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ORIGINAL ARTICLE

Titanates Deliver Metal Compounds to Suppress Cell Metabolism

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Background: Titanates are inorganic, amorphous, aqueously insoluble, particulate compounds of titanium, oxygen, hydrogen, and sodium. Two types of titanates, monosodium titanate (MST) and amorphous peroxotitanate (APT), have recently been proposed for use in biological applications where it would be advantageous to locally sequester and deliver metals to alter cellular functions.
Purpose: In the current study, the ability of MST and APT to suppress the mitochondrial function of a rapidly dividing cell line, OSC2 (oral squamous cell carcinoma) with and without loaded metals [Au(III), Hg(II), Pd(II), Pt(II), Pt(IV), and *cis*Pt] was determined.
Methods: Cellular mitochondrial activity of OSC2 cells after 72 hours exposure to titanates or titanate-metal compounds was estimated by measuring succinate dehydrogenase (SDH) activity via the 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.
Results: The results of this study showed that neither native APT nor native MST was biologically neutral to oral squamous cell carcinoma (OSC2). Increasing the concentration of either MST or APT resulted in a statistically significant decrease in SDH activity of OSC2 cells versus untreated cells (40% for APT and 30% for MST). The addition of titanate-metal compounds augmented the effects of APT and MST on OSC2 metabolism, decreasing overall mitochondrial activity compared to controls by 50–70%. However, both titanate types and metal ion species determined the degree to which the SDH activity was suppressed.
Conclusion: The findings of the current study demonstrate that APT and MST alone significantly suppress the metabolism of a rapidly dividing cell line, an effect that is augmented by specific titanate-metal combinations. These compounds may have potential as unique therapeutic agents.

1. Introduction

Metals have appeal for novel drugs because of their unique binding and redox properties.[1] Currently, the two most therapeutically employed metals are Au(I) in the form of Auranofin for the treatment of arthritis[2] and platinum-based [Pt(II)] drugs for the treatment of several cancers.[3–5] Predominantly, the systemic toxicity of metals has limited their applicability; one possible solution to this limitation is to localize the delivery of therapeutic metals. To this end, two titanate materials, monosodium titanate (MST) and amorphous peroxotitanate (APT), have been explored for use in biological environments where it would be advantageous to locally sequester and deliver metals for therapy.[6–10]

MST is an inorganic, amorphous, aqueously insoluble, particulate compound originally developed for the decontamination of nuclear waste. In this application, dissolved radioactive species are adsorbed onto MST, then separated from the aqueous phase by centrifugation.[11] APT is a closely related material that exhibits faster sorption kinetics.[12] MST and APT have spherical morphologies with an approximate diameter of 2–20 μm. Whereas initially synthesized to bind strontium and actinides in nuclear waste, these particles also bind biologically important metal ions and metal complexes, such as gold, Auranofin, mercury, palladium, gadolinium, platinum, and cisplatin.[7,13]

In studies to date, both APT and MST in their native forms are relatively innocuous to several mammalian cell types. For example, neither APT nor MST significantly increase or reduce the mitochondrial [succinate dehydrogenase (SDH)] activity of murine L929 fibroblasts or human THP1 monocytes.[6–8] Yet metal-loaded forms cause metal-specific and cell-specific changes in cell metabolism. For example, treatment of L929 fibroblasts with titanate-gold compounds decreased cellular mitochondrial metabolism 30–80% in a dose-dependent fashion.[7,8] With the exception of cisplatin,

Conflicts of interest: All authors declare no conflicts of interest.

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these decreases occur at metal ion concentrations much lower than those required to achieve decreases with the corresponding metals alone, suggesting that the titanates facilitate metal delivery to the cells.

Overall, the studies completed thus far demonstrate a potential for further development of MST and APT as vehicles for localized delivery of metal ions in biological environments. Accordingly, the current study tested a hypothesis that APT and MST deliver metal ions to suppress the metabolism of rapidly dividing cells, extending previous work with more slowly dividing cell types. Here, the ability of MST and APT to suppress the mitochondrial functions of an oral cancer cell line, OSC2 (oral squamous cell carcinoma), with and without loaded metals [Au(III), Hg(II), Pd(II), Pt(II), Pt(IV), and *cis*Pt] was measured.

