Molecular Background of Cancer Recurrence

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Abstract

Despite significant advances in treatment and diagnostics, cancer remains a major healthcare problem worldwide. The incidence of cancer had significantly increased globally due to the high rates of exposure to risk factors and increasing average life expectancy. It is known, that the immune system is responsible for development of a specific response against tumors. However, activated immunocompetent cells are frequently failed in their mission to reject the tumor, which leads to cancer progression and metastasis. Such failure of immune system is linked with the phenomenon of cancer recurrence, which is based on widespread of highly metastatic tumor cells with low immunogenicity. Therefore, the tumor cells acquire the ability to avoid the monitoring of immune system and become resistant to anti-cancer drugs.

This specificity of the tumor cell is the key barrier to the successful treatment and management of cancer. The role of specific genes, epigenetics as well as tumor microenvironment should be further investigated and determined.

Keywords: Cancer specific genes; Immune escape; PD-1/PD-L1 signalling

Introduction

The function and role of immune system to develop a T-lymphocytes based specific immune response against tumor is well known and described. However, activated tumour-specific immunocompetent cells are frequently unable to reject the tumor. This functional failure of immune system leads to cancer progression and development of metastasis. This phenomenon is based on widespread of highly metastatic tumor cells with low immunogenicity. The molecular background of antitumor immune response and cancer immunotherapy is the recognition of the human leukocyte antigen (HLA) class I complex (heavy chain/beta2-microglobulin (β2m)/tumor peptide) by cytotoxic T-cells (CTLs) [1,2].

Therefore, the altered and defective expression of HLA class I molecules in tumor is associated with cancer immune escape and metastasis development [2,3]. The stimulation by cytokines or immunotherapy might be helpful for recovery of some HLA alterations, so called “soft” lesions. We suppose, that the escape from immune recognition is linked with irreversible structural defects of tumor cells (“hard” lesions) [4]. It has been revealed, that in melanoma patients those are undergoing immunotherapy, the low response to immunotherapy and development of progressive metastases is associated with HLA-negative tumor cellular variants with irreversible defects [5]. Therefore, for selection of an appropriate immunotherapy protocol, the data on nature of the tumor HLA class I defect (regulatory or structural) acquire especial importance. Moreover, it has been demonstrated that expression of tumor HLA class I antigen in melanoma is determined as “immunological constant of rejection”. The expression of tumor HLA class I antigen in melanoma is associated with CTL-mediated tumor rejection, allograft rejection, graft-versus-host disease or an autoimmune disease development [6].

Literature Review

The data on β2m deficiencies and their importance for immune escape in melanoma and other types of cancer has been published [7]. Two genetic events (mutation of one copy of β2m gene and loss of another copy of this gene) are underlying the β2m loss in cancer cells [8], but the chronological order of these events should be further investigated. The influence of β2m loss in cancer cells on development of oncology disease correlates with HLA class I abnormalities in tumor tissue and a worse clinical outcome. HLA alterations can have been seen in tumor tissues and cell cultures derived from oncology patients [7,9]. Unfortunately, the development of β2m genetic alterations during metastatic progression have not been investigated till now. Only several research projects were focusing on association of immune escape mechanisms with HLA class I loss. In these experiments tumor tissue samples and tumor-derived cells cultures were obtained from the same patient. The research data links the genetic defects underlying HLA class I altered expression with metastasis developments [7,10]. We hypothesize, that the immune escape of HLA I negative tumor tissues correlates with β2m loss. We suppose, that this is the early event in the oncology disease progression.

The immune escape as well as acquired resistance to anti-cancer drugs are the unique and specific features of cancer cells. They are the key barriers to the successful management of oncology disease. An important mechanism of cancer immune escape is based on interaction between CTLs Programmed Death 1 (PD-1) receptor and cancer cell Programmed Death Ligand 1 (PD-L1) [11]. The PD-1/PD-L1 interaction has an important role as a part of “immune checkpoint regulators”. This interaction is important for development of self-tolerance; this is the limiting factor of immune response duration and strength. The mechanism of this interaction is based on inhibition of adaptive T cell responses [12]. The immune regulation mechanism of PD-1/PD-L1 realized by the tumor cells aims suppression of anti-cancer adaptive responses. In particular, the activation of PD-1/PD-L1 mechanism is linked with the suppression of anti-tumor adaptive responses, those are based on induction of CTL anergy, exhaustion, apoptosis and decreased cytokine production [11,13]. Furthermore, involvement of PD-1 and PD-L1 correlates with obvious resistance of cancer cell to pro-apoptotic signals. These signals are delivered by cytotoxic immune effectors, staurosporin, as well as Fas ligation [14]. The precise cellular mechanism of this phenomenon should be further determined and investigated. There is the difference in expression levels of PD-L1 by cancer cells. The expression of PD-L1 is stimulated by local

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special attention should be paid on epigenetics topics too. it is well known, that a key mechanism of epigenetics is the altered methylation of tumor-suppressor genes and of the genes encoding some miRNAs, as well as altered methylation and acetylation of the histones associated with these genes. epigenetic alterations early in tumor development may provide important predictive and prognostic tools, especially in situations where epigenetic therapies, such as HDAC inhibitors are being used to reactivate gene expression [24]. for example, in breast cancer, several genes associated with tumorigenesis are frequently methylated, including RASSF1A, HOXA5, TWIST1, CCND2, p16, BRCA1, as well as genes encoding the estrogen receptor (ESR1) and the progesterone receptor (PGR) [25]. epigenetic changes in several other tumor types may also provide prognostic and predictive profiles, including: ovarian cancer [26], prostate cancer [27], glioblastoma [28] and cutaneous tumors.

taking into account all above mentioned, it is clear that the role of molecular peculiarities, epigenetics and immunological aspects for cancer recurrence should be further clarified and determined.

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