Review Article

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Analysis of the Tests for New Life Extending Cancer Drugs

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Abstract

Since many decades basis of research for the detection of the cancer biomarkers is opted by many researcher to identify new drug for cancer. Specific biomarker assessment for the cancer will help in the diagnostic approach for the cancer diagnosis along with the assessment of the progress of the treatment. There are many cases where the association of the cancer with specific biomarker is possible. The example for reference may be the two types of colony stimulating factors, G-CSF and M-CSF. M-CSF promotes the production and activation of Monocytes, and G-CSF stimulates the production of granulocytes from stem cells in the bone marrow. G-CSF and GM-CSF, which are produced by recombinant DNA technology, have been approved by the FDA for use in patients with bone marrow depression, such as cancer patients and patients who receive bone marrow transplants. In these patients it is observed that the bone marrow depression is usually associated with intensive chemotherapy or irradiation, and the use of colony stimulating factors avoids the profound and prolonged neutropenia as seen in controls not receiving these compounds, with a corresponding decrease in morbidity and mortality. On the other hand, administration of G-CSF or GM-CSF is expensive and can be associated with severe side effects. The deployment of the new life extending cancer drugs is needed to be measured for its efficacy. The effect of drugs may be detected through the detection of the low amount of the secondary associated biomarkers of the cancer. The various oncologists have different opinion in use of the detection of the immunogenic biomarkers with cancers.

Keywords: B-Cell Signature; Biomarkers; Cancer; Immunogenic; T-Cell Signature.

Introduction

The human body consists of 1013 cells, and these are differentiated into many different types that form the different organs, and these differentiated into the many organs: skin, liver, kidney, blood cells and so on. It is the basis of research since long time for the detection of the cancer biomarkers. Specific biomarker assessment for the cancer can lead to the diagnostic approach for the cancer diagnosis as well as assessment of the progress of the treatment. There are many examples of association of the cancer with specific biomarker. The example for reference may be the two types of colony stimulating factors, G-CSF and M-CSF. M-CSF promotes the production and activation of Monocytes, and G-CSF stimulates the production of granulocytes from stem cells in the bone marrow. G-CSF and GM-CSF, which are produced by recombinant DNA technology, have been approved by the FDA for use in patients with bone marrow depression, such as cancer patients and patients who receive bone marrow transplants. In these patients it is observed that the bone marrow depression is usually associated with intensive chemotherapy or irradiation, and the use of colony stimulating factors avoids the profound and prolonged neutropenia as seen in controls not receiving these compounds, with a corresponding

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decrease in morbidity and mortality. On the other hand, administration of G-CSF or GM-CSF is expensive and can be associated with severe side effects.

Context

The various immunogenic signatures associated with cancerous cells includes the "Immune Score" in tumor microenvironment, the T-cells signatures, frequency of tumor-specific t cells in the circulation, apoptosis of CD8+ T Cells, differentiation Status of CD8+ T Cells, B-cell signature, suppressor cells in the tumor microenvironment, the neutrophils-to-lymphocyte ratio, cytokine expression and levels, tumor-derived exosomes, Programmed death-ligand 1 (PD-L1)

"Immune Score" in the Tumor Microenvironment

It is studied by the Whiteside in 1993 that nearly all the human solid tumors always infiltrated by immune cells (Whiteside, 1993). The composition and extent of these inflammatory infiltrates may vary among tumors. It was well established that the tumor microenvironment have a strong impact on immune cells, their identity, phenotype, localization, and density of immune cells present in the tumor has long been considered by immunologists to be critically important for tumor progression (von Kleist et al, 1987). Immune cells infiltrating human solid tumors have been extensively studied and found to exhibit unique phenotypic and functional characteristics (Pages et al., 2010; Fridman et al., 2012).

The T-Cell Signature

Naito et al, 1998 shown that the typing of tumor-infiltrating T lymphocyte (TIL) cells by immuno-histochemistry (IHC) and microscopic enumeration of these cells have been initially utilized to establish correlations between CD3+ CD8+ T-cell infiltrations and prognosis. The study of Sato et al, 2005 supports the potential significance of CD8+ T cells as predictors of risk. The human TIL were found to be functionally impaired relative to peripheral blood T cells of patients or of normal donors (Frey and Monu, 2008; Whiteside, 2010) and, in some instances, TIL were shown to contribute to tumor progression (Whiteside, 2006).

