promote 50% growth inhibition (IC50) for each cell line was calculated by sigmoidal regression using Origin 8.0 software. The Combination Reduction Index (CRI) was calculated as IC 50 of the metal complex + monoterpene / IC 50 of the metal complex alone. **Results:** Both silver complexes exhibited potent antiproliferative activity. The antiproliferative effect of silver complex I ranged from 4 $\mu$M to 10 $\mu$M in SCC and CM cell lines, whereas the antiproliferative effect of silver complex II ranged from 1 $\mu$M to 6 $\mu$M in the same cell lines. The association of silver complex I in combination with S-(-)-limonene resulted in synergism effect in the FaDu cell line with IC50 < 2 $\mu$M, CRI = 0.4. The association of silver complex II with both enantiomers demonstrated a partial synergistic effect in the FaDu and SK-MEL-28 cells, with IC50 <1.5 $\mu$M and CRI = 0.5. **Conclusion:** Silver complexes are promising candidates for in vivo studies as potential alternatives for the treatment of patients with SCC and CM. Additional experiments are necessary to evaluate their mechanism of action and toxicity. The study was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação de Apoio ao Ensino e à Pesquisa do Estado de São Paulo (FAPESP #2016/07729-4; #2023/09738-4 and Cancer Theranostics Innovation Center, (CancerThera), CEPID FAPESP #2021/10265-8).

**Keywords:** Combination, Limonene, Melanoma, Silver complexes, Squamous cell carcinoma.

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## ROLE OF GENETIC VARIABILITY IN METABOLIC PATHWAYS ON CISPLATIN-INDUCED KIDNEY INJURY IN HEAD AND NECK CANCER PATIENTS

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A B S T R A C T

**Introduction/Justification:** Head and neck squamous cell carcinoma (HNSCC) is a prevalent malignancy responsible for approximately 5.0% of global cancer deaths. The standard treatment for locally advanced HNSCC involves cisplatin (CDDP)-based chemotherapy and radiotherapy, which can lead to significant adverse effects, particularly nephrotoxicity. It is already well known that the efficacy of CDDP as well as its side effects vary in distinct patients with HNSCC, and single nucleotide variants (SNVs) in genes that act in CDDP metabolism constitute a plausible explanation for this finding. **Objectives:** To investigate the roles of SNVs GSTM1, GSTT1, GSTP1 c.313A>G, XPC c.2815A>C, XPD c.934G>A and c.2251A>C, XPF c.2505T>C, ERCC1 c.354C>T, MLH1 c.93G>A, MSH2 c.211+9C>G, MSH3 c.3133A>G, EXO1 c.1765G>A, TP53 c.215G>C, CASP3 c.-1191A>G and c.-182-247G>T, FAS c.-1378G>A and c.-671A>G, and FASL c.-844C>T SNVs on kidney function outcomes in HNSCC patients undergoing CDDP treatment. **Materials and Methods:** A total of 109 patients with locally advanced HNSCC treated with CDDP were included in the study. Genotypes were determined using polymerase chain reaction (PCR). Renal function was assessed by calculating estimating glomerular filtration rate (eGFR) using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, before treatment initiation and 30 days post-treatment. The percentage variation in kidney function was calculated by determining the difference between baseline (pre-chemotherapy) and follow-up (post-chemotherapy) values for eGFR divided by the pre-chemotherapy value and represented as ΔeGFR. **Results:** Patients with the GSTT1 present and ERCC1 c.354CT or TT isolated genotypes presented a decline in kidney function of 4.94% and 8.94%, respectively. A decline of 17.67% in renal function post-CDDP treatment was observed in patients with the GSTT1 present combined with TP53 c.215CC genotype. Patients with the GSTP1 c.313AG or GG and ERCC1 c.354CT or TTC>T (17.57%), MLH1 c.93GA or A (12.49%), or MSH3 c.3133AG or GG (12.19%) combined genotypes showed a reduction in renal function after CDDP treatment. Renal function declines of 18.85% and 13.38% were observed in patients with ERCC1 c.354CT or TT and MLH1 c.93GA or AA or MSH3 c.3133AG or GG combined genotypes, respectively. **Conclusion:** Our data indicates, for the first time, preliminary evidence that combined inherited abnormalities, SNVs that act in CDDP metabolism, act as independent factors for nephrotoxicity in HNSCC patients and can be used to select patients for personalized treatments that promote renal protection and reduced nephrotoxicity. **Acknowledgements:** The study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (grant number 88887.513947/2020-00), the Postdoctoral Program (PPPD) at the University of Campinas (UNICAMP) (Postdoctoral ID number: 326285), and the Fundação de Apoio ao Ensino e à Pesquisa do Estado de São Paulo (FAPESP) Cancer Theranostics Innovation Center (CancerThera) (FAPESP 2021/10265-8).

