

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 tumor-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 ($\beta 2m$)/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 $\beta 2m$ 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 $\beta 2m$ gene and loss of another copy of this gene) are underlying the $\beta 2m$ loss in cancer cells [8], but the chronological order of these events should be further investigated. The influence of $\beta 2m$ 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 $\beta 2m$ 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 $\beta 2m$ 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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factors and molecules like interferon gamma (IFN γ) [13,15]. Therefore, PD-L1 is a valuable prognostic marker; the correlation between PD-L1 expression infiltration of tumor by lymphocytes (TILs) [16], high histological grade of tumor [17] and worse clinical outcome [18] is already determined. Nowadays research activities are focused on PD-1/PD-L1 signaling through the application of humanized monoclonal antibodies (e.g., Nivolumab). The obtained results confirmed obvious clinical responses in advanced cases of melanoma, non-small cell lung cancer, and renal cell carcinoma. Furthermore, recent data suggest that PD-1/PD-L1 interaction may serve as background of cancer cell survival mechanism. It has been discovered that PD-1/PD-L1 interaction may be involved in resistance to radiotherapy and anti-CTLA-4 antibody based immunotherapy [19]. It may be estimated, that response to PD-1/PD-L1 blockade therapy depends on levels of tumor PD-L1 protein [20].

Discussion and Conclusion

Taking into account that PD-L1 expression is the protection of tumor cells from pro-apoptotic agents [14], and that the PD-1/PD-L1 mechanism correlates with severe clinical outcomes [18], we hypothesize that this mechanism is linked with development and acquiring of resistance to conventional chemotherapeutic drugs. We propose, that inhibition of PD-1/PD-L1 mechanism by applying of PD-1 targeted therapy will enhance the efficacy of conventional chemotherapy.

It has been shown by Chow et al. [21], that concrete genes are related to immune response. They are down-regulated in primary colorectal carcinomas, those later metastases. It is plausible, that the reduced expression of the immune-related genes impedes activation of CD4 T-cells mostly involving the MHC class II pathway. Platelets and circulating tumor cells (CTCs) interactions are important for hematogenous metastasis development. It has been revealed, that JAG1 and SNA1 upregulation in cancer cells is increased by platelets [22]. JAG1 is encoding a ligand for the Notch receptor, which is inducing SNAI2 expression. SNAI2 together with SNAI1 belong to a complex of transcription factors those are responsible to regulation of epithelial-mesenchymal transition and inhibition of E-cadherin. We hypothesize, that platelet adhesion to cancer cells stipulates the development of epithelial-mesenchymal transition (EMT) phenotype. We suppose, that this event is the functional and molecular background of cancer cell migration, extravasation and metastasis development.

The data by Kitamura et al. [23] indicates direct roles for myeloid cells, particularly macrophages, in promoting every step of the metastatic cascade. Thus, macrophages are particularly attractive targets for therapeutic intervention, as their diploid nature and consequent low mutation rates suggest that they will not easily evolve drug resistance. However, current therapies are likely to be limited as they either target all macrophages (for example, CFS1R inhibition) or they target essential processes such as monocyte egress from the bone marrow (for example, CCR2 inhibition). Therefore, the detailed research of molecular background of cellular interactions and importance of tumor microenvironment should be performed for development of effective and precise therapeutic intervention.

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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