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ZIKV is susceptible to the antiviral activity of IFN-alpha in vitro but fails to activate IFN response in human PBMC cultures

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Background: Interferons (IFN) are key cytokines with multifaceted antiviral and cell-modulatory properties, constituting the first line defense in the innate immune response. The activation of IFN response is triggered by the interaction of foreign material (PAMPs) with cell receptors (PRRs), and does not necessary require pathogen replication. Three IFN types are recognized, based on structural features, receptor usage, cellular source and biological activities. Since Zika virus (ZIKV) African and Asian lineages have been associated with different clinical manifestation, the purpose of this study was to explore the sensitivity of the two strains to different IFN types. In addition, we investigated their ability to induce IFN response in PBMC from healthy donors.

Material/methods: Vero E6 cells were treated for 18–20h with increasing amounts of IFN-2α (0.01-10^3IU/mL) or IFN-γ (0.1-10^4IU/mL), or a combination of them, then infected with either ZIKV African MR766 or the contemporary Asian INMI-1 strain (MOI: 0.01 TCID50/cell) and virus yield inhibition was measured. Healthy donor PBMC were exposed to increasing amounts of either ZIKV strains or cocultivated with fixed virus-infected cells, and the activation of IFN response was measured at the level of released cytokine and mRNA induction. Virus replication was assessed by RT-PCR.

Results: Both African and contemporary Asian ZIKV lineages resulted sensitive to IFN-α2b but not to IFN-γ. No synergistic effect was observed with IFN-α+IFN-γ combination. No activation of either type I, II or III was observed in PBMC at both mRNA and protein level after exposure to either live ZIKV strains or virus-infected cells. Intriguingly, despite the lack of IFN induction low MxA mRNA induction was observed in PBMC infected with MR766, peaking at 48 hpi. Consistent with this finding, MR766, but not INMI-1, was able to at least partially replicate in PBMC at different times of infection.

Conclusions: Both African and contemporary Asian ZIKV strains are sensitive to type I, but not to type II IFN. Interestingly, neither ZIKV strain is able to activate type I, II and III IFN response in PBMC. Only MR766 is able to partially replicate in PBMC and to cause transient (late) induction of MxA mRNA. Due to the susceptibility to type I IFN and the lack of its induction, IFN type I should be considered as possible therapy in ZIKV infection.