Antiproliferative and pro-apoptotic activity of sunitinib on endothelial and on anaplastic thyroid cancer cells, *via* inhibition of Akt and ERK1/2 phosphorylation and by down-regulation of cyclin-D1

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Context. Recent experimental evidence suggests a rationale for the use of multitarget tyrosine kinase inhibitors for the treatment of thyroid cancers. Sunitinib showed promising preliminary results on anaplastic thyroid cancer (ATC), and it has been used selectively for patients who are inelegible for clinical trials.

Objectives. The aims of this study were to investigate: i) the *in vitro* and *in vivo* activity of sunitinib on ATC and on microvascular endothelial cells; and, ii) the molecular mechanism for the observed sunitinib activity.

Methods. Proliferation and apoptotic assays were performed on human dermal microvascular endothelial (HMVEC-d) and on BRAF or H-ras mutated ATC cells (8305C and FB3, respectively) after *in vitro* exposure to sunitinib for 72h. VEGFR-2, ERK1/2 and Akt phosphorylation were quantified by ELISA. Cyclin-D1 mRNA expression was evaluated by real-time PCR, and cyclin-D1 intracellular concentrations were measured by ELISA. 8305C tumor xenografts in nude mice were treated with sunitinib, at 50 mg/kg/day (i.p.).

Results. Antiproliferative and pro-apoptotic activity of sunitinib was observed in both endothelial and ATC cells. Phospho-VEGFR-2 levels significantly decreased after sunitinib treatment in activated endothelial cells. ERK1/2 and Akt phosphorylation were significantly inhibited by sunitinib treatment in endothelial and in cancer cells, and cyclin-D1 mRNA and protein expression was inhibited. Sunitinib administration *in vivo* caused significant inhibition of tumor growth ($P<0.05$).

Conclusions. Sunitinib is active *in vitro* and *in vivo* against activated endothelial and ATC cells *via* the inhibition of Akt and ERK1/2 phosphorylation, and through the down-regulation of cyclin-D1.