2. Materials and methods

2.1. Titanates and titanate-metal loading

The current investigation focused on Au(III), Hg(II), Pt(IV), Pt(II), cisplatin, and Pd(II), because these metal ions have been used or proposed for therapeutic roles in medicine. MST and APT with or without gold [Au(III)], palladium [Pd(II)], mercury [Hg(II)], platinum [Pt(II) and Pt(IV)], and cisplatin (*cis*Pt) (Table 1) were assessed for their ability to suppress the growth of rapidly dividing cells. MST was obtained commercially (Optima Chemical Group, LLC Douglas, GA, USA) and APT was synthesized from MST as previously described.[6,12]

Metal-loaded forms of APT and MST were synthesized to maximize metal loading without attempting to equalize the amount of metal adsorbed to the titanate. Loaded titanates were prepared by combining 0.25 g APT or MST suspended in 1.4 g water (pH = 6.9) with 10 mL of phosphate buffered saline solution containing the metal ion or metal complex (Table 1) for 48 hours at room temperature. The titanate-metal solid was then separated from the solution via centrifugation (rpm = 1200*g* for 3 minutes). The resulting solid phase was rinsed six times with chilled phosphate buffered saline (4°C, pH = 7.4) and centrifuged (1200*g* for 3 minutes). The clear supernatant liquid was then removed by transfer pipette and the moist solid was stored with approximately 75 wt% water content.

The quantity of metal loaded onto the titanates was determined by measuring the difference in metal concentrations between the loading solution before and after contact with the titanate. Inductively coupled plasma mass spectrometry was used to determine metal ion concentration in each solution except mercury, for which cold vapor atomic adsorption spectroscopy was used. The amount of loaded metal was reported as g of metal/g of titanate (Table 1).

2.2. Cells and cell-culture

A human oral squamous cell carcinoma cell line (OSC2, gingival squamous cell carcinoma from Dr. Tokio Osaki, Kochi Medical School, Kochi, Japan) was used in this study to test the ability of titanate-metal complexes to suppress the mitochondrial activity of rapidly dividing cells. The OSC2 cells were cultured in a 1:1 mixture of Dulbecco's Modified Eagle's Medium:F12, supplemented with 10% fetal bovine serum, 100 units/mL penicillin, 100 μg/mL streptomycin, and 5 μg/mL hydrocortisone (Sigma-Aldrich, St. Louis, MO, USA; all other reagents from Invitrogen-Life Technologies, Grand Island, NY, USA). Cells were maintained in an incubator at 37 °C, 5% CO_2, and 100% relative humidity.

Cells were plated in 96-well format (n = 8, flat-bottom) at a density of 5000 cells/cm^2 in 200 μL of culture media. The plated cells were incubated for 24 hours to allow for adherence prior to exposure to metals, APT, MST, APT-metal, or MST-metal suspensions. The cytotoxicity of a range of metal ion dilutions (0–300 μM) was assessed by adding a 10 μL volume of PBS-metal ion solution to each culture well. The metal dilution range was dependent on several factors, including metal solubility and toxicity to the cells. Following the addition of metal ions, cells were incubated for 72 hours, at which point, the mitochondrial activity of the treated cells was measured via SDH activity (see next section: *Cell response*).

Similarly, titanates and metal-titanate complexes were diluted from stock suspensions to concentrations that resulted in 0 μg/mL, 0.5 μg/mL, 1 μg/mL, 10 μg/mL, 25 μg/mL, 50 μg/mL, and 100 μg/mL final concentrations when 10 μL was added to 200 μL media in each well. Again, the treated cultures were incubated for 72 hours prior to measuring SDH.

2.3. Cell response

Cellular mitochondrial activity was assessed by measuring SDH activity via the 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[14] Briefly, 100 μL of 2% MTT solution, 0.05 M Tris, 0.5 mM $MgCl_2$, 2.5 mM $CoCl_2$, 0.25M disodium succinate (all reagents from Sigma-Aldrich) were added to each well. The cells were then incubated for 45 minutes at 37°C. Following incubation with the MTT solution, 100 μL of 4% formalin (Sigma-Aldrich) in 0.2 M Tris were added to each well and allowed to react for 3–5 minutes. Upon removal of the MTT-Tris-formalin solution, each well was rinsed with 200 μL/well water (18 MOhm) and air dried for 5 minutes. Finally, the MTT-formazan product was solubilized with 100 μL/well of 6.25% (v/v) dimethylsulfoxide (Fisher Chemical, Pittsburg, PA, USA) in 0.1 N NaOH (Fisher Chemical) and mixed to homogeneity prior to reading the optical density at a wavelength 562 nm using a Spectramax M2 plate reader (Molecular Devices, Sunnyvale, CA, USA). Each experiment was completed in triplicate. The statistical significance of metal- or titanate-induced effects was determined using one-way analysis of variance and Tukey pairwise multiple comparison intervals, with $\alpha = 0.05$.

