The Applications and Prospects of Blockade of Programmed Death—1 Antibody in the Process of Treating Colorectal Cancer

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Abstract. Nowadays, malignancies has become the second killer in the world. In America, the colorectal cancer is the second major cancer among all kinds of malignancies. Recently, the antibody, PD-1 has been applied to several types of cancers, like lung cancer, cancer of liver, and melanoma etc., so has colorectal cancer. According to clinical researches, the PD-1 antibody therapy has distinctive effects on the MMR(mismatch repair) deficient colorectal cancer, neither does the non-MMR deficient colorectal carcinoma. In addition, the mechanizations of the process using PD-1 antibody to cure the MMR deficient colorectal cancer are still unknown. In this article, we summarize the evolutions and present situations of the researches about PD-1 antibody which involves in the cure for colorectal cancer and discuss the principles of it. Apart from that, the possibilities that PD-1 antibody will be applied to the treatment of non-MMR deficient colorectal cancer are also forecasted.

1. Forewords

By retrieving the majority of English articles and a few Chinese articles dating back from 2012 to 2016 and covering different subjects including immunology, genetic engineering and cytobiology, the purpose of this review is that exploring the reasonable mechanizations of PD-1 antibody therapy related to the non-MMR deficient colorectal cancer and epitomizing the current achievements of these journals. Taking a panoramic view of the articles, the professors of these articles announce the expression level of PD-1 and PD-L1(ligand) in the colorectal carcinoma in details, but none of them put forward the principles of the process that human beings apply the PD-1 antibody to colon cancer, both the limitations of the antibody using for this sort of cancer and its solution.

2. Interpretations of related concepts

PD-1(blockade of programmed death-1), an inhibitory receptor expressed by T cells, can overcome immune resistance[1], PD-1 antibody, a kind of mAbs(monoclonal antibodies) can combine with PD-1, reducing the immune resistance of PD-1 so that the T cells can recognize and kill the tumor cells.

MMR deficient(mismatch repair), actually, it is DNA mismatch repair, MMR system is a big family, which are made up of many kinds of genes, whose functions are correcting the mismatches of DNA. In this system, there are two major repairing genes-MLH-1 and MSH-2 that are in charge of the most part of fixing work. The variation of the two genes’ expression predicts the MMR deficiency and microsatellite instability (MSI).

MSI(microsatellite instability), it causes by the mutation of genes and methylation of DNA. Because of these two changes, some parts of the MMR genes have lost, as a result, the repetitive sequences of microsatellite insert or absent. Finally, the length of the microsatellites has been changed.

CIN(chromosomal instability), it means the changes of structure and quantity about chromosome[2].
3. Causes and mechanizations of colorectal carcinoma

The causes of colorectal cancer are classified as two kinds of pathways, one is that because of the chromosomal instability (CIN), the oncogenes such as Kraf, Raf have been activated, while the anti-oncogenes are out of functions. This abnormal expression accumulates constantly, leading to enterocytes’ transformation of malignancies whose procedure starts from adenoma and end with adenoma carcinoma. The other is called serrated polyps pathway. The former pathway is responsible for 85 percent of the CRC (colorectal cancer) patients, the latter contributes to 15 percent. Furthermore, about 90 percent of this 15 percent of patients are caused by hereditary non-polyposis colorectal cancer, (HNPCC) and about 10 percent belongs to metastasis colorectal carcinoma. Both of HNPCC and metastasis colorectal cancer owe the incentive to microsatellite instability (MSI), but their mechanizations of MSI are different. In the HNPCC, as the result of mutations on MMR gene system, especially the two genes- MSH-2 and MLH-1, take up 90 percent of mutant totality of MMR gene system. In terms of metastasis colorectal cancer, for overexpression of promoter CIMP which is contained by MLH-1 gene, the table genes will be silent, leading to MSI. This process is regulated and controlled by MAPK/ERK signal path, besides, the BRAF gene is an important regulating factor in it. Therefore, the mutation of BRAF can trigger MSI.

4. Expression of PD-1 and PD-L1 in the MMR deficient colorectal cancer

4.1 PD-L1 expression

By using immunohistochemistry, the scientists research on 181 cases of colorectal cancer and conclude that PD-L1 is expressed in different kinds of MMR deficient colorectal carcinoma, such as BRAF mutation, KRAS mutation and so on. On multivariate analysis, PD-L1 expression was associated with increased CD8 and TBET-positive tumor-infiltrating lymphocytes, medullary phenotype, poor differentiation, microsatellite instability, BRAF mutation (P<0.001 for each), and a lower frequency of KRAS mutation (P=0.012)[3]. Besides, it was associated with medullary morphology and frequent CD8 positive tumor-infiltrating lymphocytes, suggesting adaptive immune resistance[4]. These findings support the role of PD-L1 expression in providing normally immunogenic colorectal carcinoma a means of immune evasion[5].

4.2 The relationship between recurrence-free survival and expression of PD-1 and PD-L1

With the help of a pilot study and tissue microarray, the scientists made a conclusion that PD-1/PD-L1 expression stratified recurrence-free survival in an inter-dependent manner: an association between high PD-L1-positive tumor-infiltrating lymphocytes and improved recurrence-free survival (P=0.041) was maintained only when the tumors had low-level PD-L1 expression (P=0.006); patients whose tumors had both high PD-L1-positive tumor-infiltrating lymphocytes and high PD-L1 expression had a significantly worse recurrence-free survival (P<0.001)[6].

