.

Chemokine production in the culture supernatants of stimulated human endothelial cells

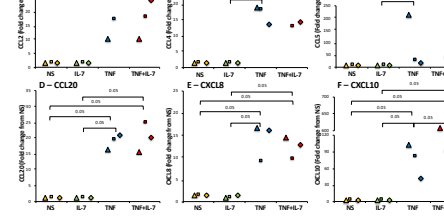


Fig 5. Chemokine production in the culture supernatants of stimulated human endothelial cells.
CCL2 (A), CCL4 (B), CCL5 (C), CCL20 (D), CXCL8 (E) and CXCL10 (F) concentrations in non-stimulated and overnight stimulated human EC culture supernatants were assessed by ELISA (MSD).

Each symbol represents one donor. Results are presented as fold increases over non-stimulated (NS) cells values or cell culture supernatant values. RT-qPCR are normalized to HPRT mRNA. Statistical analysis were made using Wilcoxon Signed-Rank Test for Paired Samples.

mRNA expression correlate together with protein production of CCL2, CCL4, CCL5 and CXCL10 in human endothelial cells

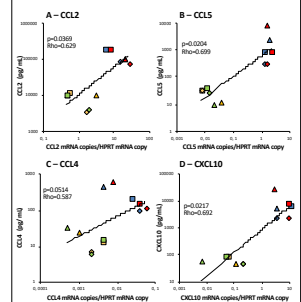


Fig 6. Correlation between chemokine concentrations and chemokine mRNA levels in stimulated human endothelial cells.
CCL2, CCL4, CCL5 and CXCL10 mRNAs were quantified by RT-qPCR and normalized to HPRT mRNA and results are expressed as chemokine mRNA copies/HPRT mRNA copy. CCL2, CCL4, CCL5 and CXCL10 concentrations were assessed by ELISA (MSD) and results are expressed as pg/mL. Regression line, Spearman's rank correlation value, and associated probability are shown.

CONCLUSIONS

- CD127 expression is increased in EC upon stimulation by TNF α with higher expression when IL-7 is added in human EC derived from blood progenitors.
- In combination with TNF α , IL-7 triggers increase in mRNA expression of CCL4, CCL5 in macaque intestinal EC and CCL2, CCL4 and CCL5 in human EC, while only increasing CXCL8 proteins in intestinal macaque or CXCL10 proteins in human endothelial cells compared to TNF α stimulation alone after overnight culture. Among the chemokines overexpressed in the gut mucosa of both SIV infected and IL-7 macaques, only CCL4 and CXCL8 were expressed upon IL-7 stimulation of TNF-stimulated endothelial cells, suggesting that other cell types participate to the IL-7-dependent chemokine expression *in vivo*. Moreover, CXCL8 levels in the culture supernatants were lower in TNF-stimulated human endothelial cells derived from blood progenitors than in simian primary intestinal endothelial cells, suggesting a specific capacity of the latter to respond to IL-7 through IL-8 expression.
- During acute phase of SIV-infection, as a result of the inflammatory environment and the IL-7 production, endothelial cells are likely to participate to the increase of chemokine production that leads to immune cell recruitment.

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