Review of the PhD Thesis

by Albert Font Haro

Title: Modulation of plasmacytoid dendritic cell function: role of immunoreceptors TIM-3 and BDCA-2.

Supervisor: Prof. RNDr. Ivan Hirsch, CSc

Co-supervisor: Mgr. Kateřina Trejbalová, PhD

The thesis contributes to understanding of the role of plasmacytoid dendritic cells in HIV latency and the role of specific kinases in regulation of interferon and cytokine production in plasmacytoid dendritic cells. PhD thesis by Albert Font Haro was prepared under supervision of Prof. RNDr. Ivan Hirsch, CSc. and co-supervision of Mgr. Kateřina Trejbalová, Ph.D.

The thesis is classically organized to parts - Preface, Acknowledgement, Abstract, Abbreviations, Contents, Hypotheses and Aims, Introduction, List of materials and methods, Results and Discussion, Conclusions, Significance of the results, Involvement of the candidate in the publications, References, and Supplement.

The thesis consist of the extensive introduction with two main chapters; first chapter describe development, regulation and function of plasmacytoid dendritic cells, and the second chapter review the biology of HIV, pathogenesis and treatment of HIV infection. The introduction includes all important aspects of these two topics and proves the interest of the candidate and his acquired knowledge in the field. The introduction contains a large number of references to the literature, but these references are in a non-uniform format. The literature review is well written with a sufficient number of very nice figures. The part Materials and methods describe the materials and methods used in this thesis; however, I miss the process of plasmacytoid cell purification.

The Results and discussion section describes the results published in three articles in scientific journals with impact factors. Albert Font Haro is the shared first author of the two papers published in Frontiers in Immunology (IF= 4.50)* and Viruses (IF= 3.761)*, and co-author of the article in Plos One (IF= 3.179)*. This part described all experiments which were done by Albert Font Haro.

First publication of Albert Font Haro is focused on study of functionality of plasmacytoid dendritic cells in a cohort of HIV-1-infected individuals monitored before the initiation antiretroviral therapy and followed up during a 9-month with dramatic decreased of HIV RNA in plasma using flow cytometry. The immunological profile was characterized by flow cytometry. The results showed that the level of TIM-3 molecule is associated with the decline of HIV-1 RNA. The candidate fully contributed to this work, he performed the experimental work concerning this article

The other two articles show the strategies for restoring the immunogenic activity of plasmacytoid dendritic cells using the inhibitors of MEK1/2-ERK or SYK kinases that block

TLR7/9-mediated type I IFN production. Albert Font Haro measured cytokine production and analysed data.

Question related to results and the topic of introduction:

You suggested TIM-3 as a predictive biomarker of the efficiency of ART in HIV-1-infected patients after 3th month of therapy. How often you suggested to test the level of TIM-3? Would it be enough to test only the level of TIM-3 or would it be necessary to know also other immunological or viral parameters for evaluation the effect of antiretroviral therapy?

Your study showed the immunological profile of plasmacytoid dendritic cells of newly diagnosed patients with detectable viral RNA in blood. What is the role of plasmacytoid dendritic cells in the earliest stages of HIV infection?

HIV-1 directly activates human plasmacytoid dendritic cells by endocytosis and Toll-like receptor interactions. How exactly Toll-like receptors interact with HIV RNAs when viral RNA is covered by nucleoproteins and capsid proteins?

You wrote that HCV is a weak inducer of plasmacytoid dendritic cells mediated IFN production when compared to Influenza virus or Herpesvirus? How it is in comparison to HIV?

In conclusion, the thesis of Mgr. Albert Font Haro fulfils requirements demanded for the level of PhD. I recommend submitted thesis for the defence, and depending on the outcome of defence procedure for approval of PhD degree.

Prague, June 8, 2021

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*impact factors from the year of publication of the manuscripts