Review

Research progress in immunotherapy of pancreatic cancer

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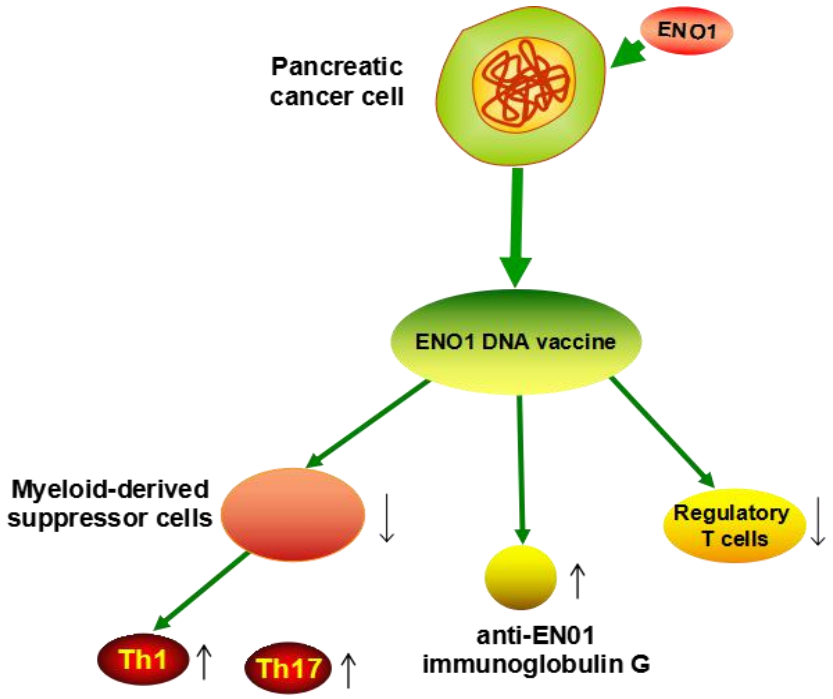
Highlights:

This paper made a review about the basic research and clinical research progress in immunotherapy of pancreatic cancer. It provided a reference for clinical treatment of pancreatic cancer. Traditional Chinese medicine as a traditional treatment method has great potential in enhancing the patient's immunity and anti-tumor.



Citation: Tang Y, Zhang HY, Zhou XL. Research progress in immunotherapy of pancreatic cancer. TMR Integrative Medicine 2017, 1(1): 2-8.
DOI: 10.12032/TMRIM201701111
Submitted: 12 January 2016, **Accepted:** 25 July 2016, **Online:** 27 October 2016.

Abstract

Pancreatic cancer is among the most lethal malignancies resistant to conventional therapies. The urgent need for new therapies has turned the spotlights on immunotherapy. In recent years, a growing body of evidence has already been gathered regarding the efficacy of genetic engineering modified T-cells, checkpoint inhibitors of T-cells, killer cells induced by dendritic cells and cytokine in patients with pancreatic cancer. Cryoimmunotherapy in situ and extra-tumor and immunotherapy combined with chemotherapy could also increase the effectiveness. Research of pancreatic cancer vaccine has made some progress. The immunity enhancing function of some traditional herbs have been reported, such as Ginsenoside Rg3, which could enhance T-cell subsets and NK cell activity in pancreatic cancer patients with chemotherapy.

Keywords: Pancreatic cancer, Modified T-cells, Checkpoint inhibitors, Killer cells, Immunotherapy plus cryotherapy, Immunotherapy combined with chemotherapy, Traditional herbal medicine

摘要

胰腺癌是恶性程度最高的肿瘤，并且对常规治疗无效。近年来，更多研究关注于基因工程修饰 T 细胞、T 细胞检测点抑制剂、树突状细胞和细胞因子诱导的杀伤细胞对胰腺癌的治疗作用；胰腺原位和瘤外肿瘤冷冻免疫治疗，免疫治疗联合化疗也可增强抗肿瘤的作用；胰腺癌疫苗研究也取得一定进展。现代药理学研究也发现中草药的免疫增效作用，比如人参皂苷 Rg3 能够增强胰腺癌化疗病人 T 细胞亚群和 NK 细胞活性。

