Instituto de Medicina Molecular João Lobo Antunes

PhD Project Proposal
"Doctorates 4 COVID-19"

Title: Shaping innate immune system response in persistent and novel viral pandemics: from HIV to SARS-CoV 2.

Brief description:

Since December 2019, the whole world has been engaged by the emergence of the new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing the Coronavirus Disease 2019 (COVID-19) in which the severe cases show rapid viral replication, massive inflammatory cell infiltration and elevated pro-inflammatory cytokine/chemokine responses, causing acute lung injury (ALI), acute respiratory distress syndrome (ARDS), septic shock and/or multi-organ failure.
The human immunodeficiency and immune reconstitution lab at IMM has an internationally recognized expertise for the study of both HIV-2 and HIV-1 pathogenesis, with a special interest in the immune response of the host against these chronic infections.
Monocytes and macrophages are innate immune cells playing critical roles in the development and homeostasis of all tissues and, together with dendritic cells, initiating adaptive immune responses after a "danger" signal. They are among the first cells to meet and counteract pathogenic agents, and their responses were demonstrated to evolve in timing and intensity after a first stimulus (trained immunity).
Viral infection can modify their function, differentiation and life span. Pro-inflammatory M1-like macrophages are prominent in acute infection, while M2-like differentiation characterizes the chronic phase. Numerous viruses use monocyte/macrophage system for entry, replication and reservoir establishment. SARS-CoV creates a productive infection of the epithelial cells of airway and alveoli, while it seems to be abortive in monocyte-macrophages and DCs. On the other hand, human macrophages and monocyte derived DCs infected in vitro with SARS-CoV show delayed but elevated levels of pro-inflammatory cytokines. Interestingly, HIV-2 features a particular interaction with the molecular machinery of innate immune cells, despite the high degree of homology with HIV-1. In contrast to the extent of HIV-1 pandemic, HIV-2 is associated with a naturally attenuated disease and reduced mortality. HIV-2 establishes disseminated reservoirs, but the plasma viral load is usually undetectable even in the absence of antiretroviral therapy, leading to low rates of transmission and to confinement of HIV-2 infection to West Africa and historically connected countries, such as Portugal.
We postulate that monocyte/macrophage system have a prominent role in the pathogenesis of the severe organ involvement in COVID-19. Moreover, we hypothesize that monocytes and macrophages have a fundamental role in the distinct course and prognosis of HIV-1 and HIV-2 infections.
To this purpose, the research plan combines an ex-vivo investigation of monocyte and macrophage phenotype from SARS-CoV-2, HIV-2 and HIV-1 infected patients, compared to healthy subjects. Additionally, with optimized in-vitro culture systems, we will investigate the impact of SARS-CoV 2, HIV-2, HIV-1 on macrophage differentiation and evaluate different phenotype functional responses compared to other stimuli, known to induce trained immunity. Ultimately, co-culture systems will be developed to determine the macrophage potential to modulate the adaptive immune system activation in presence and absence of viruses and viral particles, with possible application in immunization strategies.
Most of the available or in development treatment approaches are directed to inhibition of viral invasion and replication, while we expect to identify novel host cell targets to modulate acute and chronic immune response.

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