Prostate Cancer Metabolic Alterations Induced by Zika Virus

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INTRODUCTION

Zika virus (ZIKV) is a *flavivirus* transmitted by *Aedes aegypti* mosquito, with high incidence of cases in the Americas between 2015 and 2016. Although 80% of the cases are asymptomatic, ZIKV infection was associated to neurological complications such as Guillain-Barré syndrome and microcephaly. Based on these reports several studies tried to understand ZIKV viral infection process in human and mosquito cells. During experimental investigations it was demonstrated that ZIKV can impair neuronal growth, reduce neural stem cell and even mediate cell death [1-2]. A hypothesis about the oncolytic potential of ZIKV due its ability of cell growth impairment was raised and later confirmed by *in vitro* and *in vivo* studies with glioblastoma cells [3-4]. The antiproliferative effect of a ZIKV prototype (ZVp) was tested for several types of tumor cells resulting in ZVp activity against prostate cancer cells (PC-3) [4,5]. However, little is known about the cellular mechanisms associated with this effect. Therefore, we aimed to determine the prostate cancer cell line (PC-3) metabolic alterations induced by Zika virus particle using metabolomics through high resolution mass spectrometry (HRMS) analysis.

METHODOLOGY

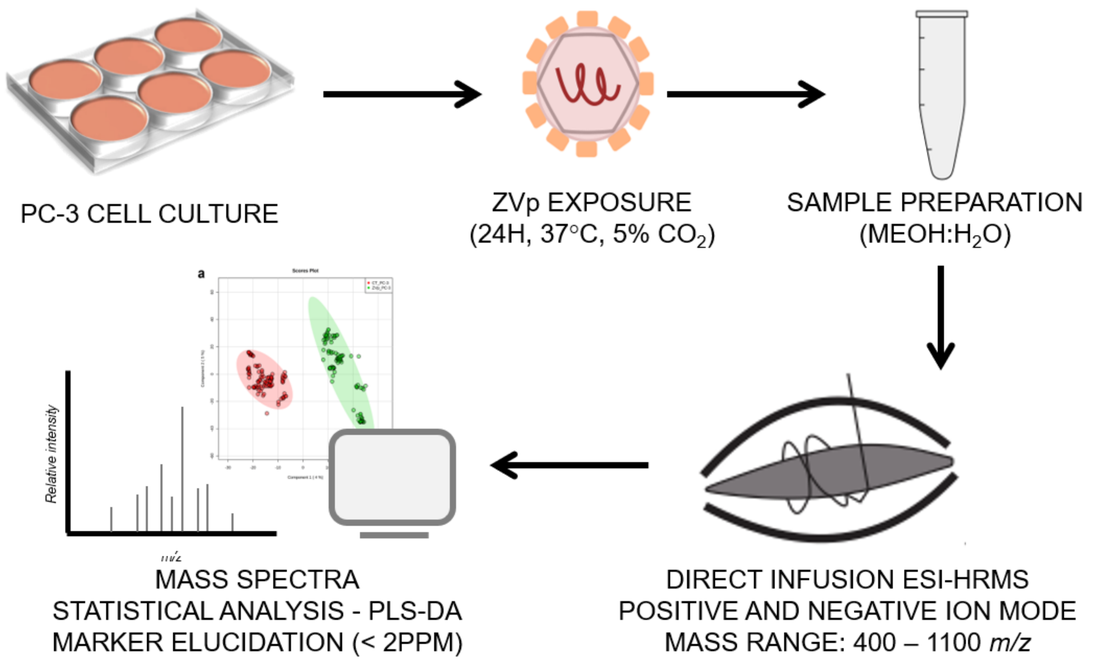

Figure 1. Experimental design and data analysis.

HRMS: ESI-LTQ-XL Orbitrap Discovery (Thermo Scientific, Bremen, Germany).

A VIP score list (Variable Importance in Projection) from MetaboAnalyst 4.0 software [6] was used to determine the characteristic ions for ZVp exposed group.

RESULTS

The comparison of spectral data using PLS-DA multivariate analysis (Figure 2) showed a marked separation among PC-3 exposed and non-exposed groups, suggesting discriminant molecules involved with ZIKV induced cell alterations..