**Keywords:** Cisplatin, Head and neck squamous cell carcinoma, Nephrotoxicity, Single nucleotide variants.

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## KIF13B C.*3163G>A SINGLE NUCLEOTIDE VARIANT ON OROPHARYNGEAL SQUAMOUS CELL CARCINOMA SUSCEPTIBILITY AND TUMOR CHARACTERISTICS

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A B S T R A C T

**Introduction/Justification:** Oropharyngeal squamous cell carcinoma (OPSCC) is a subtype of head and neck cancer with high mortality rates and aggressive behavior. Smoking, alcohol consumption, and HPV infection are well-established risk factors in carcinogenesis of the tumor. Genetic inherited variations can influence OPSCC susceptibility and tumor characteristics by altering gene expression. The KIF13B gene encodes a kinesin motor protein involved in intracellular transport, and sequence variations in its regulatory regions may affect gene expression. However, the impact of the KIF13B c.*3163G>A single nucleotide variant (SNV) on OPSCC risk and tumor features remains unclear. **Objectives:** To evaluate whether distinct genotypes of the SNV KIF13B c.*3163G>A influence the risk and tumor characteristics of OPSCC, as well as the expression of the KIF13B gene and the microRNA (miRNA) let-7e-3p in controls, and to functionally assess the interaction between let-7e-3p and the SNV region in the 3'-UTR of KIF13B. **Materials and Methods:** We evaluated 250 OPSCC patients and 250 controls seen at the Clinical Oncology Services of the General Hospital of University of Campinas. The genomic DNA was obtained from peripheral blood leukocyte samples from patients and controls entered the study. The KIF13B c.*3163G>A SNV genotypes were identified by polymerase chain reaction (PCR). The RNA was obtained from peripheral blood leukocyte samples from controls. The gene and let-7e-3p expression were evaluated by quantitative PCR. Interaction between let-7e-3p and the 3'-UTR of KIF13B was evaluated by luciferase reporter assay in FaDu and Detroit 562 pharyngeal cell lines. **Results:** KIF13B c.*3163GG genotype was more common in OPSCC patients than in controls (42% versus 32%; P = 0.03); individuals with KIF13B c.*3163GG genotype were under 1.73-fold increased risk of OPSCC than others. KIF13B c.*3163GG genotype was more common in patients with greater tumor extension (46% versus 28%, P = 0.01) than others and in patients with greater tumor extension than in controls (46% versus 32%; P = 0.004); individuals with KIF13B c.*3163GG genotype were under 2.47-fold increased risk of aggressive OPSCC than others. Individuals with KIF13B c.*3163GG genotype showed lower levels of KIF13B mRNA (1.02 arbitrary units (AUs) ± 0.35 standard deviation (SD) versus 1.28 AUs ± 0.53 SD, P = 0.05). The expression level of miRNA let-7e-3p was similar in individuals with distinct genotypes KIF13B c.*3163G>A SNV (0.52AUs ± 0.31DP versus 0.48AUs ± 0.26DP versus 0.55AUs ± 0.39DP, respectively; P= 0.85). The let-7e-3p miRNA exhibited more efficient binding to the 3'-UTR of the ancestral G allele compared to the variant A allele in the FaDu (p = 0.004) and Detroit 562 (p = 0.04) cell lines. **Conclusion:** Our data present, for the first time, evidence that KIF13B c.*3163G>A SNV is associated with increased risk of OPSCC possibly due to the variation of KIF13B gene expression, modulated by the miRNA let -7e-3p.
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**Keywords:** KIF13B, Oropharyngeal squamous cell carcinoma, Risk, Single nucleotide variants.

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## ASSOCIAÇÃO ENTRE SINTOMAS DE DEPRESSÃO E UMA VARIANTE NO GENE DA CHAPERONA ERP29 ASSOCIADA A PROCESSOS INFLAMATÓRIOS EM PACIENTES COM CÂNCER DE CABEÇA E PESCOÇO

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R E S U M O

**Introdução/Justificativa:** O câncer de cabeça e pescoço (CCP) é um problema de saúde global, frequentemente acompanhado de reações emocionais, incluindo a depressão. Genes que regulam as vias de resposta inflamatória ao estresse desempenham um papel importante nos processos depressivos. O gene ERP29 codifica uma proteína chaperona envolvida no enovelamento e secreção de proteínas no retículo endoplasmático. Estudos conduzidos pelo nosso grupo demonstraram que a supressão do ERP29 em linhagens de células de tumores de cabeça e pescoço está associada ao aumento da expressão de genes das vias MAPK e Akt, conhecidas por seu envolvimento em processos inflamatórios. Além disso, uma variante genética de base única (SNV) no ERP29 (rs7114, A>G) foi associada a um maior risco de desenvolvimento de CCP e à redução da expressão do gene. No entanto, a relação dessa SNV com os sintomas depressivos ainda não foi estabelecida. **Objetivos:** O presente estudo teve como objetivos: 1) investigar se os sintomas depressivos em pacientes com CCP estão associados a