

VAC_20 - Abnormal cellular innate responses in cases of adverse events post yellow fever immunization after *in vitro* 17DD stimulation

Tamiris Azamor da Costa Barros^{1*}; Juliana Gil Melgaço¹; Andréa Marques Vieira da Silva¹; Zilton Vasconcelos²; Otávio Cabral Marques³; Deborah Araújo da Conceição¹; Patrícia Mouta Nunes de Oliveira¹; Maria de Lourdes de Sousa Maia¹; Jean-Laurent Casanova⁴; Ana Paula Dinis Ano Bom¹.

¹Fiocruz/Bio-Manguinhos;

²Fiocruz/IFF;

³USP - Universidade de São Paulo;

⁴The Rockefeller University.

Introduction: Yellow Fever (YF) vaccine is a golden standard immunobiological in terms of effectiveness and safety. Even though, rare cases of neurological or viscerotropic adverse events following immunization (YEL-AD) occurs few days after vaccination due to Human Inborn Errors of Innate Immunity (HIEII). Previous works have characterized YEL-AD cases presented mutations within *IFNAR1* gene, or autoantibodies anti-IFN α , impairing type I interferon (IFN) response, the main antiviral pathway and innate hub. From the immunological point of view, it is known that YEL-AD lead to normal humoral responses, therefore cellular innate functional investigations are mandatory to understand the consequences of HIEII and help to formulate therapeutic strategies. Here, we report an analysis of innate cells, innate immune mediator's profile, and transcriptomics in cases from a national-based, YEL-AVD phase IV study.

Objective: To investigate the response against YF vaccine in YEL-AVD cases focusing on innate immunologic parameters: Natural killer (NK) cells and monocyte phenotypes, the production of the immune mediator's, and transcriptomic profile.

Methodology: Here, five subjects had blood samples collected 1-2 years after YEL-AD using the Brazilian vaccine (17DD) (CAAE 60575716.2.0000.5262). Peripheral Blood Mononuclear Cells (PBMC) from YEL-AD cases and ten controls at the same time post-vaccination were used to perform *in vitro* stimulation with attenuated YF virus, followed by immunophenotyping, Luminex assay, and RNA sequencing.

Results: At this moment, we have four cases of YEL-AD viscerotropic disease, one presenting *IFNAR1* deficiency, and two presenting anti-IFN α autoantibodies, and one case of neurological disease. The YEL-AD cases presented constitutive disturbances compared with controls: high percentage of NK^{bright} (mean: 7.04 vs 2.26, $p=0.04$), low NKT cells (0.61 vs 2.41, $p=0.03$), and no detectable production of CXCL10. After YF viral stimulation the YEL-AD cases presented higher frequencies of cytotoxic NK^{dim} cells (2.18 vs 0.60, $p=0.057$), and non-classical monocytes (3.03 vs 1.21, $p=0.018$), accompanied by an abnormal high IL1 β response (9.25 vs 0.42, $p=0.02$) when compared to healthy vaccinated controls. Moreover, transcriptomic analysis after YV *in vitro* stimulation demonstrated that YEL-AD cases present abnormal expression of genes related with IFN pathway, chemokine signaling and antigen processing and presentation.

Conclusion: Our results showed that YEL-AD has severe phenotypic innate defects. First, the remarkable HIEII in IFN pathway contribute to a deficient antiviral response, reflected in the high viral loads observed in the YEL-AD. Further, the high inflammatory environment reflected in the levels of IL1 β , may contribute to NK cytotoxicity, monocytes with proinflammatory profile. Hence, despite the low sample size, here we observed a functional imbalance between inborn deficient IFN antiviral response and the abnormal inflammatory cellular profile observed in YEL-AD cases, which could lead to a non-effective and immunopathogenic response to the YF virus.

Keywords: Adverse events following immunization; Yellow fever vaccine; Innate immunity