POTENTIAL IMMUNE ESCAPE MECHANISMS OF TUMORS: MHC CLASS I MOLECULES – ENEMIES OR FRIENDS

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Keywords: tumor immunology, escape mechanisms, MHC class I, CTL, NK

Abstract. It is generally accepted that tumor development is a multifactorial process which is caused by a sequential accumulation of different genetic alterations leading to aberrant cell cycle control, instability of genomic integrity as well as decreased recognition by the immune system. During the last decade, the tumor-host interaction has been well defined. It has been demonstrated that professional antigen presenting cells (APC), macrophages, natural killer (NK) cells, NKT cells and in particular T-lymphocytes play a key role in anti-tumor immunity. In general, immune cells monitor MHC class I-presented antigenic peptides. Presentation of self peptides by MHC class I molecules results in the generation of tolerance. In contrast, presentation of viral or tumor-derived foreign antigens leads to the induction of lysis by CD8⁺ cytotoxic T lymphocytes (CTL). Loss or downregulation of MHC class I surface antigen expression on tumor cells results in an impaired CTL-mediated recognition and is often associated with disease progression, whereas the HLA class I-negative cells are susceptible to NK cell-mediated elimination. The MHC class I abnormalities could be due to distinct molecular mechanisms like structural alterations, epigenetic control and dysregulation. The knowledge about the strategies essential for proper MHC class I surface expression has an important impact on the mode of immunotherapies implemented for the treatment of tumor patients. So far there exists four major lines of evidence of cancer immunosurveillance: (i) the higher incidence of non-viral tumors in immunosuppressed and/or transplanted patients, (ii) the presence of lymphocytes within the tumor, (iii) the development of spontaneous tumor

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N. M. Bilko et al. (eds.), Stem Cells and their Potential for Clinical Application, 171–181.
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regressions as well as (iv) the correlation of the type and composition of the tumor immune cell infiltrates with the clinical outcome. In particular CD4+ and CD8+ T lymphocytes are important for monitoring an effective anti-tumor response which could be further modulated by stroma cells and the tumor microenvironment. HLA class I abnormalities have been frequently found in various human tumors of distinct origin which range from total loss or downregulation of MHC class I surface expression (Marincola et al., 2000; Garcia-Lora et al., 2003; Seliger et al., 2002, 2006). The underlying molecular mechanisms of such MHC class I abnormalities are diverse and can occur at each step of the antigen processing pathway (Seliger et al., 2006). This review will concentrate on (i) the description of the antigen processing and presentation pathway which allow tumor antigens to be recognised by CD8+ T lymphocytes, (ii) the MHC class I altered profiles in tumors and (iii) the underlying molecular mechanisms of impaired MHC class I surface expression leading in T cell-mediated immune escape.

**Abbreviations:** β2-m, β2-microglobulin; APC, antigen presenting cell; APM, antigen processing machinery; BLH, bleomycin hydrolase; CTL, cytotoxic T lymphocyte; DC, dendritic cell; ER, endoplasmic reticulum; ERAP, ER-resident aminopeptidase; HC, heavy chain; IFN-γ, interferon γ; LAP, leucyl aminopeptidase; LMP, low molecular weight proteins; LOH, loss of heterozygosity; mAb, monoclonal antibody; MHC, major histocompatibility complex; NK, natural killer cells; PDI, protein disulfide isomerase; PLC, peptide loading complex; RCC, renal cell carcinoma; TAP, transporter associated with antigen processing; tpn, tapasin; TPPII, tripeptidylpeptidase II; wt, wild type

1. **The Complex MHC Class I Antigen Processing Pathway**

During the last decade the MHC class I antigen processing machinery (APM) has been well defined and appears to be more complex than initially expected. It consists of four major steps: (i) peptide generation and peptide trimming, (ii) peptide transport, (iii) MHC class I assembly and (iv) presentation of the trimeric MHC class I heavy chain/β2-m/peptide complex on the cell surface (Figure 1).