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Key Aspects on Cancer Immunology

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Abstract

Although the obvious achievements in treatment and diagnostics are available, oncology diseases remain a major healthcare problem worldwide. The incidence of cancer has significantly increased globally due to the increasing exposure of risk factors and average life expectancy. The specific response against tumors is developed and realized by the immunocompetent organs. 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 present article aims to review and summarize the key aspects of cancer immunology. It is focused on description of the role of specific genes, polymorphisms, epigenetics as well as tumor microenvironment and immunoediting in relation to cancer immunology.

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

HLA Class I complex and tumor

The function and role of immune system to develop a T-lymphocytes based specific immune response against tumor is well known and described. However, the tumor cannot be frequently rejected by activated tumor-specific immunocompetent cells. This functional downfall of immune response is the background mechanism of tumor progression and 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 by cytotoxic T lymphocytes (cytotoxic T-cells, CTLs) the heavy chain/beta2-microglobulin (β2m)/tumor peptide, which belongs to human leukocyte antigen (HLA) class I complex [1,2]. Therefore, the cancer immune escape and metastasis development are associated with altered and defective expression of HLA class I molecules in tumor tissue [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 tumor cells specific "hard" lesions - inevitable structural defects [4]. The low response to immunotherapy and progressive metastases in melanoma patients are described for HLA-negative tumor cellular variants with irreversible defects [5]. Therefore, the determination of the tumor specific HLA class I defect (regulatory or structural) is highly important for selection of an appropriate immunotherapy protocol. Furthermore, melanoma specific tumor HLA

class I antigen expression is determined as "immunological constant of rejection". The HLA class I antigen expression in melanoma correlates with tumor rejection mediated by CTLs, allograft rejection, graft-versus-host disease or development of an autoimmune disease [6].

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 targeted on β2m gene are underlying the β2m loss in cancer cell. The underlying mechanisms of these genetic events are β2m gene one copy mutation and loss of another copy of this gene [8]. 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 tumor tissue specific HLA class I abnormalities and as a consequence with a worse clinical outcome. HLA alterations can been seen in neoplastic tissues and cell cultures developed from tumor tissues clinical samples [7,9]. Unfortunately, the β2m genetic changes and alterations developed during metastasis and specific to this phenomenon have not been investigated till now. Only several research projects were focusing on correlation between HLA classes I loss and immune escape. In these experiments was investigated neoplastic tissue samples and cells cultures developed from the mentioned tissue samples. The experimental data which links the genetically altered expression of HLA class I with metastasis development have been recently published [7,10]. We hypothesize, that the immune escape of HLA I negative tumor tissues correlates with β2m loss. Probably this is cancer progression early genetical event.

CTLs Programmed Death 1 receptor and cancer Cell Programmed Death Ligand 1

The escapes of tumor from immunological reactions 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. The main mechanism of cancer escape from immunological reactions is based on interaction between Programmed Death 1 (PD-1) receptor of CTLs and Programmed Death Ligand 1 (PD-L1) of cancer cell [11]. The PD-1/PD-L1 interaction is important event 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 tumor cells realized immune regulation mechanism of PD-1/PD-L1 aims anti-cancer adaptive responses suppression. In particular, the activation of PD-1/PD-L1 mechanism correlates with anti-tumor adaptive responses suppression, those are based on induction of CTL anergy, exhaustion, apoptosis and decreased cytokine production [11,13]. Furthermore, PD-1 and PD-L1 mechanism is linked 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 cancer cells specific expression of PD-L1. PD-L1 expression is stimulated by local factors and molecules like interferon gamma (IFNγ) [13,15]. Therefore, PD-L1 is a valuable prognostic marker; PD-L1 expression correlates with the grade of tumor infiltration 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 signalling through the application of humanized monoclonal antibodies (e.g., Nivolumab). The obtained results confirmed obvious clinical responses in advanced cases of skin cancer (melanoma), lung cancer (non-small cell lung cancer), kidney cancer (renal cell carcinoma) and etc [19,20]. Furthermore, recent data suggest that PD-1/PD-L1 mechanism may be a background of cancer cell survival. It has been discovered that PD-1/PD-L1 based mechanism may be a background of resistance to radiotherapy and anti-CTLA-4 antibody based immunotherapy [21]. It may be estimated, that response to PD-1/PD-L1 blockade therapy is associated with tumor PD-L1 protein levels [22].