The Frequency of Tumor-Specific T Cells in the Circulation

In addition to scoring T cells at tumor sites, the frequency and functions of T cells circulating in the peripheral blood of cancer patients have been examined as potential biomarkers. The use of standardized single-cell assays able to detect tumor-antigen-specific T cells (ELISPOT, cytokine flow cytometry (CFC), and tetramer binding) has facilitated evaluation of epitope-specific T cells as potential biomarkers (Britten et al, 2011). These assays, especially ELISPOT, have been standardized for serial monitoring and can be reliably utilized to measure the frequency of epitope-specific T cells in blood or body fluids.

Apoptosis of CD8+ T Cells

Tumor-derived factors associated with the induction of death of immune cells at the tumor sites and in the peripheral circulation (Whiteside, 2010). The frequency of CD8+ T cells undergoing spontaneous apoptosis in the blood of patients with cancer was found to be significantly elevated relative to that in sex- or age-matched healthy controls (Hoffmann et al., 2002). CD8+ T cells were preferentially targeted for cell death compared to circulating CD4+ T cells (Tsukishiro et al., 2003).

The Differentiation Status of CD8+ T Cells

The functional potential of tumor epitope-specific T cells in situ or in the peripheral circulation of patients with cancer has been shown in some studies to correlate with outcome (Kirkwood et al., 2009) performing of functional immune assays is demanding and costly. A search for alternative biomarkers suggested that T-cell differentiation, as measured by the expression on CD8+ T cells of CCR7, a chemokine receptor for CCL19 and CCL21, discriminated cancer patients from normal controls (Czystowska et al., 2012).

The B-Cell Signature

Considerable evidence has existed for the presence of these cells in tumors, especially in breast cancer (Coronella et al., 2002). More recently, two independent reports have provided useful insights into the prognostic role of B cells in cancer.

Schmidt et al. (2008, 2012) have reported validation of the B-cell signature as the most robust prognostic factor in breast cancer and other human tumors. These investigators identified the immunoglobulin G kappa chain (IGKC) as an immunologic biomarker of prognosis and response to chemotherapy in hundreds of patients with breast cancer, non-small lung cancer, and CRC (Schmidt et al., 2012).

Suppressor Cells in the Tumor Microenvironment

Accumulations of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) in human tumors and their increased frequency in the circulation of cancer patients have been widely reported (Marigo et al., 2008; Whiteside, 2012). In ovarian carcinoma, melanoma, breast cancer, and glioblastoma, the frequency of Treg among TIL correlated with tumor grade and reduced patient survival (Lanca and Silva-Santos, 2012).

The Neutrophil-to-Lymphocyte Ratio

The chronic inflammation is closely associated with the development of specific human cancers. For example, inflammatory bowel disease predisposes to the development of CRC, and human papilloma-virus (HPV) infection is associated with oropharyngeal squamous cell carcinoma. Evidence has accumulated that the total white blood count and especially the high neutrophil-to-lymphocyte ratio (NLR) measured before oncological therapies predict adverse clinical outcome in patients with lung, breast, renal, ovarian, and HNC (Perisanidis et al., 2013).

Cytokine Expression and Levels

Cytokine gene or protein profiling, whether by multiplex immunoassays, microarrays, or proteomics technologies, is uniquely well suited to evaluations of the tumor microenvironment. Given the critical role it has in shaping local and systemic immune responses, events, and interactions between cells found in this milieu are of prime interest. Cytokines and chemokines mediate these interactions. Therefore, the potential for capturing polarization in the cytokine repertoire or differences in patterns of their production by immune or tumor cells and of relating them to a specific clinical response has a tremendous appeal.

Tumor-Derived Exosomes

Tumor-derived exosomes have recently come into the limelight as potential biomarkers in cancer. These membranous nano-vesicles (50–100nM in diameter) carry a large variety of cellular components, including proteins, RNA, microRNA, and DNA (Iero et al., 2008; Whiteside, 2013). TEX molecular content closely reflects that of tumor cells from which they originate, and thus TEX can serve as a sort of "liquid biopsy" in place of a conventional tissue biopsy. For this reason, molecular profiles of TEX are of great current interest.

Programmed Death-Ligand 1 (PD-L1)

Programmed death-ligand 1 (PD-L1) also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1) is a protein that in humans is encoded by the CD274 gene (Chemnitz JM,2004).