2.4. Scanning electron microscopy

Scanning electron microscopy (SEM) was used, on a pilot basis, to begin to investigate any interactions between the titanate particles and the OSC2 cells. Silicon segments with an approximate dimension of 1 cm × 1 cm were submerged in cell-culture medium in 8-

Table 1 Metal compounds, sources, loading concentrations, and amorphous peroxotitanate (APT)- and monosodium titanate (MST)-loaded concentrations

Metal species	Source compound	Manufacturer	Titanate loading concentration (μM)	Loaded concentration (g metal/g APT)	Loaded concentration (g metal/ g MST)
Au(III)	$HAuCl_3.3H_2O$; MW = 393.83	Sigma-Aldrich (St. Louis, MO, USA)	13,300	0.0852	0.0789
Hg(II)	$Hg(NO_3)_2.H_2O$; MW = 342.62	Sigma-Aldrich (St. Louis, MO, USA)	18,900	0.0499	0.120
Pd(II)	$PdCl_2$; MW = 177.33	Johnson Matthey, Inc. (West Chester, PA, USA)	13,200	0.0539	0.0557
Pt(II)	$PtCl_2$; MW = 265.98	Johnson Matthey, Inc. (West Chester, PA, USA)	114	0.00086	0.00084
*cis*Pt	cis-$[PtCl_2(NH_3)_2]$; MW = 790.56	Alfa-Aesar (Ward Hill, MA, USA)	4460	0.0284	0.0341
Pt(IV)	$PtCl_4$; MW = 336.89	Johnson Matthey, Inc. (West Chester, PA, USA)	14,900	0.0155	0.0686

or 12-well plates for cell culture-titanate experiments. OSC2 cells were then plated onto the silicon at an initial density of 15,000 cells/cm^2 and incubated in culture media for 24 hours. At this time, the cells were either fixed as described below, or MST was added to the media at a final concentration of 30 μg/mL and incubated for an additional 72 hours. To fix the samples, the media were decanted, the samples rinsed, and then fixed for 5 minutes with 2% glutaraldehyde (Electron Microscopy Sciences, Hatfield, PA, USA). The samples were then dehydrated in 50%, 60%, 70%, 80%, and 100% ethanol, and air dried. Silicon segments, now with cells attached, were imaged by a scanning electron microscope (JSM 7000F, JEOL USA, Inc., Peabody, MA, USA) at an acceleration voltage of 10 kV.

3. Results

3.1. Metal-APT and metal-MST loading

Loading of gold, mercury, palladium, and several platinum compounds onto APT or MST depended on several factors, including the binding specificity of each metal species, the initial loading concentration of each metal, the ratio of metal species to MST or APT in suspension, and the amount of time each metal species and titanate were in suspension together (Table 1). No attempt was made to equalize the amount of each metal species bound to MST or APT; rather, conditions were designed to maximize loading, which varied from 0.00084 g to 0.120 g metal/g titanate (Table 1). Under the conditions of the current study, Pt(IV) and Hg(II) had greater affinity for MST than APT (4.4 times and 2.4 times, respectively), whereas the other four metal complexes had approximately the same affinity for MST and APT. The greatest amount of metal loading occurred for Hg(II) onto MST (0.120 g Hg(II)/g MST). The smallest amount of loading occurred for Pt(II) onto MST (0.00084 g Pt(II)/g MST), likely due to the very low aqueous solubility of Pt(II).

3.2. OSC2 response to metal compounds alone

The ability of metal ions alone to suppress OSC2 cellular function was measured to establish a baseline against which to compare the effectiveness of metal delivery via MST or APT. Figure 1 shows dose response curves for Au(III), Hg(II), Pd(II), and Pt(IV). Cisplatin and Pt(II) were not tested because of their limited aqueous solubility. Of the metal ions tested, Hg(II) was the most potent suppressor of OSC2 mitochondrial activity, whereas Pd(II) had less effect on OSC2 cells up to a concentration of 300 μM (upper limit of solubility). Both Au(III) and Pt(IV) caused a dose-dependent suppression of mitochondrial activity of OSC2 cells, with approximately 50% suppression at concentrations of 100μM for Au(III) and 50μM for Pt(IV).

3.3. OSC2 response to APT and MST alone

For OSC2 cells, increasing the exposure concentration of either MST or APT resulted in a statistically significant decrease in SDH activity versus untreated cells (Figure 2). The magnitude of this

