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The CDK inhibitor p21$^{Cip1/WAF1}$ is induced by FcγR activation and restricts HIV-1 replication in human macrophages

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Background

Macrophages are major targets of human immunodeficiency virus type 1 (HIV-1) infection. We have previously shown that the engagement of the activating Fc receptors of the IgG (FcγR) by immune complexes (IC) suppresses the replication of HIV-1 and related lentiviruses in monocyte-derived macrophages, inhibiting both the accumulation of reverse transcripts and the proviral integration [1].

Results

We investigated the mechanisms underlying the FcγR-mediated HIV-1 restriction. Neither the degradation of incoming viral proteins or neosynthesized cDNA nor the induction of known restriction factors of the APOBEC3 and TRIM families were involved in the restriction. Analysis of the expression of cellular factors associated to HIV-1 reverse transcription/pre-integration complexes showed that IC-stimulation of macrophages induces p21$^{Cip1/WAF1}$, both at mRNA and protein levels. The induction of p21 expression by other stimuli, such as the histone deacetylase inhibitor MS-275 and phorbol myristate acetate, was also associated with a strong inhibition of HIV-1 replication in macrophages, supporting an inhibitory effect of p21 on HIV-1 life cycle. Remarkably, siRNA-mediated knockdown of p21 rescued the defect of HIV-1 replication in FcγR-activated macrophages and also enhanced HIV-1 replication in unstimulated macrophages. p21 silencing increased both reverse transcription products and integrated forms. Interaction of p21 with PIC associated HIV-1 proteins was not detected either by yeast-two-hybrid or by coimmunoprecipitation experiments, suggesting that p21 affects PIC activities independently of a specific interaction with HIV-1 proteins. Consistently, recover of viral replication in IC-stimulated MDMs, after p21 silencing, was also observed after infection with other primate lentiviruses, including SIVmac and HIV-2.

Conclusion

Taken together, our results indicate that p21 is a limiting host factor for lentiviral replication in human macrophages that contributes to the FcγR-mediated HIV-1 restriction.

References

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