Programmed death-ligand 1 (PD-L1) is a 40kDa type 1 transmembrane protein, and it is assumed that it played a significant role in suppressing the immune system during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis. In usual case, the immune system reacts to foreign antigens where there is some accumulation in the lymph nodes or spleen which triggers a proliferation of antigen-specific CD8+ T cell and the formation of PD-1 receptor / PD-L1 or B7. The receptor /PD-L1 ligand complex transmits an inhibitory signal which reduces the proliferation of these CD8+ T cells at the lymph nodes and supplementary to that PD-1 is also able to control the accumulation of foreign antigen-specific T cells in the lymph nodes through apoptosis which is further mediated by a lower regulation of the gene Bcl-2. (http://www.ncbi.nlm.nih.gov)

Test for deploying new life-extending cancer drugs is the new ray of hope for assessment of the cancer treatment progression. Before any diagnostic application of the same for the patients, intensive researches on the efficacy of the biomarker need to be done. This was the topic of debate over last many decades that whether and how the host immune system influences cancer development. The animal model studies on cancer reveal that cancer strongly supports the role of anti-tumor immunity in cancer development, progression, and therapy but the evidence from human clinical trials is not clear or straightforward. The underlying reason behind this may be in large part due to profoundly immunoinhibitory effects human tumors exert (Huang et al., 2008; Whiteside, 2008b). The study by Whiteside et al., 2012 revealed that cancer patients at best mount weak anti-tumor immune responses which are ineffective in controlling cancer progression. The tumor-induced immune suppression may promote tumor escape hence becomes a significant problem for cancer therapy (Whiteside et al., 2012).

Hence the measurement of (a) the degree of tumor-induced immune suppression by identifying a decrease in or absence of an anti-tumor immune response or (b) the degree of recovery from immune suppression after successful therapy (i.e., normalization of defective anti-tumor immune responses) will be beneficial. Both these approaches have been used in clinical trials with the hope that

intermediate biomarkers of immune suppression, as well as biomarkers of therapy-induced recovery, can be identified. Because of the complexity of host-tumor interactions and limited immune monitoring capabilities, both have been difficult to implement in practice. In a limited number of cases, such immune alterations have been shown to correlate with clinical outcome suggesting that upon validation, they might serve as future biomarkers of prognosis or response to therapy.

Discussion

Investigation for the progress of treatment through new anti-cancer drugs can be assessed by the assessment of the associated biomarker level. The new drug that boosts the immunity then it is possible to evaluate the biomarker related to the immune system as well as the development of cancer. In this context, the PD-L1 is the biomarker of choice. The understanding about its mode of actions needs to be more clear before deploying it as the test for implementing new life-extending drugs. It is well studied that the PD-L1 binds to its receptor PD-1 which is present on the activated T cells, B cells, and myeloid cells to modulate activation or inhibition. The affinity between PD-L1 and PD-1, as defined by the dissociation constant Kd is 770nM. Interestingly, PD-L1 also has an appreciable affinity for the co-stimulatory molecule CD80 (B7-1), but not CD86 (B7-2) (Butte MJ et al., 2008). CD80's affinity for PD-L1, 1.4μM, is in between its affinities for CD28 and CTLA-4 (4.0μM and 400nM, respectively). The related molecule PD-L2 has no such affinity for CD80 or CD86, but shares PD-1 as a receptor (with a stronger Kd of 140nM). Said et al. showed that PD-1, up-regulated on activated CD4 T-cells, can bind to PD-L1 expressed on monocytes and induced IL-10 production by the later (Elias A. Said et al. 2009).

Conclusion

The deployment of the new life-extending cancer drugs is needed to be measured for its efficacy. The effect of drugs may be detected through the detection of the low amount of the secondarily associated biomarkers of cancer. The up-regulation of PD-L1 may allow cancers to evade the host immune system. Thompson RH in 2004 found that on analysis of 196 tumor specimens from patients with renal cell carcinoma found that high tumor expression of PD-L1 was associated with increased tumor aggressiveness and a 4.5-fold increased risk of death. The Ovarian cancer patients with higher expression of PD-L1 had a significantly poorer prognosis than those with lower expression. PD-L1 expression correlated inversely with intraepithelial CD8+ T-lymphocyte count suggesting that PD-L1 on tumor cells may suppress anti-tumor CD8+ T cells (Hamanishi J, et al., 2007). Following the FDA approval of some PD-1 inhibitors for cancer treatment, clinical trials have begun for PD-L1 inhibitors (http://www.medpagetoday.com, 2015). The effect might be tumor type dependent; a study on patients with non-small cell lung cancer showed that greater PD-L1 protein and mRNA expression is associated with increased local lymphocytic infiltrate and longer survival(Velcheti V, Jan 2014). The various oncologists have the different opinion in use of the detection of the immunogenic biomarkers with cancers.

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