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Natural Killer Cells (NK cells) Based Immunotherapy in Treatment of Cancer: Current Progression and Remained Challenges

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Abstract: Natural Killer Cells (NK cells) based immunotherapy involving a variety of immune checkpoint inhibitors (ICIs) is becoming increasingly common and has achieved considerable success. However, at the same time, it also faces some huge burning problems. Cancer immunotherapy with NK cells enables the precise elimination of cancer cells. Besides, NK cells can be massively expanded in vitro and do not lead to graft-versus-host-disease (GVHD). Furthermore, ICIs are capable to augment the tumoricidal capacity of NK cells. These characteristics make NK cells dominated immunotherapy a key player in cancer treatment.

Keywords: Natural Killer Cell (NK Cell); Immune Checkpoint Inhibitors (ICIs)

Introduction

In the past 20 years, a large number of researches have been accomplished to accelerate the discovery and development of biological immunotherapy and found that NK cells have a unique characteristic among immune cells that they can rapidly eliminate multiple adjacent cells which display surface markers associated with the carcinogenic transformation [1]. Furthermore, NK cells are natural lymphocytes with strong cytotoxicity and are therefore key members of mediating anti-tumour immunity [2]. However, in the process of fighting against the immune system, cancer cells have evolved a series of competencies to resist the immune system. For instance: (1) Cancer cells are born with the capacity to escape immune elimination[3], such as by reducing their immunogenicity[4]; (2) Tumour can inhibit the function of immune system via a variety of mechanisms to ensure its survival[5], such as the formation of a specific immunosuppressive microenvironment[6]. Therefore, NK cell-based immunotherapy has been widely concerned. The low immunogenicity of NK cells makes them be focused by oncologists [7]. The researchers are exploring how to detect tumour cells that are masquerading as normal cells and eliminate them.

This review will focus on the discovery and development of molecular checkpoint inhibitors of NK cells, summarize some researches that are expecting to improve tumour reduction effect and cope with drug resistance through combination therapy, and analyse the challenges faced by current immunotherapy based on NK cells.

1. Molecular checkpoints

1.1 PD-1 and PD-L1

PD-1 is expressed on NK cells and PD-L1 is on tumour cells. The combination of PD-1 and PD-L1 leads to the reduction of NK cell response and even the loss of the ability to eliminate tumour cells. Blocking the two molecular sites PD-1 and PD-L1 triggers a powerful response of NK cells [2]. Currently, anti-PD-1/PD-L1 monoclonal antibodies have been widely utilized in cancer treatment. However, this therapy only shows efficacy in a small percentage of cancer patients, and there is still a large number of the patients with tumour cells and NK cells which are resistant to this kind of ICIs[8]. Consequently, they show low reactivity or even no response, leading to unsatisfactory therapeutic effectiveness.

PD-1 and PD-L1 are two pioneers of tumour immunotherapy. However, due to their limitations in clinical treatments are gradually manifested and amplified, the exploration of new molecular examination sites is quite urgent. Hsu et al. (2018) indicate that local injection of PD-1 or PD-L1 blockades can reduce systemic side effects compared with systemic injection [2]. However, the article does not indicate what particular side effects can be caused by these two molecular blockades and the specific proportion of the patients undergo each side effect. Side effects can also be a driving force in exploring new molecular checkpoints so that patients will have substantial alternative drugs to select, which is the key to overcoming drug resistance. While André et al. (2018) pointed out the resistance of cancer patients to anti-PD-1/PD-L1 monoclonal antibodies [8], but they did not provide the exact percentage of the patients with innate or later developed resistance to ICI in clinical practice.

1.2 NKG2A

The research by André et al., (2018) aimed to discover an innovative ICI to make up for the defects of previous cancer immunotherapy approaches (e.g., PD-1 or PD-L1 blocker) and found that the combination of HLA-E on the surface of tumour cells and NKG2A on NK cells leads to NK cells' loss of their tumour-killing ability, while anti-NKG2A mAb can specifically bind to NKG2A to induce the high reactivity of NK cells to tumour tissues[8]. Immunotherapy with the participation of anti-NKG2A mAb has significantly improved the therapeutic effect of head and neck squamous cell carcinoma (about 31%) [8]. In support of this conclusion, Kamiya, Seow, Wong, Robinson & Campana (2019) conducted a research and found that tumour cells show drug resistance by connecting HLA-E to NK cell inhibitory receptor CD94/NKG2A, and developed an approach for mass production of high-function NK cells lacking NKG2A with retrovirus[9]. The researches carried out by these two teams have obvious advantages. André et al., (2018) summarizes the side effects associated with NKG2A in combination therapy, and give the specific proportions of patients with side effects[8]. However, Kamiya, Seow, Wong, Robinson & Campana (2019) do not mention the possible side effects of infusion of specially designed high-function NK cells lacking NKG2A. At present, both of the results of these studies have been clinically applied, and a large amount of clinical data have been obtained, which is helpful to explore the possibility of further improvement.

