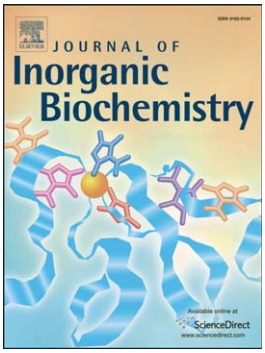

Insights into molecular mechanism of action of salan titanium(IV) complex with *in vitro* and *in vivo* anticancer activity

Maya Miller, Ori Braitbard, Jacob Hochman, Edit Y. Tshuva

PII: S0162-0134(16)30089-7
DOI: doi: 10.1016/j.jinorgbio.2016.04.007
Reference: JIB 9965

To appear in: *Journal of Inorganic Biochemistry*

Received date: 14 December 2015
Revised date: 14 March 2016
Accepted date: 3 April 2016

Please cite this article as: Maya Miller, Ori Braitbard, Jacob Hochman, Edit Y. Tshuva, Insights into molecular mechanism of action of salan titanium(IV) complex with *in vitro* and *in vivo* anticancer activity, *Journal of Inorganic Biochemistry* (2016), doi: 10.1016/j.jinorgbio.2016.04.007

Insights Into Molecular Mechanism of Action of Salan Titanium(IV) Complex with *In vitro* and *In vivo* Anticancer Activity

Maya Miller,[a] Ori Braitbard,[b] Jacob Hochman,*[b] and Edit Y. Tshuva*[a]

[a]*Institute of Chemistry, The Hebrew University of Jerusalem, Jerusalem 9190401, Israel. Email: edit.tshuva@mail.huji.ac.il* Fax +972-2-6584282
[b]*Department of Cell and Developmental Biology Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel. Email: hochman@mail.huji.ac.il* Fax +972-2-5617918

Abstract

Titanium compounds, in particular, Ti(IV) based diaminobis(phenolato) "salan" complexes demonstrate high cytotoxicity toward a wide range of cancer cell lines *in vitro*, and still, very little is known on their mode of action. A representative salan Ti(IV) complex was tested both *in vitro* and *in vivo* on human HT-29 colorectal adenocarcinoma and A2780 ovarian carcinoma cells. Both cell lines were sensitive *in vitro* with A2780 demonstrating an enhanced rate of uptake and intracellular accumulation and thus an earlier response to the drug. HT-29 cells responded *in vivo* by impaired tumor development in nude mice. Both cell lines responded *in vitro* (but to a different extent) by upregulation of p53 with no apparent effect on p21 followed by cell cycle arrest, apoptosis and necrosis as demonstrated by sub-G1 cell accumulation and staining by Annexin-V and propidium iodide. Furthermore, time dependent activation of cysteine-aspartic proteases9 (caspase9) as well as some minor activation of cysteine-aspartic proteases3 (caspase3) support a direct effect on the apoptotic pathway. The differential response of the two cell lines to the salan titanium(IV) complex suggests that more than one pathway is involved in their growth regulation and thus could inhibit development of drug resistant variants.

Keywords: cytotoxicity mechanism, metallodrugs, cisplatin, *in vivo*, cell cycle, apoptosis