Singular CD4⁺ and CD8⁺ T cell proteomic profiles in PLHIV Immunological Non-Responders before ART

01198

Marina Flores-Piñas[1,2], Silvia Chafino[2,3], Consuelo Viladés[1,2,3,4], Pere Domingo[5], Miguel López-Dupla[1,2,3,4], Alexy Inciarte[6], Jordi Navarro[7,8], Julià Blanco[3,9,10], Francesc Vidal[1,2,3,4], Joaquim Peraire[1,2,3,4], Anna Rull[1,2,3,4]✉

[1]Institut Investigació Sanitària Pere Virgili (IISPV), Tarragona, Spain. [2]INIM Research Group, Hospital Universitari de Tarragona Joan XXIII (HJ23), Tarragona, Spain. [3]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain. [4]Universitat Rovira i Virgili (URV), Tarragona, Spain. [5]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. [6]Infectious Diseases Department, Hospital Clínic, University of Barcelona, Barcelona, Spain. [7]Servei de Malalties Infeccioses, Vall d'Hebron Hospital Universitari, Barcelona, Spain. [8]Grup de recerca en malalties infeccioses, Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain. [9]IrsiCaixa AIDS Research Institute, Badalona, Spain. [10]Germans Trias i Pujol Research Institute (IGTP), Can Ruti Campus, Badalona, Spain. ✉ anna.rull@iispv.cat

BACKGROUND

A significant proportion of people living with HIV (PLHIV) who achieve virological suppression with antiretroviral therapy (ART) fail to recover CD4⁺ T cell counts; these patients are known as Immunological Non-Responders (INR). Multiple complex mechanisms are involved in the failure of immune recovery, and intracellular proteins of CD4⁺ and CD8⁺ T cells may have an important role.

The main aim is to identify proteins that may explain the different immune response to ART and to determine the metabolic pathways or biological processes that may be involved in the failure of the immune recovery process.

METHODS

Untargeted CD4⁺ and CD8⁺ T cell proteomic analyse has been performed on 100 HIV-infected adult patients recruited from 5 different hospitals and classified according to their baseline CD4⁺ T cell count (cases < 200 CD4⁺ T cells/µl, controls ≥ 200 CD4⁺ T cells/µl).

Cases were divided into immunological responders (IR) or immunological non-responders (INR) based on the CD4⁺ T cell counts after 48 weeks of being on ART. IRs were defined by a CD4⁺ T cell count greater than 250 CD4⁺ T cells/µl after treatment, and INR patients were those that showed less or equal to 250 CD4⁺ T cells/µl.

RESULTS

In both cellular subtypes, significant proteins have been identified in association with the glycolysis, gluconeogenesis, and phagosome pathways, indicating an elevated degree of metabolic activity within the cells (Fig. 1).

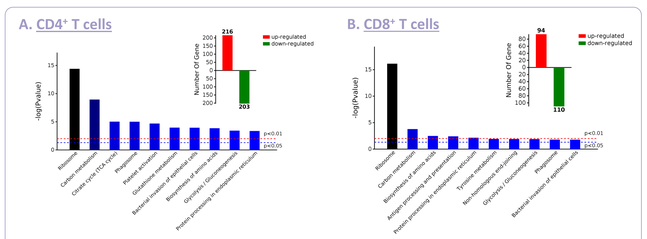

Figure 1. Significant pathways associated with the different T cell subtypes. (A) CD4⁺ T cells. (B) CD8⁺ T cells.

In CD4⁺ T cells, KEGG pathway analysis revealed the presence of significant metabolic pathways, including the citrate cycle, pentose phosphate pathway, oxidative phosphorylation, and glutathione metabolism. Cellular processes associated with cell death were also found to be significant, which is in accordance with the observed events within these cells (Fig. 2A).

SERPINA1, IDH1, and SEPTIN7 play a crucial role in upholding the balance and viability of CD4⁺ T cells. CBR1 is intricately linked with folate biosynthesis, a pathway acknowledged for its influence on the growth of CD8⁺ T cells.

A Random Forest (RF) analysis revealed three notable candidate proteins that differentiated the two groups (Fig. 2B). SERPINA1 functions as a protease inhibitor that regulates inflammation and safeguards cells during stress; IDH1 plays a crucial role in energy production and metabolic regulation; and Septin7 governs cellular organization and division (Fig. 2C).