5. Enhancements and reformations about the PD-1 antibody therapy

5.1 Enhancements of the effects about PD-1 antibody

The researches on the effects of PD-1 antibody indicate that in terms of colorectal cancer, the objective responses rate of PD-1 antibody is 62 percent. Considering the proportion of MMR deficient patients only take ups 10-15 percent of totality, the clinical value of using PD-1 antibody only seems a little deficient, so scientist find a series of approaches.
TLR7/8 agonist administration alone markedly enhanced antitumor responses in a selected tumor model and the combined treatment with PD-L1 blockade and a TLR7/8 agonist further amplify their effects[7]. The reason for the discovery is that TLR7 agonist(Tlr7a) has the ability of strengthening the reproduction of CIK cells. After the activation of this agonist, the execution of CIK cells on killing the tumor cells is stronger [8].

The scientist Yingjuan June Lu’s preliminary results suggest that folate-targeted chemotherapeutics may also be enhanced by PD-1/PD-L1 blockage by means of overcoming tumor-mediated immune suppression[9].

Apart from that, in the experiment of professor Xiaoran Wu showed that BGB-A317, a new PD-1 antibody led to significantly higher IFN-γ production than that in nivo and pembro (nivo and pembro are both PD-1 antibodyies) treated groups at concentration levels of 0.1, 1 and 10 μg/mL[10].

Also, BGB-A317 showed better activation of TILs in the liver metastasis TME where macrophages were more abundant[11].

These findings demonstrated that BGB-A317 exhibits potent TILs activation in ex vivo assay, which support its clinical development for the treatment of human cancers[12].

5.2 Evolution of testing methods on results of PD-1 antibody treatment

Colon tumors with defective DNA mismatch repair (dMMR) have a well-characterized phenotype and accounts for 15% to 20% of sporadic colon cancer as well as those colon cancer patients with Lynch syndrome. So, at first, the presence of dMMR seems to be a favorable prognostic marker[13].

Multivariate analysis revealed that Immunoscore was superior to microsatellite instability in predicting patients’ disease-specific recurrence and survival. These findings indicate that assessment of the immune status via Immunoscore provides a potent indicator of tumor recurrence beyond microsatellite-instability staging that could be an important guide for immunotherapy strategies[14]. Immunohistochemistry has shown utility as a predictive marker for response to anti-PD-1 therapies. This utility, however, remains to be determined in colorectal carcinoma[15].

6. Discussions of the principles for PD-1 antibody applied to the treatment of MMR deficient colorectal carcinoma

Human cancers harbor numerous genetic and epigenetic alterations, generating neoantigens that are potentially recognizable by the immune system[16]. Although an endogenous immune response to cancer is observed in preclinical models and patients, this response is ineffective, because tumors develop multiple resistance mechanisms, including local immune suppression, induction of tolerance, and systemic dysfunction in T-cell signaling[17-20]. Moreover, tumors may exploit several distinct pathways to actively evade immune destruction, including endogenous “immune checkpoints” that normally terminate immune responses after antigen activation or both[21].

As I said on the above, in the process of the normal colorectal cancer cells’ proliferation and breaking up, DNA may happen mismatching. At this time, it needs the MMR gene system to repair it, but the two major genes-MSH-2 and MLH-1, have been mutant, so they lost the ability of mismatch repairing. At last, the normal colon cells reproduce unusually, turning tumors and the proteins which are expressed by the two major genes-MSH-2 and MLH-1, express abnormally, changing into other proteins. These variations become the signals to activate T cells, CD45 Ro cells and CD8 cells that prevent tumors from growing.

Programmed death-1 (PD-1) is a key immune-checkpoint receptor expressed by activated T cells, and it mediates immunosuppression. PD-1 functions primarily in peripheral tissues, where T cells may encounter the immunosuppressive PD-1 ligands PD-L1 (B7-H1) and PD-L2 (B7-DC),
which are expressed by tumor cells, stromal cells, or both[22-25]. Inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical antitumor activity[26-28]. When PD-1 antibodies combine with PD-1 and PD-L1, the secreting of them has been decreased and their interaction has been inhibited, then T cells and other immune lymphocytes could swallow and clear the tumor colorectal carcinoma cells.

7. **Prospects of the possible applications on the non-MMR deficient colorectal cancer using PD-1 antibody**

The cause of non-MMR deficient is chromosomal instability(CIN). In terms of the mechanization that CIN triggers colorectal cancer, there are two hypotheses-mutation and CIN hypotheses. The people who support the mutation hypothesis hold the view that the constitution of some appropriate mutant genes is too enough for occurrence of colorectal cancer. CIN is just a consequence of canceration and phenomenon of the final period. Weinberg group did an experiment trying to justify this assumption[29]. According to this hypothesis, we must testify whether the tumors reproduced in this situation yield PD-1 or PD-L1 or not. Only in this way, can we decide to use anti-PD-1 or not. The CIN hypothesis, maintains that the structure and quantity of chromosome have changed, leading to the colorectal cancer. The essence of CIN is the augmentation or reduction of genes exponentially. It refers to several or many different genes and these genes are not MMR genes. As far as I'm concerned, the possibility of using PD-1 antibody to cure this kind of colorectal cancer seems vague.

8. **Summary**

This review summarizes the expression of PD-1 and PD-L1, the enhancement of PD-1 antibody and mechanization of colorectal cancer. In addition, it also discusses the principles of PD-1 antibody on treating the colorectal carcinoma and possibility of anti-PD-1 therapy applied to non-MMR deficient colon cancer.

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