Taking into account that PD-L1 expression protects of tumor cells from influence of 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.

Cell Signaling and Immune Response during Cancer

It has been shown [23] that concrete genes are related to immune response. Their expression rates are low in primary colorectal carcinomas with ability of later metastasis development. It is plausible, that the immune-related genes reduced expression alters activation of CD4 T-cells mainly through the MHC class II pathway. Platelets

and circulating tumor cells (CTCs) interactions are important for haematogenous metastasis development. It has been revealed, that JAG1 and SNA1 upregulation in cancer cells is increased by platelets [24]. 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 for epithelial-mesenchymal transition and E-cadherin inhibition. Accordingly with our hypothesis 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.

FOXP3 Gene and Metastasis Development

Although the genes critical for the concrete cancer disease development are identified, the genes responsible for metastasis development and as a consequence for cancer recurrence aren't identified till now. One of candidates is FOXP3. FOXP3 (Forkhead box protein P3) is important as regulatory T cells (Tregs) key transcription factor. It is important for suppression of Tregs immune functions [25]. The recent research confirmed the expression of FOXP3 in tumor cells [26-28]. This gene expression in tumor is linked with the mechanism of cancer immune escape [29]. It has been revealed, that FOXP3 is expressed in cancer cells and Tregs. Cancer cells can induce transform of T cells into Tregs and by this realize the immune escape mechanism [30]. The availability of Tregs in neoplastic samples probably is making influence on tumor microenvironment. Furthermore, the availability of Tregs in tumor samples is linked with poor prognosis and worse clinical outcomes [31-33]. The molecular features of FOXP3 should be noted too. FOXP3 is located at the short arm of X chromosome. The conserved non-coding sequences in intronic regions of FOXP3 bind with transcriptional factors; the expression regulation of the gene is complex [34]. Polymorphisms of above mentioned intronic regions of FOXP3 could alter not only binding of transcriptional factors, but also expression of FOXP3 and function of Tregs by themselves [35]. The polymorphism rs2232365 (A to G) of FOXP3 regulatory region correlates with immunologic diseases. These data are emphasizing the importance of FOXP3 gene for Tregs function regulation. The role of FOXP3 and its polymorphism rs2232365 (A to G) has not been investigates in cancer till now.

Taking into account all above mentioned we hypothesize, that FOXP3 gene and its rs2232365 A/G polymorphism is associated with cancer.

Cellular Interactions in Cancer

Myeloid cells, especially macrophages, are important for metastatic cascade development [36]. The macrophages are diploid; these cells are characterized with low mutation rates. Therefore, macrophages cannot easily develop drug resistance and may be used as effective targets for anti-cancer therapy. It should be noted, that modern anti-cancer therapies are targeting all macrophages through inhibition of CFS1R or CCR2 for example; which the limitation factor of macrophage targeted therapies is. The focused investigation of cellular interactions, their molecular mechanisms and specific microenvironment of tumor is required and essential for development of effective and precise anti-cancer therapy.

Epigenetical Aspects

Epigenetics is also important aspect of cancer immunology. Tumor-suppressor genes and some miRNAs encoding genes pathological methylation, these genes associated histones altered methylation and acetylation is the key epigenetical mechanisms specific to cancer. They can be used as important predicitive and prognostic tools of cancer. Such approach acquires the especial importance during application of HDAC inhibitors for target gene expression activation [37]. In breast cancer the methylation of RASSF1A, HOXA5, TWIST1, CCND2, p16, BRCA1, as well as genes encoding the estrogen receptor (ESR1) and the progesterone receptor (PGR) has been reported. These genes are associated with cancerogenesis [38]. Epigenetic changes specific to other tumor types may also provide prognostic data in ovarian cancer [39], prostate cancer [40], glioblastoma [41] and cutaneous tumors.