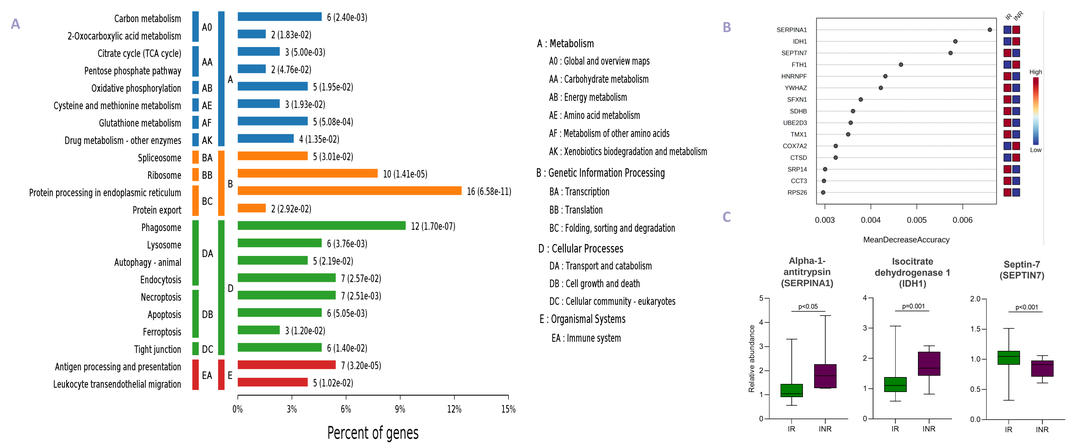

Figure 2. CD4⁺ T cells results. (A) Kegg pathway analysis of the significant proteins. (B) Random forest analysis (RF). (C) Boxplots (Mean + SEM) of the top 3 RF proteins.

In CD8⁺ T cells, RF found that carbonyl reductase is the protein that differentiates the groups the most (Fig. 3A) and is the only protein that does not exhibit significant protein-protein interactions with the other proteins (Fig. 3C). A further examination of CBR1's function revealed its connection to folate biosynthesis (Fig. 3D). This finding corroborates the outcomes of the Joint Pathway Analysis, which identified folate biosynthesis as a significant pathway (Figure 3B).

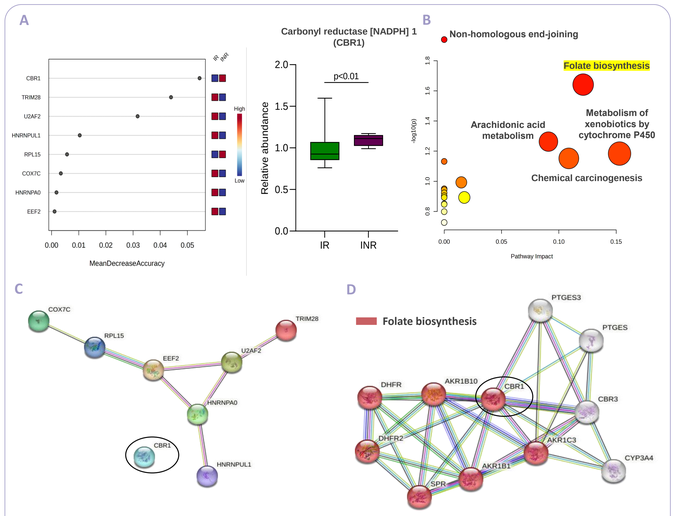

Figure 3. CD8⁺ T cells results. (A) Random forest analysis and boxplot (Mean + SEM) of CBR1 protein. (B) Joint Pathway Analysis. (C) Protein-protein network analysis of the nine significant proteins. (D) Protein-protein connexions of CBR1.

CONCLUSIONS

- SERPINA1, IDH1, and SEPTIN7 play a crucial role in maintaining the homeostasis and viability of CD4⁺ T cells. Alterations in these proteins compromise the proliferation of CD4⁺ T cells, potentially accounting for the reduced cell count.
- CBR1 is intricately associated with folate biosynthesis, a pathway known to influence the proliferation of CD8⁺ T cells. Elevated CBR1 levels are positively correlated with enhanced folate production, offering a plausible explanation for the observed heightened CD8⁺ T cell proliferation.

FUNDING

Funding: This research was funded by the Fondo de Investigacion Sanitaria [PI19/01337 and PI20/00326]-ISCIII-FEDER (co-funded by the European Regional Development Fund/European Social Fund; "A way to make Europe"/ "Investing in your future"); the Programa de Suport als Grups de Recerca AGAUR (2021SGR01404) and the CIBER -Consorcio Centro de Investigación Biomédica en Red- (CB21/13/00020), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación and Unión Europea – NextGenerationEU. AR is supported by GeSIDA through the "III Premio para Jóvenes Investigadores 2019" and by the Instituto de Salud Carlos III (ISCIII) under grant agreement "CP19/ 00146" through the Miguel Servet Program. MFP is supported by SOC under grant "Pla de Recuperació, Transformació i Resiliència —NextGenerationEU." through the programme "Primera experiencia en les administracions públiques".

Funded by the European Union NextGenerationEU · Gobierno de España · Plan de Recuperación, Transformación y Resiliencia · Next Generation Catalunya

HJ23 Hospital Universitari Joan XXIII ICS Camp de Tarragona · IISPV Institut d'Investigació Sanitària Pere Virgili