关键词：胰腺癌，改良 T 细胞，检查点抑制剂，杀伤细胞，免疫治疗加冷冻治疗，免疫治疗联合化疗，中药

Abbreviations: CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1/PD-L1, programmed death-1/ programmed death ligand-1; CAR-T, chimeric antigen receptor T; PDA, pancreatic ductal adenocarcinoma; CAFs, carcinoma-associated fibroblasts; FAP, fibroblast activation protein; CXCL12, chemokine (C-X-C motif) ligand 12; DC, dendritic cells; MDSCs, myeloid-derived suppressor cells; CIK, cytokine-induced killer cell.

Funding: This study was supported by National Natural Science Foundation of China (81341068).

Competing interests: The authors declare that there is no conflict of interests regarding the publication of this paper.

Executive Editor: Jian Hao, Xiao-dong Wang

Introduction

Pancreatic cancer is the most lethal malignancy and the fourth leading cause of cancer-related death, with a 5-year survival of less than 10% [1]. With the intensive study of tumor immune mechanism, the advent of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed death-1/ programmed death ligand-1 antibody (PD-1/PD-L1), chimeric antigen receptor T (CAR-T), tumor immunotherapy once again become the focus of attention [2-4]. In this paper, we made a review about the research progress in immunotherapy of pancreatic cancer.

1. Basic research

1.1 Individual immunotherapy

Immune cells modification

In recent years, scientists attempted to modify the immune cells by genetic engineering to increase the immune effect on the tumor.

A-enolase (ENO1), a glycolytic enzyme, is detected in more than 60% of patients with pancreatic ductal adenocarcinoma (PDA). Cappello et al. injected and electroporated a plasmid encoding ENO1 (or a control plasmid) into KrasG12D/Cre (KC) mice and KrasG12D/Trp53R172H/Cre (KPC) mice. They found that the ENO1 vaccine induced antibody and a cellular response and increased survival times by a median of 138 days in KC mice and 42 days in KPC mice compared with mice given the control vector. Further study of its mechanism showed that the vaccinated mice had increased serum levels of anti-ENO1 immunoglobulin G, which bound the surface of carcinoma cells and induced complement-dependent cytotoxicity. ENO1 vaccination reduced numbers of myeloid-derived suppressor cells and T-regulatory cells and increased T-helper 1 and 17 responses (Figure 1). ENO1-specific T cells also inhibited the growth of human pancreatic cancer xenograft tumors in mice, compared with the control group. The median overall survival of KPC mice was prolonged (138 days vs 42 days) [5].

Maliar et al. engineered T cells with a chimeric antigen receptor (CAR) with antibody-defined specificity for a target expressed on cancer cells. Then Maliar et al. adopted the modified T-cells to the primary or transplanted mice model of pancreatic cancer. They found that the re-directed T-cells could target pancreatic cancer antigen and clear the tumor and suppress tumor metastases. Using SCID mice with different pancreatic cancer xenografts as the experimental model, the researchers injected the genetic engineering T cells to the mice model and found that specific T cells which contained CD24 and Her2/neu could completely remove the tumor from most animals [6].

Rossi et al. found that constructs of bispecific antibodies (bsAbs) to redirect effector T cells for the targeted killing of tumor cells have shown considerable promise in both *vitro* and *vivo* studies. The single-chain variable fragment (scFv)-based formats, including bispecific T-cell engager and dual-affinity re-targeting, which provide monovalent binding to both CD3 on T cells and to the target antigen on tumor cells, can exhibit rapid blood clearance and neurological toxicity due to their small size (~55 kDa). The vivo experiment of NOD/SCID showed that the T-cells could obviously inhibit the growth of tumor. The potential advantages of this design include bivalent binding to tumor cells, a larger size (~130 kDa) to preclude renal clearance and penetration of the blood-brain barrier, and potent T-cell mediated cytotoxicity. These prototypes were purified to near homogeneity, and representative constructs were shown to provoke the formation of immunological synapses between T cells and their target tumor cells in vitro, resulting in T-cell activation and proliferation, as well as potent T-cell mediated anti-tumor activity [7].

