PUBLISHABLE SUMMARY

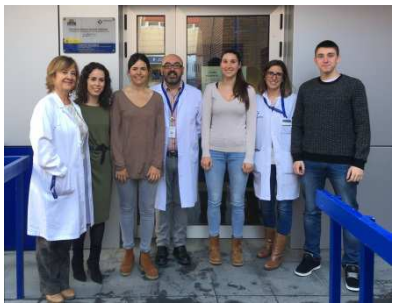
Significant advances in antiretroviral therapy have allowed the control of the viremia in most patients infected with human immunodeficiency virus (HIV), which has led to a large reduction in mortality associated with this disease. However, it is not clear yet all the causes of chronic activation as well as the mechanisms leading to immunosuppression and exhaustion, and why the Immune System is not able of controlling the virus in most infected individuals.

The human CD300 (CD300a-h) molecules are capable of recognizing phospholipids, such as phosphatidylserine (PS) and phosphatidylethanolamine (PE), which are exposed on the outer leaflet of the plasma membrane of dead and activated cells. PS and PE are to the inner sheet of the plasma membrane of live and resting cells. Loss of plasma membrane asymmetry, with exposure of PS and PE on the outer leaflet, occurs during apoptosis, cell injury, cell activation, malignant transformation and viral infection. To efficiently replicate, viruses such as human immunodeficiency virus (HIV), activate the host cells leading to an increase in the intracellular calcium, which in turn causes externalization of PS and PE. Moreover, translocation of these two phospholipids to the outer leaflet of the plasma membrane is one of the earliest events associated with apoptosis induced by viruses, such as HIV.

Our hypothesis predicts that inhibitory and activating receptors of the CD300 family of molecules have a role in the chronic immune activation and in the T cell exhaustion that are observed in patients chronically infected by HIV, and in the mechanisms that the virus use to evade the attack by cytotoxic lymphocytes, namely CD8+ T cells and natural killer (NK) cells. Therefore, the project's main objective is to study the role of the CD300 receptor family in the pathogenesis of the infection by HIV and viral escape mechanisms.

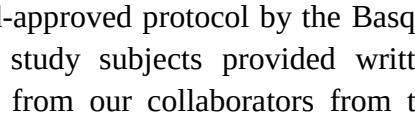
During the four years of this project we have made important advances in our knowledge about the expression and function of human CD300 receptors, in the establishment of our group (Immunopathology Group https://biocrucesbizkaia.org/web/biocruces/bc4.09) and collaborating with several research groups:

1.-: Our group was created in March 2013 with only funding for the principal investigator (PI) salary. Until today the PI (and other members of the group) has gotten several funded projects and currently the team consists of the PI, four medical doctors, two postdoctoral researchers and four predoctoral fellows. In addition, several students have performed their Master and Bachelor Degrees projects in our laboratory. One of the predoctoral fellows was briefly funded with this Career Integration Grant until she got a fellowship from the Basque Government. Also, a postdoctoral fellow is partially funded with this Career Integration Grant.

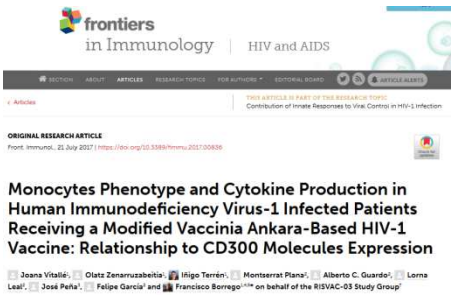


2.-: We are using blood samples collected from HIV-infected patients as well as from healthy donors. Samples are collected through the Basque Biobank and National Biobank for HIV under an institutional review board-approved protocol by the Basque Committee of Ethics and Clinical Research. All study subjects provided written informed consent. We have also obtained samples from our collaborators from the *Virgen del Rocío* Hospital in Seville, Spain.

3.-: A fundamental part of our efforts have been dedicated to the dissemination of our results. In addition to the communications and posters submitted to several meetings and conferences and the invited talks and lectures we have published three original articles. In the first article we have described the differences in the expression and function of the CD300 family of receptors in mononuclear cells from neonates and adults. The second article describe the findings we have obtained from a cohort of HIV-infected patients that have received a modified vaccinia Ankara-based HIV-1 vaccine and its relationship to CD300 molecules expression on circulating monocytes. The results from the third original article show that HIV-1 infection has an impact in the regulation of CD300a inhibitory receptor expression levels on CD4+ T cells. We have also observed an increase of CD300a expression on exhausted (PD1+) CD4+ T cells from HIV-1 infected people. Interestingly, a triple positive (CD300a+PD1+CD38+) subset was expanded in naïve HIV-1 infected patients, while it was very rare in healthy donors and patients under antiretroviral therapy. Finally, we found a negative correlation of CD300a expression on CD4+ T lymphocytes and some markers associated with HIV-1 disease progression.


SCIENTIFIC REPORTS

OPEN The expression and function of human CD300 receptors on blood circulating mononuclear cells are distinct in neonates and adults

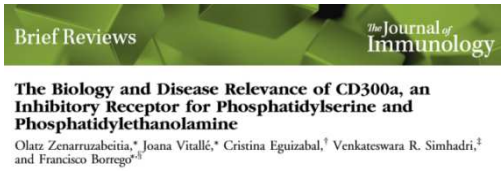

frontiers in Immunology | HIV and AIDS

Monocytes Phenotype and Cytokine Production in Human Immunodeficiency Virus-1 Infected Patients Receiving a Modified Vaccinia Ankara-Based HIV-1 Vaccine: Relationship to CD300 Molecules Expression


frontiers in Immunology | Viral Immunology

Altered Expression of CD300a Inhibitory Receptor on CD4+ T Cells From Human Immunodeficiency Virus-1-Infected Patients: Association With Disease Progression Markers

We have also published a review article about the biology and disease relevance of the CD300a inhibitory receptor, and we have recently submitted for publication a review article about the emerging role of the CD300 molecules in viral infections. In addition, we are in the process of writing another original article about the characterization of CD300a+ HIV-1 specific CD8+ T cells. Our results show that CD300a is a marker a highly polyfunctional cell subset. We expect to submit the paper for publication within the next three months. Finally, we are still working and obtaining very interesting results about the role of the CD300a receptor in the attachment and internalization of HIV-1 viral particles in CD4+ T cells. Hopefully, we will publish these results in 1-2 year.


Brief Reviews — The Journal of Immunology

The Biology and Disease Relevance of CD300a, an Inhibitory Receptor for Phosphatidylserine and Phosphatidylethanolamine

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