

# Rediscovering an old story: HLA class I alterations and immune escape of tumors in the context of immunotherapies

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Despite the successful implementation of immunotherapies, the response rates of tumor patients are still limited and often resistances develop. This might be a result of the immune suppressive nature of the tumor microenvironment as well as the immune escape mechanisms of tumor cells. While several tumor infiltrating immune cell subpopulations can foster tumor development, exhibit immune suppressive activity and decrease the efficacy of effector immune cells, tumor cells have also developed multiple mechanisms to escape immune recognition and to modulate immune cell function. These include in particular abnormalities in the classical HLA class I antigen, the interferon (IFN) signal transduction pathways and overexpression of non-classical HLA antigens as well as of immune checkpoint molecules. These different strategies have recently been shown to be crucial for the efficacy of immunotherapies against solid tumors and might be associated with the acquired resistances to these treatment options. Thus, a deeper understanding of the key immune players and regulatory pathways of tumor cells involved in the complexity and dynamic interaction between tumor and immune cells might be important for the identification of prognostic factors and the reversion of the immune escape processes. This might lead to increased immune responses against cancer cells and avoidance of immune resistances in order to improve the efficacy of immunotherapies. HLA class I abnormalities frequently occur in tumors, which are associated with a worse prognosis of patients. These defects are mainly due to deregulation rather than structural alterations of HLA class I antigens and antigen processing machinery (APM) components. Reversion of loss or downregulated HLA class I APM component expression could be obtained by cytokine treatment, in particular IFN- $\gamma$ , but also by epigenetic drugs, proteoglycans, and anti-oxidant substances as well as microRNAs and RNA-binding molecules. Thus, the control of HLA class I APM expression is highly complex and this novel knowledge could be used for the design of immunotherapeutic approaches to enhance treatment efficacy.