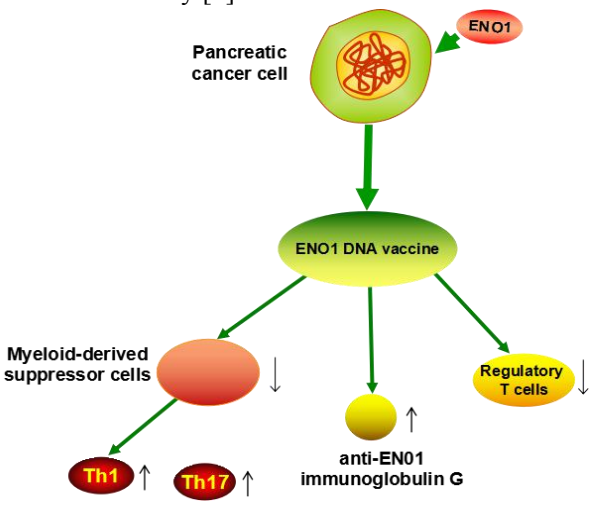


Figure 1 Anti-tumor mechanism of ENO1 DNA

Regulate tumor immune response

Anti-tumor regimens designed based on the immune response of tumors also achieved a significant effect in animal experiments.

Using mice as model, Zhu et al. found that inhibiting signaling by the myeloid growth factor receptor CSF1R can functionally reprogram macrophage responses that enhance antigen presentation and productive antitumor T-cell responses. CSF1R blockade also upregulated T-cell checkpoint molecules, including PD-L1 and CTLA-4, thereby restraining beneficial therapeutic effects. Further study found that PD-1 and CTLA-4 antagonists showed limited efficacy as single agents to restrain PDAC growth, but that combining these agents with CSF1R blockade potently elicited tumor regressions, even in larger established tumors [8].

Feig et al. used mice with in situ pancreatic PDA as model and found that PDA-bearing mice had cancer cell-specific CD8+ T cells did not respond to two immunological checkpoint antagonists that promote the function of T cells: anti-CTLA-4 and α-PD-L1. Immune control of PDA growth was achieved, however, by depleting carcinoma-associated fibroblasts (CAFs) that express fibroblast activation protein (FAP). They found that chemokine (C-X-C motif) ligand 12 (CXCL12) explained the overriding immunosuppression by the FAP+ cell: T cells were absent from regions of the tumor containing cancer cells, cancer cells were coated with the chemokine, CXCL12, and the FAP^+ CAF was the principal source of CXCL12 in the tumor. Administering AMD3100, a CXCL12 receptor chemokine (C-X-C motif) receptor inhibitor, induced rapid T-cell accumulation among cancer cells and acted synergistically with α-PD-L1 to greatly diminish cancer cells, which were identified by their loss of heterozygosity of Trp53 gene [9].

1.2 Immunotherapy combined with chemotherapy

Chemotherapy is commonly treatment either for postoperative adjuvant or advanced cancer currently. In the past, chemotherapy was often believed to cause damage to immunity. Current studies demonstrated that immunotherapy combined with chemotherapy could enhance the anti-tumor effect.

Bauer *et al* made the pancreatic cancer mouse model by subcutaneously injecting Panc02 into C57BL/6 mice and treated the mice with gemcitabine (GEM) plus dendritic cells (DC) vaccine. Bone marrow-derived DCs were loaded with soluble OVA protein (OVA-DC). Animals received gemcitabine twice weekly. The results showed that GEM had no impact on the response of CD8+ T-cells and B cells induced by DC vaccine, but improved the effectiveness of the vaccine in the treatment of pancreatic cancer. Interestingly, gemcitabine significantly suppressed the vaccine-induced frequency of antigen-specific CD8+ T-cells and antibody titers. Despite reduced numbers of tumor-reactive T-cells in peripheral blood, in vivo cytotoxicity assays revealed that cytotoxic T-cell (CTL)-mediated killing was preserved. In addition, gemcitabine facilitated recruitment of CD8+ T-cells into tumors in DC-vaccinated mice. T- and B-cell suppression by gemcitabine could be avoided by starting chemotherapy after two cycles of DC vaccination [10].

