

Meeting abstract

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## Up-regulation of HLA class I antigen expression and antigen-specific CTL response in cervical cancer cells by the demethylating hydralazine and the histone deacetylase inhibitor valproic acid

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### Background

DNA hypermethylation and histone deacetylation are epigenetic events that contribute to the absence or downregulated expression of different components of the tumor recognition complex. These events affect the processing and presentation of antigenic peptides to CTLs by HLA class I molecules. In this work we evaluated the effect of the DNA hypomethylating agent hydralazine (H) and the histone deacetylase inhibitor valproic acid (VA), on the expression of HLA class I molecules and in the antigen-specific immune recognition of cervical cancer cells.

### Materials and methods

Cell lines C33A (HPV-), CaSki (HPV-16+) and MS751 (HPV-18+) were treated with hydralazine and valproic acid to assess cell proliferation and to evaluate the expression of HLA class I molecules on cell surface by flow cytometry. Primary cervical tumors of five HLA-A\*0201 allele patients were typed for HPV and their CTLs stimulated in vitro with the T2 cell line previously loaded with 50  $\mu$ M of the HPV peptides. Cytotoxicity of stimulated CTLs was assayed against Caski and MS751 cells pretreated with hydralazine and valproic acid.

### Results

The combination of HV acid had antiproliferative effect in C33 and CaSki cells. VA and VA+H up-regulated the constitutive HLA class I expression as evaluated by flow cytometry. In addition, the antigenic immune recognition of CaSki and MS751 cells by CTLs specific to HPV-16/18 E6 and E7-derived epitopes, was more prominent on cells treated with VA or H+VA than cells treated with either H or IFN- $\gamma$ .

### Conclusion

These results support the potential use of H and VA as an adjunct for immune intervention in cervical cancer patients whenever clinical protocols based on tumor antigen recognition is desirable, such as in those cases where the application of E6 and E7 based therapeutic vaccines is used.