THE HIV-1 PROTEASE INHIBITORS INDINAVIR AND SAQUINAVIR INDUCE KAPOSI'S SARCOMA (KS) REGRESSION BY INHIBITING KS CELL INVASION, ANGIOGENESIS AND VASCULAR PERMEABILITY

Sgadari C.,[(a)] Barillari G.,[(a,b)] Toschi E.,[(a)] Monini P.,[(a)] Palladino C.,[(a)] Carlei D.,[(a)] Bacigalupo I.,[(a)] Bugarini R.,[(a)] Stürzl M.,[(c)] and Ensoli B.[(a)]
[(a)]Laboratory of Virology, Istituto Superiore di Sanità; [(b)]Department of Experimental Medicine, Università di Tor Vergata, Rome, Italy; [(c)]GSF-National research Center for Environment and Health, Neuherberg, Germany.

HIV-1 protease inhibitors (PI) have potent antiviral activity that reduces HIV-1 viral load and increase CD4 T cells restoring the immune response toward HIV-1 and other infectious agents. Treatment with PI is frequently associated with the regression or resolution of both initial or advanced Kaposi's sarcoma (KS), an angioproliferative tumor arising in HIV-1 and human herpesvirus-8 (HHV-8) co-infected individuals (*Stürzl M et al., Adv. Cancer Res, in press*). At least in part, these effects may be mediated by the block of HIV replication and Tat production and, consequently, by a better immune response against HHV-8. However, PI have also shown effects on several methabolic pathways, cellular proteasome 20S and fungal proteases, suggesting that they may have a direct effect on KS cell locomotion, angiogenesis or vascular permeability, all key features of KS that require proteolytic activity.
Here we show that indinavir or saquinavir induce the regression of angiogenic KS-like lesions and the vascular permeability promoted by inoculation of KS cells in nude mice (*Sgadari et al., in preparation*). In vitro, indinavir and saquinavir inhibited the invasion of KS cells but not their adhesive, proliferative or migrating responses. This suggested that PI inhibit the activity of proteases degrading the extracellular matrix and that are required for cell invasion and vascular permeability, two key events for angiogenesis and tumor growth. In fact, PI inhibited the secretion and the proteolytic activation of matrix-metalloproteinase (MMP) -2 produced by KS cells both in vitro and in primary human KS lesions. Moreover, PI inhibited different steps of the angiogenic process in vitro and in vivo and the secretion of activated MMP-2 by EC in response to bFGF (*Sgadari et al., in preparation*). Thus, HIV-1 PI have direct inhibitory effects on KS and may be effective in the treatment of angiogenic diseases and tumors.

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