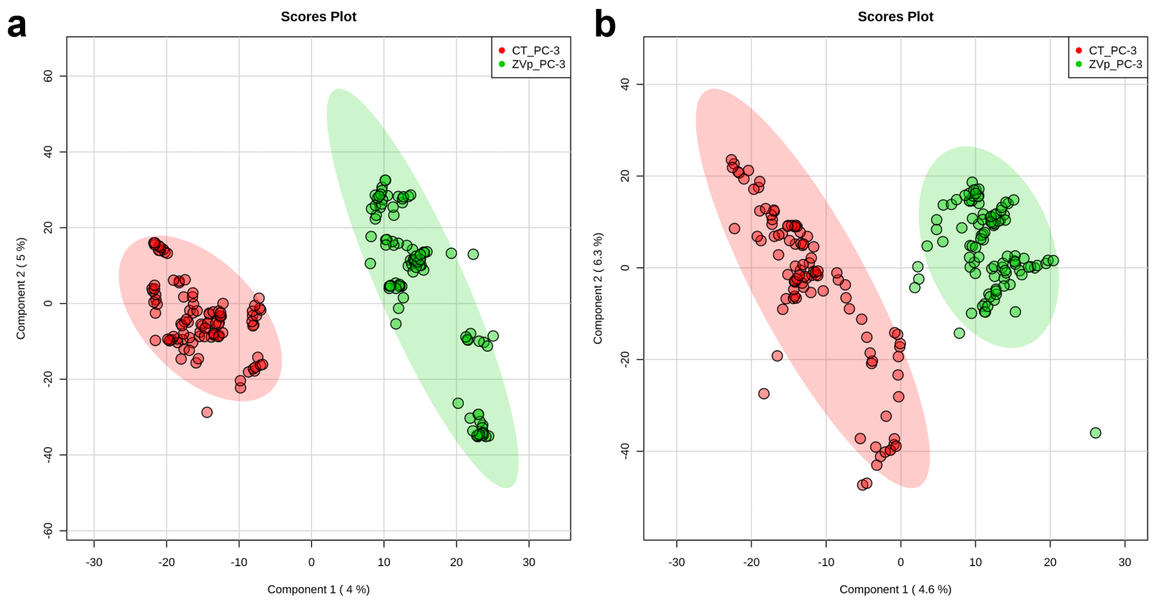

Figure 2. Partial Least Square-Discriminant Analysis (PLS-DA) score plot model of control PC-3 cells (red) and PC-3 cells exposed to ZVp (green) clustering with data on positive ion mode (a) and negative ion mode (b).

A heat map analysis (Figure 3) demonstrated the distribution of the 20 most relevant markers among samples identified in this study.

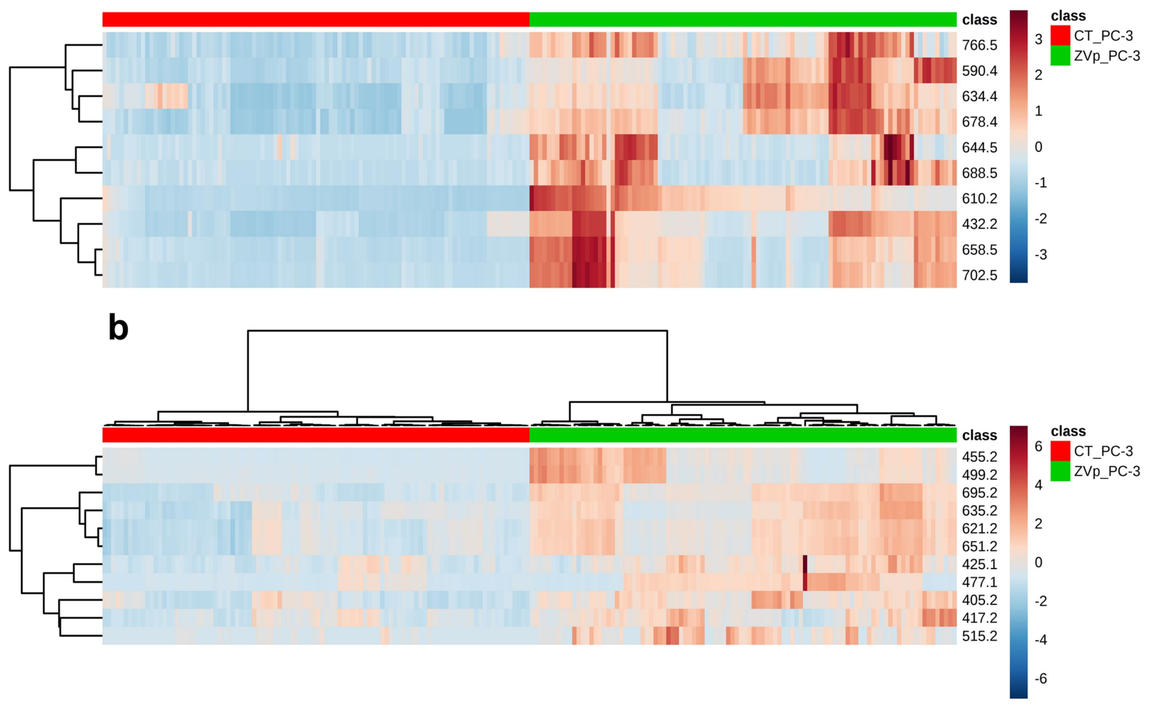

Figure 3. Heatmap analysis of selected markers distribution (a) on positive and (b) on negative ion mode.

The proposed chemical markers translate lipid metabolism remodeling associated to the interaction of ZVp and PC-3 cell, inflammatory mediators and inductors of cell death. In addition, based on markers, we proposed the involvement of one carbon metabolism, porphyrin pathway and protein glycosylation mechanism on ZVp antiproliferative effect.

Table 1. Antiproliferative effect of attenuated ZIKV prototype (ZVp) against PC-3 (prostate cancer cell line) [4].

Sample	Parameter	Cell lines	
		PC-3	HaCat
Doxorubicine	GI_{50} (ng/mL)	< 25	< 25
ZVp	GI_{50} (*10^6 ZVp/mL)	14.7	590

GI_{50}: concentration that inhibits 50% cell growth or cytostatic.

DISCUSSION AND CONCLUSIONS

The versatility of the metabolomic screening helped to indicate pathways that may be involved with ZIKV antiproliferative effect and are not so obvious for a first target study. To our knowledge this is the first metabolomic investigation of ZIKV moieties interaction with prostate cancer cells. Metabolomic strategies associated with HRMS have been supporting advances in ZIKV research, bringing innovation to viral infection biomarkers elucidation, developing diagnostic methods and understanding of ZIKV mechanisms and oncolytic potential.

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