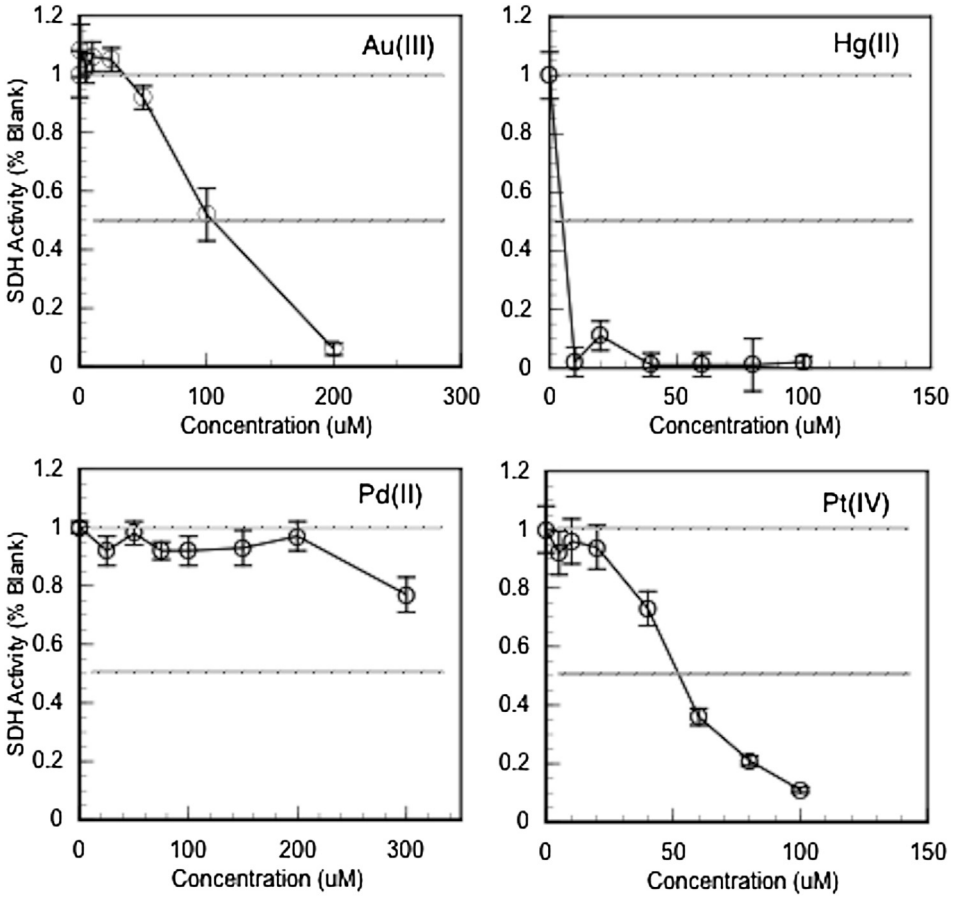

Figure 1 Dose-response curves for 72-hour treatment of OSC2 cells with Au(III), Hg(II), Pd(II), and Pt(IV). Cellular response was estimated using succinate dehydrogenase (SDH) activity normalized to controls (no metal ions added). Horizontal broken lines indicate the level of activity in control cells and the 50% level. Values are plotted as means of eight replicates; error bars indicate one standard deviation. Pt(II) and *cis*Pt were not tested because of limited solubility in aqueous solutions; higher concentrations of Pd(II) were not achievable also because of limited solubility.

decrease was approximately 40% for APT and 30% for MST, but MST and APT were statistically indistinguishable. For both MST and APT, the maximum suppression of mitochondrial activity appeared asymptotic and occurred at approximately the same 50 μg/mL dose.

3.4. OSC2 response to metal-loaded APT

When OSC2 cells were treated with metal-loaded APT, the observed effects were distinct from those of APT alone, for some metals (Figure 3). Several metal-APT complexes enhanced the suppression of OSC2 mitochondrial activity versus APT alone, but no metal diminished the effect. The decrease in SDH activity remained asymptotic regardless of the loaded metal, which was in contrast to the dose-response curves for metals alone (Figure 1). Furthermore, the maximum reduction of SDH activity by APT-metal complexes was metal specific. Treatment of OSC2 cells with APT-Au(III), APT-Pt(II), and APT-Pd(II) resulted in no significant differences in SDH activity versus APT alone. For APT-Pt(IV), a statistically significant decrease in SDH activity of 15% was observed.

The most dramatic decreases in OSC2 mitochondrial activity resulted from treatment of the cells with either APT-*cis*Pt or APT-Hg(II). At a 10 μg/mL concentration, APT-*cis*Pt significantly reduced the overall SDH activity of OSC2 cells compared to APT alone. This reduction reached an asymptotic maximum of 60–70% at a 50 μg/mL treatment dose. Hg(II) also significantly augmented the effects of APT on SDH activity. However, the overall effect of the APT-Hg(II) was attenuated compared to treatment with Hg(II) alone.

3.5. OSC2 response to metal-loaded MST

As with APT, MST-metal compounds sometimes increased mitochondrial suppression over native MST, but did not reverse MST-induced suppression (Figure 4). All suppression curves were asymptotic.

Considering each metal species individually, MST-Pt(II) or MST-Pd(II) did not change OSC2 mitochondrial activity versus MST alone. MST-Hg(II) reduced mitochondrial activity the most. Yet the effect was smaller than was expected for the treatment of OSC2 cells with an equivalent dose of Hg(II). Like APT, *cis*Pt increased suppression of OSC2 mitochondrial activity versus MST alone. The overall additional reduction in activity was approximately 20% (significant, $\alpha = 0.05$). MST-Au(III) also suppressed SDH activity approximately 20% more than MST alone (significant, $\alpha = 0.05$). At this Au(III) dose, only 10% suppression of OSC2 mitochondrial activity occurred (Figure 1). The results for MST-Pt(IV) were similar to those for MST-Au(III).

