Immune escape of tumors: Emerging concepts and therapeutic opportunities

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Tumor cells use different strategy to evade the host's immune system including the expression of immune suppressive molecules, downregulation of immune stimulating molecules as well as shifting the phenotype and function of normal immune cells to immune suppressive cells. Although immunotherapies, in particular the immune checkpoint blockade, has received considerable attention during the last years tumors employ effective mechanisms to inhibit anti-tumoral immune responses and reduce immunotherapeutic efficacy. Focussing on classical and non-classical HLA class I abnormalities, which were frequently found in tumors of distinct origin leading to T and/or NK cell-mediated immune escape, the undergoing molecular processes are diverse. While structural alterations of HLA class I antigens represent a rare event, HLA class I abnormalities are mainly due to a deregulation of the expression of HLA antigens and/or components of the antigen processing machinery (APM). This could occur at the transcriptional, epigenetic as well as posttranscriptional level. Recently, increasing evidence suggest that also changes in the tumor metabolism and signal transduction pathways contribute to the inhibition of the anti-tumor response. For example, tumor-mediated shifts in abundant metabolites and accumulation of metabolic waste products result in local immune suppression and/or alter immune modulatory molecules. In addition, oncogenic signaling also negatively interferes with the expression of immune stimulatory molecules, but upregulates immune suppressive factors thereby facilitating tumor progression. Thus, there exists a link of tumor immune escape mechanisms with signal transduction and metabolism, which might facilitate immune evasion. This will be also discussed in the context of immunotherapies, novel concepts and therapeutic opportunities.