Modulation of HLA class I expression in multidrug-resistant human rhabdomyosarcoma cells*

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An abnormal HLA expression has been detected in some tumors including rhabdomyosarcoma (RMS). Classical cytotoxic treatment of these tumors, the most common childhood soft tissue malignacy, may induce multidrug resistance (MDR) associated with the expression of a 170-kDa membrane-associated glycoprotein (P-glycoprotein). In order to analyse the connection between modulation of HLA expression and the development of the MDR phenotype mediated by P-glycoprotein in RMS, we used three resistant RMS cell lines; two of these resistant cell lines (TE.32.7.DAC and RD-DAC) were established by *in vitro* exposure to actinomycin D, a drug of choise in the treatment of RMS; the resistant RMS-GR cell line was established from an embryonal RMS tumor after polychemotherapy. Our results showed that all the resistant cell lines showed a significant increase in the expression of HLA class I surface antigens in comparison to drug-sensitive cells. Blockade of P-glycoprotein with verapamil led to a decrease in HLA class I expression in RMS resistant cell lines. However, no modulation of HLA class II expression was observed in any of the three analyzed cell lines. These findings support the hypothesis that the development of resistance mediated by *mdr 1*/P-glycoprotein, directly influences the expression of HLA class I in RMS cells, inducing to upregulation. This effect may be relevant to the application in RMS of immunotherapy against tumor-associated antigens presented by HLA class I molecules.

Key words: MDR, P-glycoprotein, rhabdomyosarcoma, HLA, verapamil.

The development of multidrug resistance (MDR) remains the major limitation in the chemotherapy of malignancies [33], as show the large amount of strategies which have been developed to modulate this phenomenon [30]. Although several mechanisms have been described by which tumor cells may express drug resistance, classical MDR has been associated with the expression of a 170-kDa membrane-associated glycoprotein (P-glycoprotein) that serves as a drug efflux pump [17]. Rhabdomyosarcomas (RMS), the most common childhood soft tissue malignacy [26], are characterized by poor response to cytotoxic treatment and significant morbidity [2, 9]. Clinical [24] and experimental [7, 25] studies showed an increase in *mdr 1*/P-glycoprotein expression after chemotherapy, suggesting that this resistance mechanism may explain the frequent failure of cytotoxic therapy in RMS. Recently, it has been showed that the development of this resistance may be preventable in RMS by using modulators of MDR [6].

Modulation of HLA expression has been detected during malignant transformation. The clinical significance of this change in tumor cells is not clear, although it has been related with the degree of differentiation and prognosis, metastatic potential [1] and with the development of the MDR phenotype mediated by P-glycoprotein [34]. This member of the ABC superfamily is able to transport across plasma

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