3.6. SEM

In pilot experiments, SEM images of OSC2 cells (Figure 5A) after 72 hours exposure to native MST showed titanates adherent to cells despite several rounds of washing prior to image capture (Figure 5B). Higher magnification localized the titanates to what appeared to be the nuclear region of the OSC2 cells (Figure 5C).

4. Discussion

The current study confirmed the hypothesis that titanates deliver metals to reduce mitochondrial activity of rapid dividing cells *in vitro*. Unexpectedly, neither native APT nor native MST was biologically neutral to OSC2 cells (Figure 2). Rather, both native APT and MST significantly reduced the mitochondrial activity of both these cell types. These results are in contrast to previous findings for L929 fibroblasts and THP1 monocytes, where titanates alone did not significantly affect mitochondrial activity.[6–8,10]

The addition of metals further augmented the effects of APT and MST on OSC2 metabolism, decreasing overall mitochondrial activity compared to controls by 50–70% (Figures 3 and 4). Both titanate type and metal ion species determined the degree to which the SDH activity was suppressed, which ranged from no additional suppression [Pd(II) and Pt(II)] to nearly 70% by Hg(II). Interestingly, Hg(II) did not reach 100% suppression despite a theoretical ion delivery that should have completely suppressed cellular function if all the Hg(II) bound to the titanates was delivered to the cells. One possible explanation is the high affinity of Hg(II) to both APT and MST[13] thus resulting in the titanate acting more as a chelation agent than as a delivery vehicle.

The overall toxicity to OSC2 caused by titanates complexed with Au(III), Pt(IV), and *cis*Pt was titanate specific. For Au(III) and Pt(IV), the decreases in SDH activity (Figures 3 and 4) were as much as 15-fold greater than would be expected from the theoretical delivery of the metal alone. This result is consistent with previously published data in which various metal ions absorbed to titanates showed enhanced activity over the action of metal ions alone in decreasing SDH activity in L929 fibroblasts.[7] Interestingly, the activities of titanate complexes with Au(III) and *cis*Pt were significantly

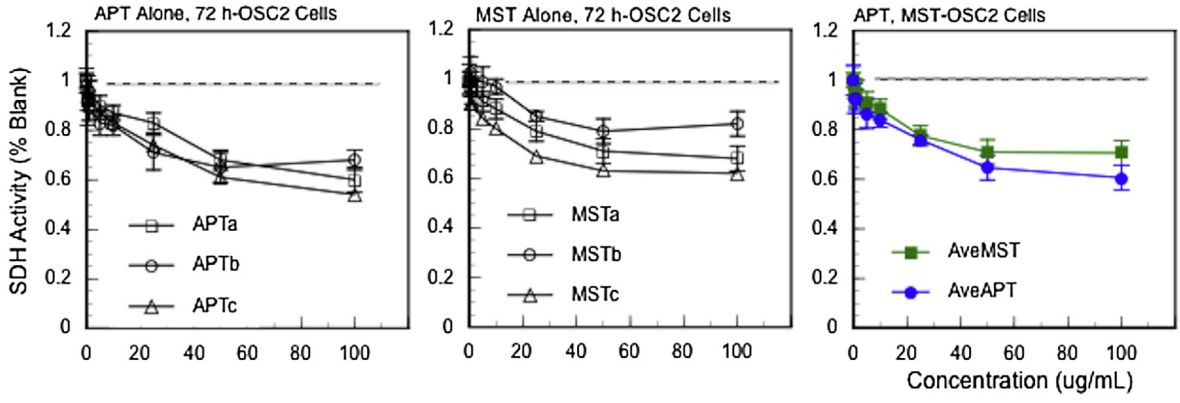

Figure 2 Activity of OSC2 cells treated for 72 hours with native monosodium titanate (MST) or amorphous peroxotitanate (APT) (with no metals). Cell activity was estimated using succinate dehydrogenase (SDH) activity, normalized to controls without titanate added. The left panel shows three replicate experiments for APT; the center panel shows equivalent data for MST. In all cases, the effects of titanates were statistically distinct from controls (horizontal broken lines); error bars denote standard deviations ($n = 8$). Average curves for APT or MST are shown in the right panel.

