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Oral presentation

Ritonavir inhibits NF-AT activation through modulation of the PI-3 kinase/Akt Ppathway

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The HIV protease inhibitor ritonavir has activities apparently unrelated to its inhibition of the HIV protease, including anti-tumor activity in vivo and in vitro, induction of lipodystrophy in vivo, proteasome inhibition, and inhibition of NFκ. Here we show that ritonavir inhibits activation of NF-AT induced by PMA plus ionomycin and by the human herpes virus-8 chemokine receptor homologue, vGPCR. Inhibition occurred by modulation of the PI-3 kinase/Akt/GSK-3 pathway. Ritonavir treatment led to decreased Akt phosphorylation and a resultant decrease in GSK-3 phosphorylation and failed to inhibit NF-AT in GSK-3β -/- knockout cells. Inhibition of multiple signaling pathways by ritonavir may partly explain its anti-tumor activities as well as other effects of ritonavir that are unrelated to its anti-retroviral activity. Taken together, the data suggest that ritonavir may have intrinsic immunomodulatory activities. This work was supported in part by grant RO1 CA099905-01 from NCI.