1.3 CCL5 and XCL1

The protagonist of the research by Böttcher et al., (2018) is the conventional type 1 dendritic cells (cDC1), a key member of anti-tumour immunity, and found that the recruitment of cDC1 in tumours depends on NK cells, which can secrete CCL5 and XCL1, the chemical inducers of cDC1[10]. Tumour derived prostaglandin E2 (PGE2) can impair the activity of NK cells and reduce the production of related chemokines, resulting in immune escape of cancerous cells [10]. Furthermore, CCL5 and XCL1, two newly discovered molecular checkpoints, can be used in cancer treatment [10]. So it is likely to generate a new branch of oncology based on this theory. Moreover, cDC1 has more key roles in tumour immunity[11]. cDC1 activates NK cells, CD8+ T cells (CTL) and a series of cytotoxic lymphocytes, which indicates that the function of NK cells and cDC1 complement each other, so it is significant to search for a way to prevent tumour-derived PGE2 from damaging NK cells' function[11]. The research of Böttcher et al., (2018) is still in the early stage, and the anti-tumour mechanism of molecular checkpoints explored by them is obviously different from that of traditional types. However, the research does not specifically point out the how CCL5 and XCL1 can be applied to tumour treatments and does not mention the research direction of the solution to the problem of tumour-derived PGE2 impairing NK cells' function. On the other hand, the function of cDC1 in tumour immunity is far more than activating NK cells, CTL and cytotoxic lymphocytes.

2. Combination therapy

2.1 NK cells combined with traditional tumour therapy

The combination of radiotherapy and NK cell systemic therapy effectively improves the prognosis of patients with solid tumours[12]. Besides, an earlier study also found that the immune cells were more likely to penetrate the tumour microenvironment (TME) after a certain dose of radiation[13]. Based on their theories, a research by Kim et al. (2020) aimed at exploring whether the combination of systemic therapy with NK cells activated in vivo and local radiotherapy can improve the efficacy in treating human triple-negative breast cancer (TNBC) found that the combination effectively inhibited the growth of the tumour and promoted the penetration of NK cells into solid tumours[14]. This study not only monitored the growth of carcinoma in situ but also recorded the probability of tumour metastasis events[14]. However, whether the results of this study on breast cancer can be applied to tumours in other parts of the body is still unknown, therefore further research is of great necessity. Another similar study by Kokowski et al. (2019), which explored the efficacy of the combination of radiotherapy, chemotherapy and NK cells in treating non-small cell lung cancer (NSCLC), obtained similar conclusions -- the combination of PD-1 antibody inhibition, mhsp70 targeted NK cells and radiochemotherapy (RCT) significantly improved the patients' tolerance and the induction effect of anti-tumour immunity[15]. However, the sample size of this study was insufficient, therefore, more randomized trials are necessary to further verify this conclusion. Both these two studies indicate that NK cells have great potentiality in combination with traditional therapies[14, 15].

2.2 Combined application of inhibitors for different molecular checkpoints

With the more in-depth research on NK cells and immunotherapy, more molecular checkpoints have been discovered, and the drugs targeting these molecular checkpoints have sprung up. This brings great potentiality for another category of combination therapy involving NK cells.

One research recognized a new molecular checkpoint that can lead to NK cell inactivation and generated the corresponding monoclonal antibody (anti-NKG2A mAb)[8]. The research detected the efficacy of anti-NKG2A mAb alone and combined it with anti-PD-x or anti-EGFR antibodies and showed that the combination of two or more immunosuppressants could evidently impede the expansion of the tumour and improve therapeutic efficacy[8]. Another research[16] achieved similar results in the experiment of combining ICIs. Their experiment was based on the use of PD-1 and TIM-3 blockers combined with IL-21 to treat MHC-I deficient tumours and evaluate the efficacy. The results showed that contrasted with PD-1 or TIM-3 blockers alone, the antitumor activity of NK cells was significantly improved by the combined use[16]. Although the latter experiment was interfered by other drugs (IL-21), both of them pointed out the direction and possibilities for the next stage of tumour combination therapy[8, 16].

Conclusion

NK cells are constantly being explored and are occupying a dominant position in tumour immunotherapy. This article summarizes some of the molecular checkpoints related to NK cells and reviews their current clinical and experimental applications. Traditional ICIs are losing their capacity in treating drug-resistant tumours. Therefore, discovering more innovative immune checkpoints is necessary[8]. Recent discoveries suggest that the functions of immune checkpoint include activating suppressed NK cells in TME and preventing the sites on NK cells and tumour cells from binding to each other to cause inactivation. Moreover, it can be utilized to generate chemokines to recruit tumour killing cells.

While the list of immune checkpoints has been significantly expanded, combination therapy has been applied to address drug resistance. However, the quantity of experiments and the participants involved is still insufficient. Currently, the large amount of data on safety, side effects and other aspects is required to prove the usability of combination drugs. Furthermore, exploration of the possibility of combining multiple ICIs with traditional tumour therapies and other drugs should be continued.

Most of the current research on NK cell-based immunotherapy are not ground-breaking. Therefore, gathering clinical data related to the feasibility and side effects of various immunological therapies in treating tumours of different histological types and locations, and how to progress the current unsatisfactory effectiveness of NK cell-based immunotherapy is necessary.

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