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A.C.Camargo Cancer Center

Especializado em Vida

EFFECTS OF A PHTHALATE METABOLITE MIXTURE ON BOTH NORMAL AND TUMORAL HUMAN PROSTATE CELLS

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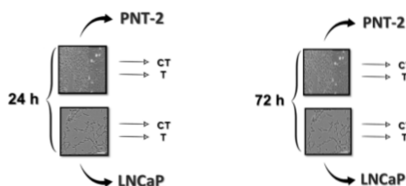
Introduction

Phthalates represent a group of substances used in industry and it is found in different concentrations in human urine and plasma. More than 8 billion tons of phthalates are used each year, predominantly as plasticizers in polyvinyl chloride (PVC) products. Thus, this study was aimed to investigate cell turnover, oxidative stress and miRNAs synthesis markers proliferation in tumor prostatic cells exposed to an environmentally phthalate monoester mixture at similar levels found in humans.

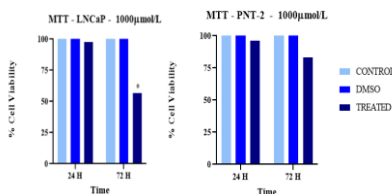
Methods

Cancer prostate cells (LNCaP) were exposed to a phthalate mixture (1000µmol/L) composed of 36.7% MEP, 15.3% MBP, 10.2% MiBP, 8.2% MBzP, 19.4% MEHP and 10.2% MiNP; diluted in 0.05%DMSO and RPMI culture medium. Cells were exposed to the mixture for 24h and 72h, and divided into three groups: CT (RPMI+DMSO) and T(DMSO+RPMI+phthalate mixture). *BAX, BCL2, CASP3, CASP8, DROSHA, DICER1, SOD1, CAT, GSR, CCND2,CDKN2A, KI67, Erα, miR 141-3P and miR 184* gene expression was performed by qRT-PCR and migratory potential was measured using cell migration assays.

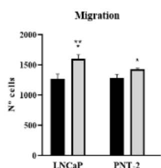


Results

MTT assay showed no significant difference among the groups at 24h and decrease of 45% of cell viability after 72h of exposure for LNCaP at 1000µmol/L.

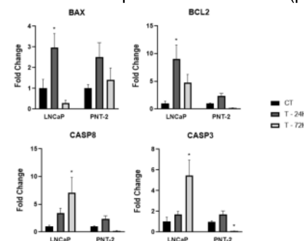


In this study, the mixture of phthalates proved to be able to alter the cellular migratory potential, with an increase in the number of migratory cells in the treated group compared to the control group ($p \leq 0.05$) in both cells lines. Interestingly, the treated LNCaP cells showed a significant increase in migration when compared to the treated group of PNT-2, demonstrating that the mixture of phthalates was able to more markedly influence the migratory behavior of the LNCaP cell line than the PNT-2 cell.

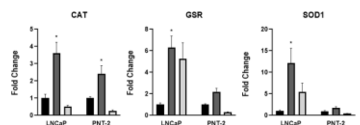


Results

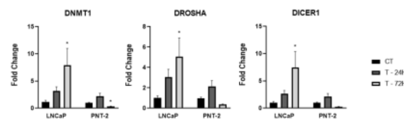
In LNCaP cells, the mixture increased the expression of BAX and BCL2 compared to the control ($p \leq 0.05$) after 24h of exposure and it increased the expression of CASP3 and CASP8 ($p \leq 0.05$) at 72h compared to control. For the PNT-2, the mixture decreased expression of CASP3 at 72h compared to the control ($p \leq 0.05$)



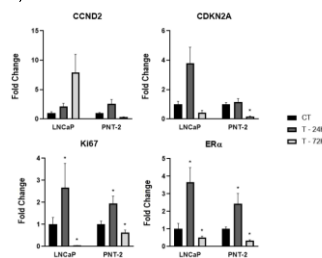
For the LNCaP cells, the phthalate mixture increased expression of CAT, GSR and SOD1 compared to the control ($p \leq 0.05$) after 24h of exposure. There is an increase in CAT expression after 24h of exposure in PNT-2 cells. After 72 hours, the mixture did not significantly affect expression of antioxidant enzymes in any cell type.



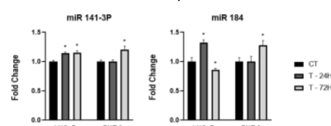
The phthalate mixture increased expression of DMNT1 (DNA methyltransferase I), DROSHA and DICER expression compared to the control ($p \leq 0.05$) after 72 hours of exposure in LNCaP cells. In contrast, the phthalate mixture decreased DMNT1 expression in compared to the control ($p \leq 0.05$) after 72 hours of exposure in PNT-2 cells.



In PNT-2 cells, the mixture decreased expression of CDKN2A compared to the control after 72h of exposure. In both LNCaP and PNT-2 cells, the mixture increased expression of Ki67 and ERα compared to the control ($p \leq 0.05$) after 24 h of exposure. However, the mixture, decreased Ki67 and ERα expression in the compared to the control ($p \leq 0.05$) in both LNCaP and PNT-2 cells at 72 h.



After 24h of exposure, the mixture increased expression of miR141-3P and miR184 compared to the control ($p \leq 0.05$) in LNCaP cells. After 72 hours, the mixture increased miR141-3P expression and decreased miR184 expression compared to the control group ($p \leq 0.05$) in LNCaP cells. However, there was increase in miR184 expression in treated PNT-2 cells compared to the control after 72h.



Conclusion

Our results show that the mixture of phthalates at a dose of 1000 µmol/L can increase cell turnover, oxidative stress, biosynthesis, and expression of miRNAs, in LNCaP cells, thus, increasing the cellular expansive and migratory potential and modulating the tumor behavior, making them aggressive. However, in normal cells, these effects are less pronounced, demonstrating that, in the short term, normal cells are able to develop more effective mechanisms and responses against the insult, or even that PNT-2 cells are more resistant to exposure at the selected dose.

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