Antiproliferative Effects of new Vanadyl Complexes with Acetilacetonate Derivatives on non-Tumor and Tumor Cell Lines

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Evidence of the antiproliferative and proapoptotic activity of a number of vanadyl complexes, together with their low toxicity, establish these metal compounds as promising antitumoral therapeutic agents (Evangelou, 2002). We have previously synthesized and fully characterized six new vanadyl complexes with acetylacetonate derivatives bearing asymmetric substitutions on the beta-dicarbonyl moiety. The complexes were characterized in the solid state as well as in solution, through a number of complementary techniques such as X-ray crystallography, IR, Raman, UV-Vis and EPR spectroscopies. DFT calculations were applied as well (Sgarbossa et al., submitted).
Then we evaluated the effects of these vanadyl complexes on cell viability of two non-tumor cell lines, hTERT-HME1 and podocytes, and two colorectal cancer cell lines, HCT116 and HT29, by measuring the cellular ATP content. We evaluated the effect of our complexes on the above-mentioned cell lines treating them with at least six concentrations of each complexes. As controls we utilized vanadyl sulphate and each ligand used to complex the vanadyl moiety. Our results evidenced that non-tumor cell lines were more sensitive to all complexes compared to tumor cells and they are also responsive to vanadyl sulphate suggesting that the effect of complexes is mainly due to the vanadyl moiety and the influence of the ligands is negligible in the case of non-tumor cells. Interestingly, tumor cell lines are sensitive to complexes but resistant to vanadyl sulphate as well as to ligands.
These preliminary data allowed us to select two vanadyl complexes that showed the better antiproliferative activity, VIVA1 and VIVA3. We performed experiments aimed at clarifying the molecular pathways involved in the antiproliferative effects of these compounds, with the final goal of identifying their mechanism of action and modulate their structure in order to improve their selectivity. In particular we focused on MAPK, cell cycle and apoptotic pathway modulation.
These preliminary data provide useful hints to understand the correlations between the biological behaviour of the complexes and the structural refinements required to get more effective compounds. Further studies aimed at increasing the selectivity and the uptake of the complexes, through structural modulation or conjugation with specific carriers, are ongoing.

Evangelou (2002). *Crit Rev Oncol Hematol*. 42, 249–265.
Sgarbossa et al. *J Inorg Biochem. submitted*.