HIV Antiretroviral, Efaverinz Stimulates Cysteine Cathepsin Activity in Macrophages: Implications of HIV-Associated Atherosclerosis

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Approximately 1.2 million individuals in the United States are living with HIV. Antiretrovirals (ARV)effectively manage viral loads, both preventing progressionto AIDS and enhancing patient survival. However, reports indicate thatpeople with HIV exhibit an increased risk fordeveloping atherosclerosis, a form a cardiovascular disease characterized by lipid and macrophage-filledplaque formation andarterialremodeling.Recent research implicatesARVsin the development of atherosclerosis, as efavirenz correlates with endothelial dysfunction and elevations in low-density lipoprotein. Yet, the mechanisms underlying this association are not completely understood. Cathepsins are potent proteases, known to promote vessel remodeling via collagen and elastin degradation.Therefore, we hypothesize that efavirenz contributes to atherosclerotic vascular remodeling by increasing cathepsin protease activity. To test this, we exposed Thp-1 monocytes or monocyte-derived macrophages to efavirenz(25 μM) for 24 hours. Cells were then collected and analyzed for cathepsin protein and active enzyme by immunoblot and multiplex cathepsin zymography, respectively. Our results demonstrate that efavirenz exposure causes a 50% decrease in monocyte levels of active cathepsins ($n=6$; $p<0.05$), which was reflected by significant reductions in their ability to degrade elastin ($n=4$, $p<0.05$). Efavirenz also reduces cathepsin mRNA and protein expression, but increases the levels of cystatin C, the extracellular protein cathepsin inhibitor. Conversely, in monocyte-derived macrophages,efavirenzexposure induced2-fold increases incathepsins V, S, and L expression and activity ($n=6$; $p<0.05$).Overall, our findings demonstrate that efavirenz increases macrophage-derived cathepsin activity.

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