CC-GENOTYPE (IFNL4) IN HCV/HIV COINFECTION: CELLULAR EXHAUSTION BUT BALANCED INFLAMMATORY PROFILE

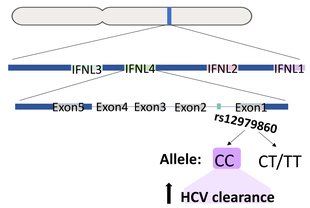
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BACKGROUND

CC genotype of the rs12979860 polymorphism on the *lambda 4 interferon (IFNL4)* gene has been related to spontaneous resolution of Hepatitis C virus (HCV) infection.



However, the role of CC genotype in those who develop chronic HCV infection is still unknown, particularly notable during human immunodeficiency virus (HIV) coinfection.

To study its role in HCV/HIV coinfection, a characterization of the oxidative and immune profile of rs12979860 genotypes (CC vs CT/TT) has been conducted.

METHODS

Study population

HCV HIV

45 **CHC**

38 **SC**

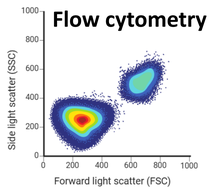
35 **HIV**

CHC: Chronic Hepatitis C
SC: spontaneous clearers

Cell surface markers

CD4+ and CD8+ memory T cells

Flow cytometry



rs12979860 genotyping



qPCR

Soluble markers

Oxidative stress markers:
UV-Vis Spectrophotometry

Cytokines:
Multiplex immunoassays

R Studio

Differences among genotypes were evaluated by generalized linear model (GLM), or generalized additive model for location, scale, and shape (GAMLSS), adjusted for the most significant variables and corrected by *false discovery rate* (FDR)

RESULTS

Higher frequency of CC carriage was observed among SC group (76.32%), 2.5 times higher than in CHC group (31.11%).

Cellular immune profile

CHC group. CC-carriers resting CD8+T cells significantly decreased, including EM and TEMRA (total and pE2).

Opposite, they showed higher levels of cellular immune exhaustion in CD8+T cells. This was depicted by the significant increase in cellular surface expression of markers of middle (CD25) and late (CD38) activation, and senescence (PD1/CD57), **Fig.1**.

CC-carriers. Similarly, significantly higher expression was observed in CD4+ and CD8+T cells in **CHC-CC than SC-CC and HIV-CC** controls.

Oxidative stress markers

CHC group. CC-carriers had slightly lower oxidative stress levels than CT/TT-carriers: significantly higher GSH/GSSG but lower GSSG and lipid-soluble antioxidants (**Fig.2a**).

CC-carriers. Compared to SC-CC carriers, a trend to significantly reduced oxidative stress was observed, although nitrate levels were significantly higher in CHC-CC individuals (**Fig.2b**).

No significant differences were found with HIV group.

Soluble immune markers

CHC group. CC-carriers had higher levels of 14 immune biomarkers compared to CT/TT carriers, including pro- and anti-inflammatory cytokines (**Fig.2b**).

CC-carriers. CHC-CC had higher levels of 11 immune biomarkers relative to SC-CC, (**Fig.2b**). No significant differences were found with HIV group.

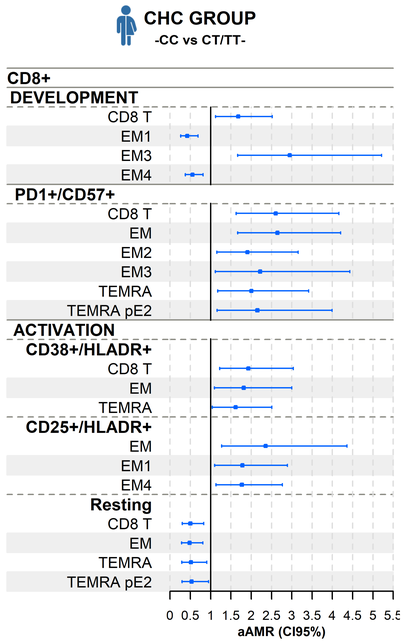


Fig. 1 Analysis of cellular immune profile ($p < 0.05$, $q < 0.15$); Values are expressed as arithmetic median ratio adjusted by the most significant clinical variables (aAMR) obtained using a GAMLSS model.

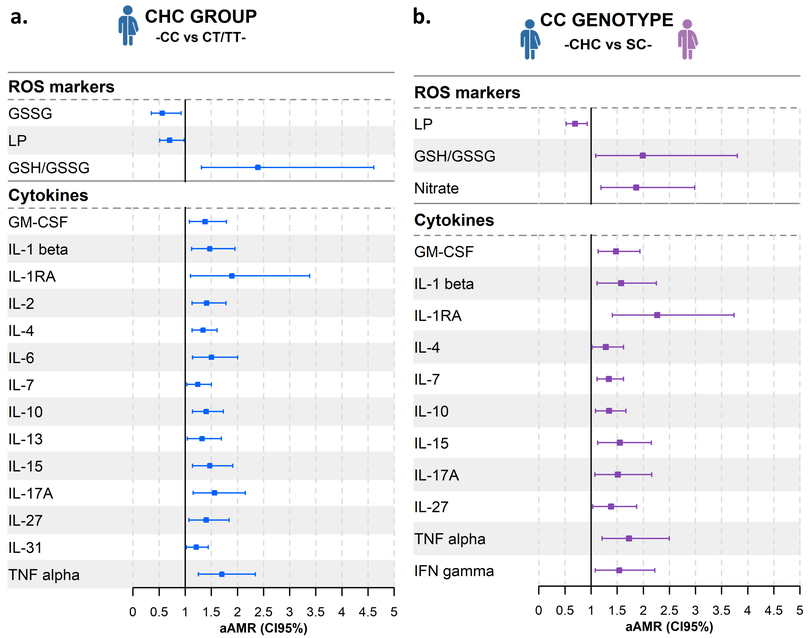


Fig. 2 Analysis of ROS and soluble immune markers ($p < 0.05$, $q < 0.15$) comparing **(a)** CC genotype versus CT/TT within CHC group (in blue); **(b)** CHC versus SC groups carrying CC genotype (in purple). Values are expressed as arithmetic median ratio adjusted by the most significant clinical variables (aAMR) obtained by GLM model. Abbreviations: GM-CSF, Colony stimulating factor 2; GSH, Reduced glutathione; GSSG, Oxidized glutathione; LP, lipid-soluble antioxidants; ROS, Reactive oxygen species.

CONCLUSIONS

- The favourable genotype for HCV clearance rs12979860-CC is associated with increased levels of exhausted CD8+T cells in PWH with chronic HCV infection
- This cellular exhaustion may be masked during clinical monitoring by their ability to buffer the oxidative stress and the general altered levels of anti- and pro-inflammatory cytokines.
- Once that **chronic HCV** infection is established, **CC carriage** may result in an **unfavourable environment** along HCV/HIV coinfection and should be considered during clinical management.

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