HYPOXIA AND INFLAMMASOME ACTIVATION IN CD14^{+} CD16^{-} MONOCYTES SHAPE HIV VACCINE PROTECTIVE RESPONSE

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Of the six independent HIV vaccine trials conducted so far, only the RV144 vaccine trial demonstrated limited, but significant, efficacy (31.2%). In RV144, volunteers were vaccinated twice with the HIV recombinant canarypox vector ALVAC, and then two additional times with the ALVAC in combination with two gp120-envelope proteins formulated in alum. Vaccine-induced CD4 polyfunctional cells and IgG to the envelope V1/V2 were immunological correlates of risk of HIV acquisition. However, vaccine efficacy was limited and not sustained, requiring improvement. Vaccination with a similar SIV-based vaccine regimen in macaques also significantly decreased the risk of SIV_{mac251} acquisition (44% efficacy, which associated with the level of mucosal antibodies to V2 as well as the frequency of mucosal NKp44^{+} cells. To improve the efficacy of the ALVAC/gp120 platform, we used the same macaque model and contrasted innate and adaptive immune responses of vaccine regimens of varying efficacy in macaques that shared the ALVAC+ gp120 protein boost with an ALVAC, DNA, or Ad26 prime modality. Comparison of the immunogenicity of the DNA and ALVAC prime regimens, both protective, to that of the non-protective Ad26 prime revealed that vaccine efficacy was associated with qualitative temporal-spatial differences in the innate CD14^{+} and CD16^{+} cells in blood and tissues. The activation of hypoxia and the inflammasome in CD14^{+}DR^{+} CD16^{-} classical monocytes and CD4^{+} Th2 responses correlated with a decreased risk of SIV_{mac251} acquisition. Th2 cells, in turn, correlated with mucosal NKp44^{+} cells and mucosal protective antibodies to V2. In contrast, a STAT3 gene signature in CD16^{+} monocytes was associated with Th17 differentiation and a lack of vaccine efficacy. These data posit that the engagement of CD14+ monocytes and inflammasome activation by the ALVAC vectored vaccine is central for the the elicitation of protective innate and adaptive responses by an ALVAC-based HIV vaccine platform.