Multiple immunoregulatory cells are involved in pancreatic cancer, including regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs) that limited the effectiveness of antitumor immunotherapy for pancreatic cancer patients or tumor-bearing mice. Regulation of these sub-groups could enhance the anti-tumor immunity. Ghansah studied the tumor immunotherapy based on removal of immunomodulatory cells and enhanced DC function using mice model of pancreatic cancer, they found that Tregs and MDSCs of treated group decreased significantly. Cleared Tregs alone or combined with DC-based vaccines had no effect on growth of pancreatic cancer or overall survival. GEM significantly decreased the percentage of spleen MDSCs in tumor-bearing mice, but did not enhance overall survival. However, combined with GEM and then treated with DC vaccine could make the growth of tumor in pancreatic cancer-bearing mice delayed and improve the overall survival. These results suggested that GEM could also decrease these immune-modulating subgroups in pancreatic cancer patients. Combined DC-based vaccines with GEM can improve the therapeutic effect in pancreatic cancer patients [11].

Taking the normal immunized mice as a model, Bunt, SK / 2013 used rosiglitazone combined with GEM to reduce pancreatic cancer immunosuppression and regulatory T cells to produce pancreatic cancer suppression models by implanting pancreatic cancer cells either subcutaneously or in situ. Compared with the GEM alone, the combined regimen significantly reduced tumor progression and metastasis, enhanced tumor cell apoptosis, and prolonged survival. Further mechanism studies indicated that rosiglitazone largely changed immunosuppressive mediators by limiting early MDSC proliferation and intra-tumor regulatory T cells. Combination therapy improved T cell subsets by potentiating circulating CD8+ T cells and intratumoral CD4+ CD8+ T cells and limited regulatory T cells simultaneously [12].

1.3 Immunotherapy combined with other ways

Meng et al. treated melanoma and pancreatic carcinoma in syngeneic mice with ionizing radiation (IR) combined with the poly (ADP-ribose) polymerase inhibitor (PARPi) veliparib to inhibit DNA repair and promote accelerated senescence. Further, they discovered that senescent tumor cells induced by radiation and veliparib express immunostimulatory cytokines to activate CTLs that mediate an effective antitumor response. When these senescent tumor cells were injected into tumor-bearing mice, an antitumor CTL response was induced which potentiated the effects of radiation, resulting in elimination of established tumors. Applied to human cancers, radiation-inducible immunotherapy may enhance radiotherapy responses to prevent local recurrence and distant metastasis [13].

2. Clinical research

Dendritic cell (DC)-based and cytokine-induced killer cell (CIK)-based therapy can induce specific antitumor T-cell responses. This clinical pilot study examined the safety, the feasibility, and the outcome of tumor-specific immunotherapy for patients with advanced pancreatic adenocarcinoma. Qiu et al.

injected DC and CIK into 14 patients with unrespectable stage III / IV pancreatic cancer to explore the safety and efficacy of this immunotherapy. Alpha-Gal epitopes were synthesised on pancreatic carcinoma cell membranes with α 1,3-galactosyltransferase in vitro. Subsequently, the addition of natural human anti-Gal IgG to the processed membranes resulted in opsonization and effective phagocytosis by DCs, which were co-cultured with newly differentiated CIKs from bone marrow stem cells to generate tumor-specific immune responders ex vivo. Clinical observations showed that 12 patients had strong positive delayed-type IV hypersensitivity to the autologous cancer cell lysate; robust systemic cytotoxicity elicited by interferon (IFN) γ expression by peripheral blood mononuclear cells; and significant increases in CD3+CD8+, CD3+CD45RO+, and CD3+CD56+ cells in peripheral blood lymphocytes after 3 injections. During the follow up, the percentages of CD3+CD8+, CD3+CD45RO+, and CD3+CD56+ cells returned to the normal range at 6 to 9 months after the third injection and IFN γ expression in the cells stayed at the higher level from the third injection to 24 months after the treatment [14].