Immunoediting

The immune system is of utmost importance for determination of tumor immunogenicity. The link with RAG2 gene deficiency and immunogenicity of tumor has been revealed [42]. The immunoediting ensures the elimination of a developing cancer through the recognition of tumor specific antigens by T-cells. Unfortunately, the role and functional importance of antigens expressed by tumor cells are not fully investigated. The data concerning these antigens capability to induce anti-tumor immune response is controversial. The expression of tumor cells antigens after interaction with immune system should be investigated further. Point mutation in Spectrin- β2 has been determined as the background of production of a major

immunodominant rejection antigen in the unedited Rag2−/− d42m1 MCA sarcoma [43]. It has been experimentally determined, that immunoediting is the T-cell-dependent immunoselection process of tumor cell lineages without immunodominant rejection antigens [44,45]. The clinical trials provide data that immunoediting is a consequence phenomenon of immunotherapy in human cancer patients [46]. Therefore, the need to focus on multiple tumor antigens during cancer immunotherapy is obvious. By this the suppression of the outgrowth of tumor cell variants with low or no expression of individual tumor specific antigens will be achieved.

The measurable anti-tumor effects of immunotherapies in cancer are DNA based studies for the aim to define the most appropriate and effective biomarkers and differentiate responders from non-responders. We have witnessed a tremendous explosion in the identification of immune signatures for various types of human cancer [47-50]. Similar immune signatures are characteristic for cancers with a better prognostic outcome, and tumor cases with an increased sensitivity to therapy. The parameters related to the immune signatures are the density of CD3+, CD8+, and CD45RO+ T cells as well as their location at the tumor center and invasive margin combined with the quality of the tertiary lymphoid islets in the affected organ. These parameters are linked with a production of IFN-γ, STAT1, IL-12, IRF1, T-bet, perforin, granzymes, CXCR3 and CCR5 ligand chemokines, CXCL9, CXCL10 and CCL5, and expression of adhesion molecules (MAD- CAM1, ICAM1 and VCAM1) [48]. The tumor infiltrates can be successfully used as a prognostic biomarker to predict the outcome of treatment [51,52].

Conclusion

Immune reactions during cancer as well as the underlying this phenomenon, molecular mechanisms of cancer cells and immunocompetent cells are important and actual research topics. The special research emphasis is given to the cellular communications and tumor tissue microenvironment. The immunology response against cancer cells can be determined as the complex task, which can be successfully performed only in the conditions of the adjusted and coordinated intracellular mechanisms, cell-cell and cell-matrix interactions. The target of modern research is focused on determination of genes critical for immune escape and metastasis as well as on their regulation. The determination of cancer immunoediting mechanisms has the potential to justify the pathways specific to immune-based cancer treatments. These treatments, alone or in combination, are demonstrating remarkable responses in cancer patients. It has been determined and revealed, that in cancer, the immune system is not ignorant of the presence disease, but rather is actively suppressed by it. The challenge now is to apply the approach of personalized medicine and focus on molecular features of tumors and tumor microenvironments. The overall details and specificities of immunotherapy in different human cancers are still not determined. Despite of the objective fact, that the mechanisms of tumor escape and equilibrium are clarified in general, questions related to tumors escape immune control should be investigated further. Is the T-cell mediated response to tumor antigen central for elimination of neoplasm? What is the molecular background of further progress of some tumor clones? What is the molecular background of cancer immune escape? In the cases of successful and effective immune reaction, what will be the best combination of cancer therapies? Have we enough knowledge and understanding of the cancer related mechanisms for development of personalized cancer immunotherapies? It is obvious, with recent research activities and our possibilities to analyze the existed experimental and clinical data, the significant improvements in the next few years in cancer treatment in general and cancer immunotherapy in particular is expected.

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