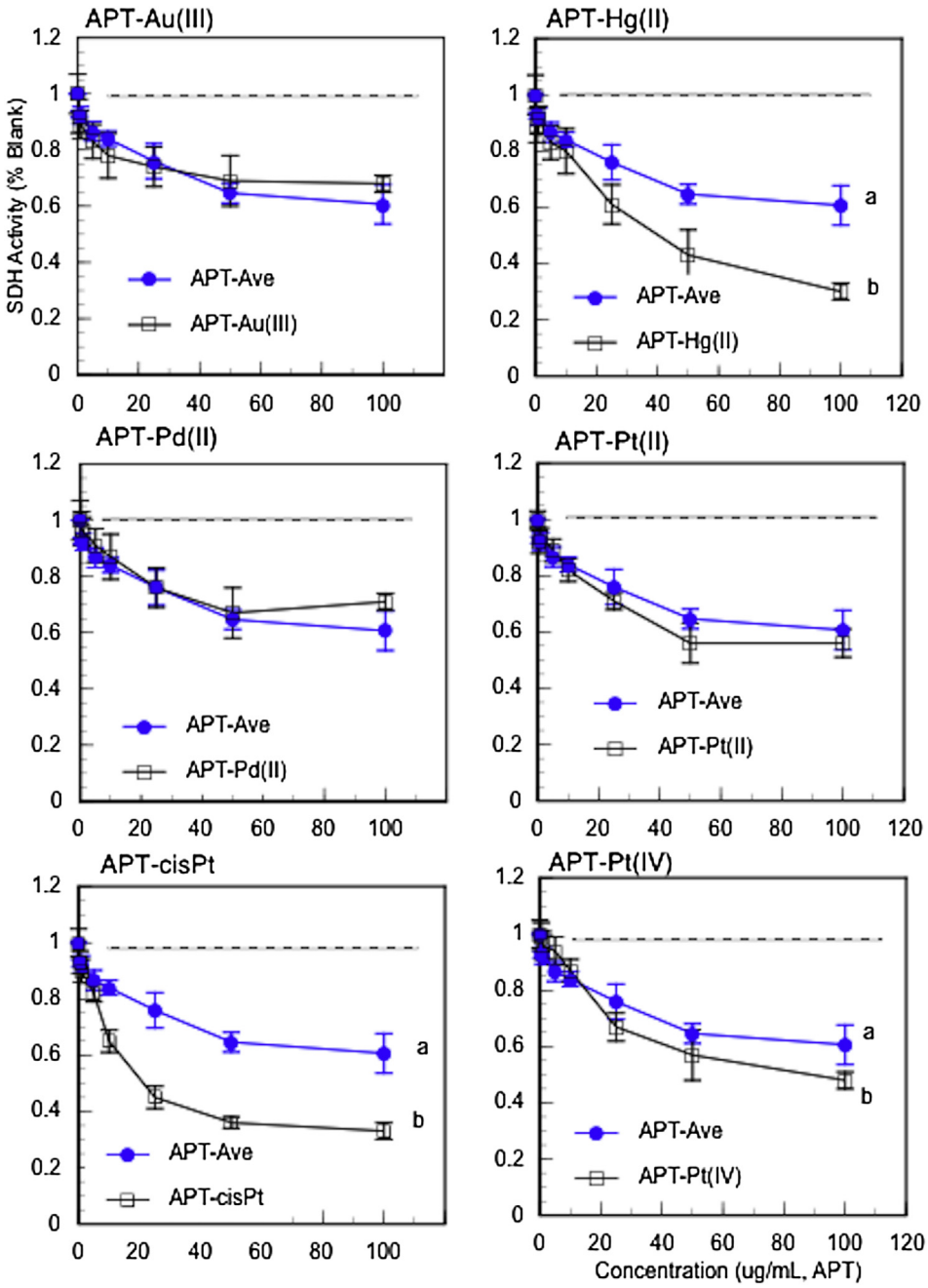

Figure 3 Activity of OSC2 cells treated for 72 hours with amorphous peroxotitanate (APT)-metal complexes. Cell activity was estimated using succinate dehydrogenase (SDH) activity, normalized to controls without titanate added. In each case, cell responses to APT-metal compounds are compared to treatment with APT alone. In all cases, APT and metal-loaded APT effects are statistically distinct from controls (horizontal broken lines); error bars denote standard deviations ($n = 8$). Statistically significant differences between APT and APT-metal are shown by lower case letters (a, b) when appropriate (analysis of variance/Tukey *post hoc*, $\alpha = 0.05$, $n = 8$).

different depending on the specific titanate to which each was absorbed. Au(III) had a greater effect when associated with MST, whereas *cis*Pt was more potent when associated with APT. In both instances, APT and MST had similar affinities for *cis*Pt or Au(III) and thus absorbed a similar quantity of each complex.

One possible explanation for these variations may be that MST and APT interact differently with cells which could result in distinct paths for the delivery of metal ions and complexes to the cells. Because each metal has a different point of action within a cell (e.g., cisplatin binds with DNA creating adducts[3,4] whereas mercury disrupts proteins[15]), some delivery paths may be better suited for the overall action of one ion or complex versus another.