In recent years, CAR-T Immunotherapy showed an amazing therapeutic effect in hematologic malignancies [15]. Researchers at the Pennsylvania University produced CAR-T cells that resistant to pancreatic cancer and administered it to six patients with refractory disease [16]. The metastasis focus in one of the six patients disappeared. Four patients suffered disease progression and two patients were stable for 3.7 months and 5.3 months, respectively. Tumor metabolic activity in the four patients was also reported in the study. The study found that the specialized adapted T-cells, namely CAR-Tmeso cells (for the specific antigen Mesothelin), could move to the tumor site of the patient. In the study, 6 patients received CAR-Tmeso cells. Observed adverse effects included dysglycemia, abdominal pain and fatigue. No off-target and tumor-independent toxicity was found and cytokine release syndrome was not serious. CAR-T was a novel cell therapy that had been appeared for many years whereas was improved to use in clinics only in recent years. It had a significant effect in the treatment of acute leukemia and non-Hodgkin's lymphoma and was regarded as one of the most promising cancer therapies. Just as all of the technologies, CAR-T technology go through a long evolutionary process, and CAR-T technology is becoming more mature under the series of evolution.

Shindo et al. treated 42 pancreatic cancer patients who underwent surgical or postoperative recurrence with GME combined adoptive immunotherapy [17]. DC were cultured with granulocyte-macrophage colony stimulating factor, interleukin-4 and tumor necrosis factor-a. MUC1-mRNA was transfected into mature DC by electroporation. MUC1-CTLs were induced by co-culturing with YPK-1+ human pancreatic cancer cell lines and interleukin-2. Patients were treated with GEM at the same time administered with MUCl-DCs intradermally and MUC1-CTLs intravenously. The median overall survival of the patients was 13.9 months and the one-year survival rate was 51.1%. Chung et al. conducted a phase II trial of CIK (clinicalTrials.gov number NCT00965718) [18]. A total of 20 advanced pancreatic cancer patients with GEM resistant were treated with second-line therapy. Peripheral blood samples from each patient were collected. CIK cells were produced by means of co-cultured with anti-CD3 monoclonal antibody and interleukin-2 and were given to the patients 10 times by intravenous injection. The median overall survival (OS) was 26.6 weeks (95% CI, 8.6-44.6), with a disease control rate of 25% (4/16), the median disease progression free survival (PFS) was 11 weeks (95% CI 8.8-13.2). The 3-degree toxicities included general weakness in 2 patients and thrombocytopenia in 1 patient. 4-degree toxicity was not detected.

Niu et al. retrospectively analyzed the effects of cryotherapy combined immunotherapy on patients with pancreatic in situ and extra-pancreatic tumors [19]. A total of 106 patients, 31 patients treated with cryotherapy combined immunotherapy, 36 patients treated with cryotherapy, 17 patients treated with individual immunotherapy, 22 patients treated with individual chemotherapy. The results showed that the median overall survival of cryotherapy combined immunotherapy group and cryotherapy group was 13 months and 7 months, respectively, both of which was longer than that of chemotherapy group (3.5 months, both $P < 0.001$). The median overall survival of cryotherapy combined immunotherapy group was longer than that of cryotherapy group and immunotherapy group（5 months) ($P<0.05$, $P<0.001$). As for cryotherapy combined immunotherapy group and cryotherapy group, the median overall survival of patients with multiple cryoablation was higher than those with single cryoablation ($P=0.0048$, $P=0.041$). Patients with normal immunity had a higher median overall survival than those with immunodeficiency ($P<0.0001$, $P=0.0004$). Cryotherapy combined immunotherapy could significantly improve the overall survival of metastatic pancreatic cancer patients. This indicated that cryotherapy and immunotherapy could mutually promote its anti-tumor effects.

