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Table of contents

Identification of protein target molecules for [Pd(dach)Cl$_2$] complex in HeLa cervical carcinoma cells

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Abstract: In this work, we have applied the Informational Spectrum Method (ISM) to discover a potential protein target in the HeLa cervical cancer cell line for [Pd(dach)Cl$_2$] complex. Since Pd complexes are considered an alternative to traditionally used Pt complexes in anti-cancer therapy, it is essential to elucidate the mechanism of their action. A detailed analysis that also involves screening the known protein databases revealed the proteins of the SOSS complex as the most probable [Pd(dach)Cl$_2$] targets. Since this protein maintains genomic stability, this result shows the potential of the Pd(II) complex as an anti-cancer drug.

Keywords: Informational Spectrum Method, Cervical Cancer, palladium complex, SOSS protein

1. Introduction

Computational methods in drug discovery are helpful tools to elucidate the signaling pathways affected by a drug [1]. In our previous work [2], we have identified signaling pathways that can be affected mainly by the interaction of ovarian cancer (A2780 cell line) and osteosarcoma (CAL72) cell lines with carbon-based nanoparticles (carbon dots, CDs) loaded with Ru-complex. The genes with abundant expression in one of these cell lines are analyzed using specific tools, and the proteins, which are associated with individual signaling pathways and specific secondary structures, are recognized as the most probable cell-specific target for the interaction with CDs loaded with Ru complex.

An additional possibility that can accelerate the drug discovery process is to calculate the informational spectrum of a drug, which enables more precise identification of specific target molecules [3]. ISM analysis can predict protein-protein interactions [4,5], but it was also successfully applied for discovering new therapeutic targets [6]. Recently,

ISM was applied during the COVID-19 outbreak as a strategy for *in- silico* drug repurposing approach [3].

Cervical cancer is women's fourth most frequently diagnosed malignant disease [7]. Current treatments for cervical cancer include radiotherapy and platinum-based chemotherapy, which can cause severe side effects. Palladium(II) complexes are one of the leading contenders for replacing cisplatin due to the similarity of their metal center to platinum(II) complexes [8], but with less toxicity. Therefore, in this work, we wanted to discover a protein in the HeLa cervical cancer cell line that will be most likely targeted by Pd(II) complex metallodrug, dichloro(1,2-diaminocyclohexane)palladium(II) ([Pd(dach)Cl$_2$]).

Our results show that a DNA-binding protein complex named SOSS is the most probable target for HeLa cells for Pd(dach)Cl$_2$]. These results encourage further development of anti-cervical cancer therapeutic agents based on Pd.

2. Methods

The Informational Spectrum Method (ISM) was focused on the cross-spectral analysis of the informational spectrum of the Pd(II) complex and informational spectra of all gene products expressed as a baseline in the HeLa cells [9,10]. With this goal, several steps were conducted: 1. Molecules were presented as a series of numbers based on Electron-Ion Interaction Potential (EIIP) [11]; in proteins, each amino acid in the sequence of the protein's primary structure is replaced by the value of EIIP for that amino acid; 2. This numerical sequence was transformed into an Informational Spectrum (IS) using Fourier Transform; 3. The spectra of two molecules were multiplied to obtain cross-spectrum (CS). Modification of ISM applied to small molecules (ISM-SM) was used to generate IS of the Pd(II) complex [13].

The list of Ensemble identifiers of genes (TPM>=2.0) that encode HeLa cell baseline expression was retrieved from Expression Atlas [9]. The FASTA format of protein sequences needed for further ISM analysis was obtained using UniProt Retrieve/ID mapping tool [10]. Accession numbers of proteins the ISM gave were analyzed using the bioinformatics resource for gene enrichment analysis, DAVID [12].

3. Results and discussion

Potential targets for the Pd(II) complex in the HeLa cells are investigated using the ISM method. As the first step, the informational spectrum of the complex was analyzed. The structure of the Pd(II) complex and its IS are given in Fig. 1. An IS of the Pd(II) complex generated by the ISM showed a dominant peak at the frequency 0.402, which was used for further cross-spectral analysis [3]. HeLa cell's 9462 baseline proteins, more precisely, their sequences, were screened for potential interactions with the Pd(II) complex using cross-spectral analysis [6].

Cross-spectral analysis recovered 106 proteins that were analyzed using the bioinformatics resource for gene enrichment analysis, DAVID, to determine which pathways/GO terms were enriched in this list [12]. Functional Annotation Chart revealed that the GO terms with the highest statistical significance were nucleoplasm and SOSS complex, which is involved in maintaining genomic stability [13]. Three

proteins, out of 106 predicted as Pd complex interactors, in the SOSS complex are SOSS C (gene name: INIP), SOSS B1 (gene name: NAPB2), and SOSS B2 (gene name: NAPB1).

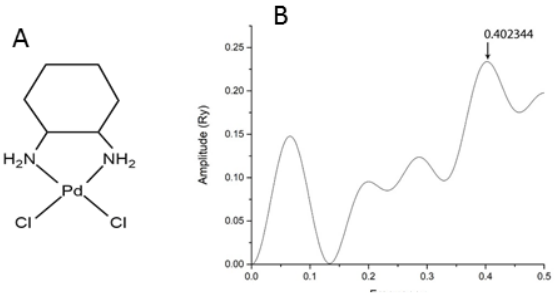

Figure 1. The structure of [Pd(dach)Cl₂] complex (A) and its informational spectrum (B). An arrow and number in the figure indicate the peak position for finding potential interactions with HeLa cell protein sequences.

Fig. 2 shows the interaction network of these proteins. These proteins vary in their secondary structure regarding the content of α-helices and β-secondary structures.
The computational method applied in this work implied that the SOSS complex could be a protein target of the inspected Pd(II) complex. The SOSS complex is a protein complex involved in maintaining genomic stability. Therefore, the interaction with Pd(II) complex can affect the function of the SOSS complex, as it responds to DNA double-strand breaks. In addition, the interaction network of SOSS complex proteins predicted as Pd interactors includes TP53 and EP300. Since these proteins are involved in the cellular response to DNA damage, programmed cell death [14,15], and regulation of the cell migration process, treatment of HeLa cells with the Pd(II) complex might inhibit cell migration, as well [16]. The latter demonstrates the anti-metastatic potential of the tested Pd(II) complex.

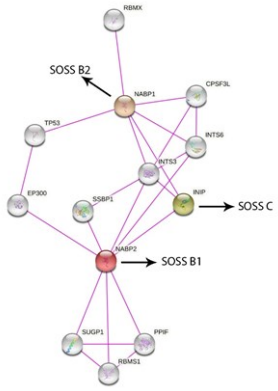

Figure 2. Interaction network of NAPB1, INIP, and NAPB2, retrieved from the STRING database, only including experimentally verified interactions.

The SOSS complex subunit A is a central assembly factor of the entire complex and holds together the other subunits, SOSS-B1, SOSS-B2, and SOSS-C [13]. SOSS-B1 can localize at sites of DNA breaks, and cells deficient in this protein exhibit increased sensitivity to DNA damage and a diminished capacity for DNA repair [17].

3. Conclusions

In this work, we have applied the bioinformatics approach to identify the most probable target in HeLa cells for [Pd(dach)Cl₂] complex, which can be further tested as a potential anti-cervical cancer metallodrug. The results are promising, as the protein complex

SOSS, which is involved in the maintenance of genomic stability, indicates a potential interference of [Pd(dach)Cl$_2$] with the cancer cell cycle and triggering apoptosis.

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