Chapter 5
Conclusions

Altered MHC Class I expression is a hallmark of malignant transformation and tumor immune escape. Using immunohistochemistry and molecular techniques it has been demonstrated that many types of tumor can lose up to 80 % of normal MHC class I expression. Both reversible and irreversible structural defects of MHC class I have been described in solid tumors, in cancer cell lines and metastatic lesions. As a result, malignant cells develop low immunogenic phenotypes with altered antigen-presentation ability. It leads to the loss of tumor recognition by cytotoxic T lymphocytes, providing an immune escape route for MHC-negative cells, and limits the efficacy of cancer immunotherapy. A growing body of evidence supports a hypothesis that the irreversible genetic defects underlying abnormal MHC expression are, at least partially, responsible for the emergence of immunotherapy-resistant tumor escape variants. We have obtained clinical data demonstrating that progressing melanoma metastases that develop after immunotherapy have more alterations causing abnormal HLA class I expression that lesions that regress. Similarly, recurrent bladder tumors developed after BCG therapy showed more profound genetic defects in HLA class I molecules. Results obtained from cancer animal models also support the importance of MHC class I expression in response to therapy. These results indicate that the success of immunotherapy as anti-metastatic treatment may depend strongly of the MHC-I expression level on primary tumor cells. Thus, in our era of "personalized medicine" it seems to be important to include tumor MHC expression into the list of biomarkers to be closely monitored before, during and after cancer immunotherapy to increase the clinical efficacy of the treatment. It is also important to develop more uniform techniques of the tumor MHC class I expression and more consistent ways to interpret the data. We believe that a combination of immunotherapy with chemotherapy and gene therapy is the most promising approach in fighting cancer.

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