The clinical application of tumor vaccines is a hot spot in immunotherapy of tumors. Hardacre et al. reported the results of a Phase II multicenter, open clinical trial (ClinicalTrials.gov identifier, NCT00569387) which evaluating the application of algenpantucel-L (NewLink Genetics Corporation, Ames, IA) immunotherapy for postoperative

pancreatic cancer patients treated with chemotherapy and radiochemotherapy [20]. The 12-month DFS was 62% and 12-month OS was 86% for 70 patients received gemcitabine with 5-FU modulated radiation therapy plus algenpantucel-L. However, the Phase III study of the vaccine algenpantucel-L (ClinicalTrials.gov identifier, NCT01072981) found that the algenpantucel-L vaccine showed neither significant side effects nor significant efficacy in the 722 volunteers of clinical phase III study. Hashimoto et al. reported a case of patients with stage pT4N0M (-) pancreatic tail cancer, who received TS-1 (100mg / day, 4 courses) combined with polypeptide DC loading with WT1 (Wilms'tumor 1). The DFS time for this patient is 16 months without serious side effects [21]. GVAX® is a granulocyte-macrophage colony-stimulating factor gene-transfected tumor cell vaccine. Combined with low-dose cyclophosphamide, a common anti-cancer drug could enhance the efficacy of the vaccine. The second vaccine CRS-207, a kind of Listeria monocytogenes, was engineered to stimulate the production of mesothelin-protein immune response. High levels of cortisol proteins exist in pancreatic cancer cells. The combination of the two vaccines could stimulate the production of pancreas anti-tumor cell immune response. GVAX induced a broad response to multiple tumor proteins, then CRS-207 stimulated the production of an anti-mesothelin immune response. Le et al. reported a new randomized phase II study of patients with metastatic PDA [22]. 90 patients with metastatic PDA were included in the study and randomized to GVAX treatment sequential CRS-207 treatment (Group A) or GVAX treatment alone (group B). The results showed that the median overall survival of the two vaccine combined treatment group significantly longer than that of GVAX treatment alone (6.1 months versus 3.9 months). One year later, about 24% patients in group A survived, compared with 12% in group B. In the patients who received at least three doses of vaccine (70% of all patients), the median overall survival of patients receiving two doses of GVAX and at least one dose of CRS-207 in group A was 9.7 months, while that of patients treated with GVAX alone was 4.6 months. The side effects of this vaccine were relatively light, could be quickly relieved and did not aggravate after each treatment dose.

3. Chinese medicine

Although many literatures mentioned the Chinese medicine could improve the immunity of tumor patients, there is still few studies deeply observed the mechanisms of immune effect of Chinese medicine on pancreatic cancer patients.

Shaojun Ma et al. used chemotherapy combined with ginsenoside Rg3 (capsule) in pancreatic cancer patients and found that compared with the control group, T cell subsets and NK cell activity increased in patients of the combination treating group [23]. Coixenolide (Kanglaite) (Figure 2) successfully passed the phase Ⅱ clinical trial for pancreatic cancer treatment in the United States and entered Phase III clinical trial approved by the US FDA [24]. In the early study, Mingsan Miao et al. found that Coixan could significantly improve the phagocytosis percentage index of macrophage in the enterocoelia of immunocompromised mice and promote the formation of hemolysin and hemolytic plaque as well as lymphocyte transformation [25].

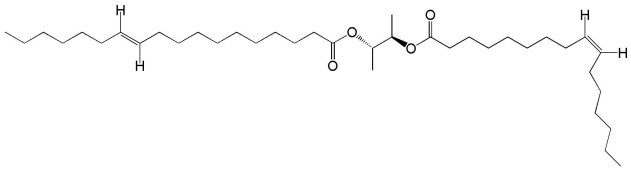


Figure 2 Coixenolide

Conclusion

Early detection is difficult in pancreatic cancer. Suboptimal response to standard therapies remained a challenge. Immunotherapy has the potential to treat patients with PC especially in early stages in patients with residual disease but also in advanced stages. This provides a strong rationale for the development of immune therapy in pancreatic cancer.

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