In general, the various data discrepancies are not explained alone by the total amount of metal ion or metal complex loaded, the potency of the metal ion, or the affinity of the metal complex for the titanates, and instead, suggest complex interactions amongst the titanates, metals, and cells that result in the ultimate perturbations of cellular functions. Thus, there is a need to further investigate both APT and MST, especially the mechanism by which these materials affect cells, both alone and when associated with metals. Some clues can be ascertained from the data already available. For example, the asymptotic shape of the SDH activity curves (Figures 2–4) may be due to saturation of a particular pathway through which the titanates are interacting with the cells. Or, if the

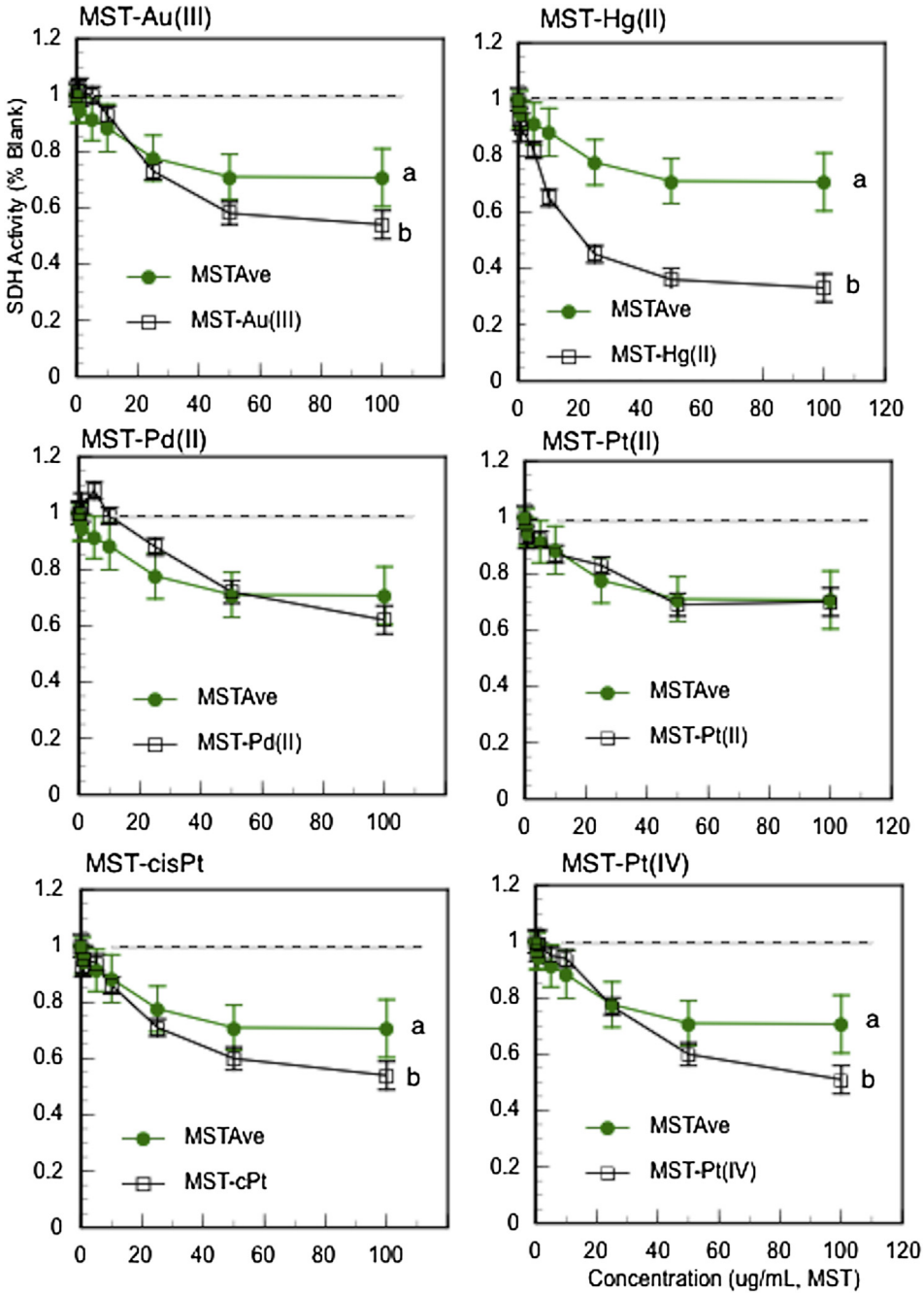

Figure 4 Activity of OSC2 cells treated for 72 hours with monosodium titanate (MST)-metal complexes. Cell activity was estimated using succinate dehydrogenase (SDH) activity, normalized to controls without titanate added. In each case, cell responses to MST-metal compounds are compared to treatment with MST alone. In all cases, MST and metal-loaded MST effects are statistically distinct from controls (horizontal broken lines); error bars denote standard deviations ($n = 8$). Statistically significant differences between MST and MST-metal are shown by lower case letters (a,b) when applicable (ANOVA/Tukey *post hoc*, $\alpha = 0.05$, $n = 8$).

particles are engulfed, size may prevent further uptake by cells. Alternatively, there may be a subpopulation of cells that are resistant to the titanates. Finally, the asymptotic shape may simply be due to interference of cell-bound titanates with the optical density readings during the MTT assay. However, very recent pilot data suggest that whereas some interference may be occurring, the decrease in SDH activity is still reaching an asymptote. Overall, more study is needed.

