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African non human primates are natural hosts of SIV. The infection is non-pathogenic despite plasma viral load levels similar to those in HIV-1 infected humans and SIVmac-infected macaques (MAC) progressing towards AIDS. The most striking difference between non-pathogenic SIV and pathogenic HIV-1/SIVmac infections is the lack of chronic T cell activation in natural hosts. In HIV and SIVmac infections, chronic T cell activation is known to drive $CD4^+$T cell depletion. Intense research efforts are worldwide put on the search of the mechanisms that can control chronic T cell activation in HIV/SIV infections. Innate immune responses play a determinant role in the regulation of T cell activation profiles. Type I interferons (IFN-I) are part of the first-wave response of the innate immune system in viral infections. We compared the IFN-I responses between pathogenic (MAC) and non-pathogenic SIV infections (African Green monkey, AGM) at the level of blood and lymph nodes (LN) during the early and chronic stage of infection. During the acute SIVagm infection, we detected high amounts of IFN-α in the plasma of AGMs, although the mean levels at the peak were three times lower than in MAC. The microarray data revealed a rapid and strong up-regulation of type I Interferon-Stimulated Genes (ISG) in AGMs during acute SIVagm infection. ISGs denote the *in vivo* activity of IFN-I. Using a functional assay, we demonstrated that low IFN-α concentrations (50 times lower than the IFN-α levels in plasma at the peak) were sufficient to induce strong ISG responses in AGM and MAC cells. Surprisingly, our direct comparison of blood and LNs showed that ISG induction was broader in blood of AGMs than in MAC, while in LN, it was the contrary. Thus, in AGMs, less ISG were induced in LNs as compared to MAC already during the acute phase of infection. Moreover, our tight kinetic analysis showed that this ISG expression was efficiently controlled after day 28 post-infection in AGMs, while in MAC the ISGs expression remained uncontrolled. Finally, we identified genes that were differentially expressed between the two species and which might be involved in the discriminating responses. Altogether, this shows that AGMs are capable to mount a well coordinated and efficient regulative response to innate immune activation.