INTERLEUKIN 32: MOLECULAR EXPRESSION, EPIGENETIC REGULATION AND BIOLOGICAL ACTIVITIES IN HUMAN IMMUNODEFICIENCY VIRUS-1 INFECTION

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Abstract

Interleukin-32 (IL-32), previously called natural killer cell transcript 4, has been recently recognized as a proinflammatory cytokine. It also participates in the responses to infection with viruses such as HIV-1 and influenza and, unexpectedly, is able to trigger classical interferon (IFN) pathways. More recently, it has been demonstrated that IL-32 promoter methylation modulates antiviral activity of this cytokine in the course of influenza virus infection. However, whether such epigenetic modifications may modulate IL-32 expression also during other viral infections, such as HIV, remains unclear. Given the mounting evidence for a role of IL-32 in the immune response to viral infections and its regulation by and induction of several proinflammatory cytokines, we set out to investigate both in vitro and in vivo the role of this cytokine in HIV-1 infection. In particular we plan to perform a research project mainly aimed to address the following main issues: a) to characterize the biological activities of IL-32 in experimental models of HIV-1 infection; b) to examine the IL-32 epigenetic regulation during HIV-1 infection; c) to evaluate the prognostic value of IL-32 single-nucleotide polymorphisms and its expression in HIV-1 infected patients.

The project will start by evaluating the effect of IL-32, used alone or combined with antiviral drugs, on viral transcription and replication in experimental models of HIV-1 infections. Furthermore, considering that microRNAs (miRNAs) are significantly involved in the modulation of cytokine activity, we will examine whether IL-32 could alter the expression of cellular miRNAs who target HIV-1 genes and/or regulate IL-32 pathways. To further investigate the role of HIV-1 in regulating the IL-32 expression, we will explore whether the epigenetic mechanisms, such as DNA methylation, and/or HIV-induced miRNAs contributed to IL-32 expression during HIV-1 infection. In addition, considering that a growing body of evidence suggests that host genetic factors play an important role both in susceptibility to HIV-1 infection and in progression to AIDS, we will focus on the evaluation of the influence of the IL-32 polymorphisms on the clinical progression of HIV infection, as well as on IL-32 protein/mRNA production. To determine whether IL-32
participate in the regulation of IFN pathways, we will also determine whether there are any relationships between IL-32 production and activation of type I-III IFN antiviral signaling.

We firmly believe that performing such a project may help to understand the delicate balance between IL-32 activation and HIV replication and will improve our knowledge on the processes by which HIV hijacks immune response. In addition the characterization of IL-32 mediated miRNAs production and HIV-1 induced epigenetic regulation of IL-32 may help in a better understanding of the ability of pro-inflammatory cytokines and/or virus to regulate immune response by using epigenetic mechanisms and will provides a basis for identifying novel gene targets, mechanisms and cross-talk between antiviral immune response pathways.

GROUP COMPONENTS
The current project will be carry out at Sapienza University of Rome by a multidisciplinary team of young researchers with proven expertise in HIV infection, immunology and viral infectious diseases.
Dot. Corrado De Vito Assistant professor (Ricercatore MED42) (Department of Public Health and Infectious Diseases)
Dott.ssa Gabriella D’Ettore Medical Doctor in Infectious Diseases/Post-doc researcher (Department of Public Health and Infectious Diseases)
Dott.ssa Simona Trombetti Post-doc researcher (Department of Molecular Medicine)
Dott.ssa Katia Monteleone PhD student in Experimental Medicine (Department of Molecular Medicine)
Dott.ssa Lucia Spano PhD student in Infectious Diseases (Department of Public Health and Infectious Diseases)
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