Analysis of the response of human primary blood DC (pre-DC) upon HIV-1 infection at the single-cell level

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Dendritic cells (DC) are critical to elicit anti-viral immunity against HIV-1 but are also key players in the establishment and spreading of the infection. Recently, the presence of conventional DC progenitors, named pre-DC (or AS DC), was revealed in human blood. While essentially defined through their ontogeny, little is known regarding pre-DC immune functions. We previously showed that pre-DC are the most susceptible blood DC to HIV-1 infection (see Ruffin et al.), that they can produce de novo particles and can transmit in vitro the newly formed viruses to activated CD4+ T cells. This prompted us to evaluate pre-DC response following HIV-1 exposure by Single-cell RNA sequencing (scRNAseq). Transcriptomic analysis was performed on in vitro infected pre-DC at 12h and 24h post-infection. Quantification of viral RNA allowed us to distinguish cells producing new viral transcripts from bystander cells. Moreover, an unbiased analysis only considering cellular transcripts, clustered separately cells producing HIV-1 from other cells, and revealed functional heterogeneity in response to HIV-1 exposure. During early steps of infection, pre-DC engaged either rapidly in a DC maturation program towards T cell help, or gradually in a robust Interferon Stimulated Genes (ISG) response. At 24h of infection, pre-DC producing viral transcripts exhibited both responses simultaneously: a sustained DC maturation, and a large induction of ISG expression. We confirmed the HIV-1-induced increased expression of maturation markers (CD86, CCR7) and secretion of cytokines such as IL-8 at the protein level. Importantly, the wide ISG response observed in infected pre-DC was dependent of the activation of cGAS/STING sensing and type-I IFN signaling.
Our single-cell high-dimensional analysis reveals that highly purified and homogeneous pre-DC exposed to a unique viral stimulus, i.e. HIV-1, exhibit a dual response that may impact on the physiopathology of HIV-1 infection.

Keywords : pre-DC, single-cell, HIV-1, ISG, DC maturation
Authors :
References : , , ,

Authors

Flavien Brouiller 1, Nicolas Ruffin 1, Francesca Nadalin 1, Aymeric Silvin 2, Peter See 2, Charles-Antoine Dutertre 2, Constance Delaugerre 3, Jean-Michel Molina 4, Florent Ginhoux 2, Philippe Benaroch 5,

1. U932 Immunity and Cancer, Institut Curie, Paris, FRANCE
2. SIgN, A*STAR, Singapore, SINGAPORE
3. CNR VIH, Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, Paris, FRANCE
4. Maladies Infectieuses, Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, Paris, FRANCE
5. Institut Curie, Paris, FRANCE