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### Exogenous HIV-1 proteins induce alterations in differentiation and modulation of HIV-1 receptors in primary human mesenchymal stem cells

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**OBJECTIVES:** Osteopenia, osteoporosis and osteonecrosis have been recently described in HIV-infected patients. The mesenchymal stem cell, resident in the bone marrow, is the cellular precursor of both osteoblasts and adipocytes. The objectives of this study were to determine the effect of HIV p55, gp120, TAT and REV on mesenchymal stem cell (hMSC) differentiation to the osteoblast lineage and to determine the role of these proteins in presenting the receptor repertoire for HIV infection.

**METHODS:** Primary hMSC cultures were cultured in osteoblast differentiating media containing 100 ng/ml of the HIV-1 proteins TAT, REV, p55 or gp120. Calcium deposition and alkaline phosphatase activity, hallmarks of osteoblast activity, were detected by quantitative alizarin red staining and p-NPP assay and normalized to the total protein extracted. To determine the effect of HIV proteins on the receptor complement of hMSCs, cells were exposed to 100 ng/ml of HIV proteins for 24 h. CD4, CCR5 and CXCR4 mRNA expression from treated cells were analysed using quantitative real-time PCR.

**RESULTS:** Exposure to REV at 100 ng/ml induced a significant increase in osteogenesis, revealed by an increase in calcium deposition ( $P<0.05$ ) and alkaline phosphatase activity ( $P<0.01$ ), while the p55 protein induced a decrease in calcium deposition ( $P<0.01$ ) and alkaline phosphatase activity ( $P<0.01$ ) subsequent to a decreased differentiation in osteoblast cells. An upregulated expression of CD4, CCR5 and CXCR4 mRNA was detected after p55 treatment ( $P<0.001$ ) and CXCR4 mRNA after gp120 ( $P<0.01$ ), while REV and TAT treatment decreased the CCR5 and CXCR4 mRNA expression ( $P<0.001$ ).

**CONCLUSIONS:** Herein we have demonstrated the capacity of exogenous HIV p55 and REV to modulate the differentiation of primary hMSCs to osteoblasts, suggesting that these proteins may contribute to decreased osteoblast cell number with consequent osteopaenia, in vivo. In addition we have demonstrated an increase in HIV-1 receptors CD4, CCR5 and CXCR4 expression in hMSCs in response to the structural proteins p55 and gp120, while a decreased expression after regulator proteins REV, TAT treatment, suggesting a selective role of the HIV-1 proteins during the replicative phase. These data present exciting new avenues for exploration in our efforts to determine the molecular mechanism of HIV associated osteopaenia.



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