Previously proposed mechanisms depicted three routes of potential interaction between titanates and cells: dissociation of metal into media prior to cellular uptake, engulfment of titanate-metal complex prior to internal metal dissociation, and titanate-receptor interaction (Figure 6).[7] Data in previous publications have strongly suggested that direct release of metal into the media is unlikely due to the enhanced effect of the metal when associated with titanates.[9,10] The current data further support this conclusion. The more likely mechanisms of action are engulfment of titanates by cells or attachment of titanates to the cells (Figure 6). Preliminary SEM images of native MST and APT support one of these mechanisms (Figure 6). Images of OSC2 cells prior to and after treatment with metal-free MST followed by aggressive washing appear to show titanates localized in the nuclear region of the OSC2

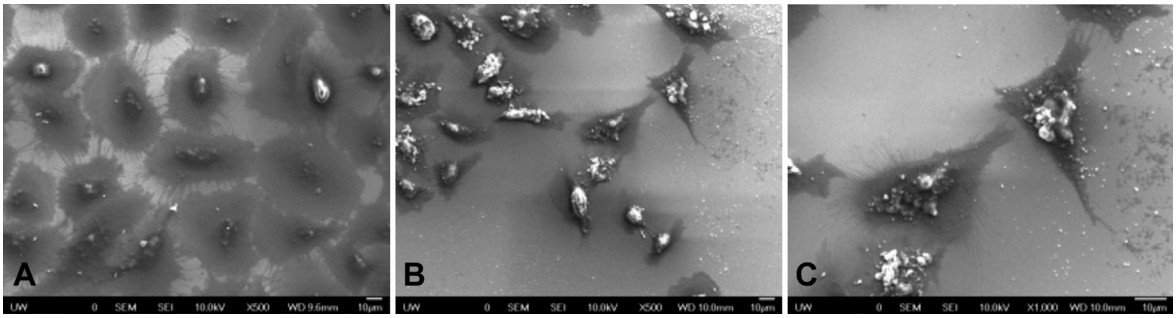

Figure 5 Composite of scanning electron microscopy images: (A) OSC2 cells alone, 500×, 72 hours post-plating; (B) OSC2 cells treated with native MST, 500×, 72 hours post-treatment; and (C) OSC2 cells treated with native MST, 1000×, 72 hours post-treatment.

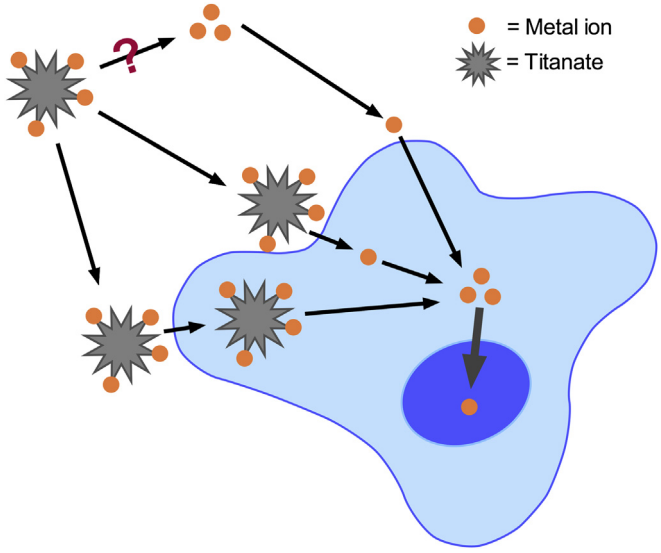

Figure 6 Proposed mechanisms of metal delivery to cells by titanates. The arrows signify possible paths of titanates and metals. The question mark indicates a previously suggested pathway which appears less likely as a predominant pathway, given the current and other studies.

cells. This localization provides clues to the mechanism by which titanates interact with cells and interrupt mitochondrial activity.

It should be noted that López et al[16] demonstrated the potential utility of titanium dioxide in the delivery of metals and metal complexes in the treatment of cancer. In these studies, the titanium dioxide particles were similar to titanates in that they were amorphous particles of titanium dioxide. However, titanates of the current study differ in that they have a more complex and well-defined (crystalline) surface.[7,12,13] This difference is significant, as it is at the surface where metal and cell interactions likely occur. To this end, titanium dioxide alone showed no effect on cancer cell metabolism or tumor growth in the López et al[16] study, whereas the current study demonstrated a significant toxicity of titanate alone to cancer cells; an effect that was significantly enhanced by low concentrations of several titanate-absorbed metal ions and metal complexes.

Overall, the findings of this study demonstrate that APT and MST alone have the potential to significantly suppress metabolism of rapidly dividing cells, an effect that is augmented by specific titanate-metal combinations. These results suggest that titanates, with and without metals, may be good candidates for therapy for cancer or other diseases where cells divide inappropriately. Still, much work is yet to be completed with regard to the mechanism through which titanates and titanate-metal complexes cause these effects.

Acknowledgments

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