The Potential use of Dendritic Cell-based Immunotherapy for Treatment of Pancreatic Cancer

Mohamed Labib Salem*

Surgery Department and Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, USA; Zoology Department, Faculty of Science, Tanta University, Egypt

Abstract: Pancreatic cancers are classified as either exocrine or endocrine tumors depending on which type of tissue they arise from within the gland. Endocrine tumors of the pancreas are very rare, accounting for only 5% of all pancreatic cancers. The majority of endocrine pancreatic tumors are functional adenocarcinomas that overproduce a specific hormone. Pancreatic cancer is a devastating disease and has an extremely poor prognosis. Most patients die within a year of diagnosis and the overall 5-year survival rate is <1% despite the use of extensive treatment approaches, including surgery, chemotherapy, and radiation. Therefore, innovative anti-tumor therapies for this group of patients is of a great significance. Recent preclinical and clinical studies demonstrated that immunotherapy, in particular vaccination with dendritic cells (DCs) loaded with tumor antigens, is a potential approach with promising anti-tumor effects. Therefore, augmenting the efficacy of immunotherapy with DCs would significantly improve the health of this group of patients. One strategy to augment DC-based vaccination is the use of potent adjuvants that can induce the full activation and maturation of the injected antigen-loaded DCs and their migration to the tumor draining lymph nodes, the site of antigen recognition by T cells. One of the most potent adjuvants is the microbial products that are recognized by more than 13 toll-like receptors expressed on DCs. This review article will highlight the use of DC-based vaccination toward pancreatic cancer and how it can be augmented by toll-like receptor agonists.

Keywords: Dendritic cells, immunotherapy, pancreatic cancer, T cells, Toll-like-receptor, TLR, vaccination.

INTRODUCTION

1. Pancreatic Adenocarcinoma

A healthy pancreas is important for normal food digestion and plays a critical role in the body's metabolic processes. The pancreas has two main functions, each performed by distinct types of tissue [1-3]. The exocrine tissue secretes pancreatic juices containing enzymes that help break down proteins and fatty food. The endocrine tissue secretes hormones that control how the body stores and uses nutrients. Pancreatic tumors are classified as either exocrine or endocrine tumors depending on which type of tissue they arise from within the gland. Endocrine tumors of the pancreas are very rare, accounting for only 5% of all pancreatic cancers [4-7]. The majority of endocrine pancreatic tumors are functional adenocarcinomas that overproduce a specific hormone. Cancer of the pancreas is the fourth leading cause of cancer deaths in both men and women, with an estimated 37,680 new cases and 34,290 deaths in the USA in 2008 (http://www.cancer.org). Median survival with locally advanced non-metastatic disease is 6-10 months. Patients with metastatic disease have a survival of 3-6 months determined by the extent of disease and performance status, only 20% of patients have tumors confined to the pancreas, 40% have tumors that invade local organs or to regional lymph nodes and 40% have disease that has distant metastases to the liver or other organs [8].

2. Standard Therapy of Pancreatic Cancer

Complete surgical resection offers the only chance for long term cure of this disease. However, even in patients who appear to be completely surgically resected, the overall 5 year survival rate is only 21% with a median survival of 15.5 months [9, 10]. For patients with negative margins and negative nodes, actuarial five year survival in these reports was 40%. For patients with regional lymph nodes involved the 5 year survival was 14% and in patients with positive margins it was 8%. Following surgical resection, combined chemotherapy and radiation given to...
increase the risk of recurrence has been the standard therapy [11]. Metastatic disease patients are treated with chemotherapy with median survival of approximately 6 months. Despite many attempts at combining newer agents, little progress has been made in extending survival [12]. Patients with locally advanced unresectable disease are generally treated with a combination of chemotherapy and radiation therapy with median survival of 6-10 months [13, 14]. Currently for patients with unresectable disease, no metastases and good performance status, 5-FU based chemoradiation is the standard treatment [15]. Single agent gemcitabine has been the standard of care for patients with metastatic disease based on a randomized Phase III trial showing it to be superior to bolus 5-FU [16]. Combinations of gemcitabine with oxaliplatin, cisplatin, or irinotecan have failed to show significant survival benefit compared to gemcitabine alone [17, 18]. The National Cancer Cooperative Network recognizes that because of the poor outcome of patients with every stage of pancreatic cancer, investigational options may be considered for all phases of disease management. Interventions based on immunotherapy could significantly benefit pancreatic cancer patients by specifically targeting the tumor with the potential of developing anti-tumor memory responses.

3. Anti-tumor Immune Responses in Pancreatic Cancer

For many years, the treatment of cancer was primarily focused on surgery, chemotherapy, and radiation. But as researchers learn more about how the body fights cancer on its own, anti-tumor immunotherapies are being developed. In contrast to the antitumor chemotherapy and radiation therapy, which kill tumor cells as well as hurt healthy cells, tumor immunotherapy is based on the capability of T cells to discriminate between self and non-self. To the immune system, however, a cancer cell is different in very small ways from a normal cell. As a result, the immune system largely tolerates cancer cells rather than attacking them [19]. Therefore, anti-tumor immunotherapeutic regimens must not only provoke an immune response, but stimulate the immune system strongly enough to overcome this tolerance [20].

As early as 1977, studies have indicated the presence of active antibody and cellular responses in the majority of patients with pancreatic cancer [21]; these responses were specifically directed against antigens expressed on pancreatic tumor cells [22-30]. Interestingly, these immune responses were not present in patients with chronic pancreatitis [31, 32]. Antibodies detected in the sera of patients with pancreatic cancer have defined a number of antigenic epitopes that are recognized because they are overexpressed, underglycosylated, mutated, or inappropriately expressed in the tumor cells themselves [33-35]. The detection of immunity to autologous pancreatic tumors and allogeneic pancreatic tumor cell lines in patients with pancreatic cancer supports the evidence for the presence of tumor-associated antigens in pancreatic tumors. It also supports the rationale that the immune cells, in particular lymphocytes, of pancreatic tumor patients can significantly respond to tumor antigens and lyse pancreatic tumor cell targets [21]. On the other hand, studies have showed evidence for downregulation of T cell activities in pancreatic tumor, suggesting that this tumor have evolved immune escape mechanisms from the immune cells [36-39]. Therefore, for effective immunotherapeutic treatments capable of eradicating pancreatic tumors, these down-regulatory mechanisms must be blocked.

The possibility to develop tumor-specific immune responses in pancreatic cancer patients as discussed above indicate that by enhancing preexisting immunity, or by eliciting broader immune responses to pancreatic tumor antigens, the patients’ immune systems might be able to arrest tumor growth or even eradicate the established tumors. Indeed, several antigens expressed by pancreatic tumors have been defined [40-43]. Results from both the preclinical and clinical studies have indicated that immunotherapy using these antigens could be a potential approach to the treatment of pancreatic cancer [21, 44, 45]. Potential targets for the immunotherapy of pancreatic carcinoma are antigens such as carcinoembryonic antigen [46-49], HER-2/neu [28-30], MUC-1 [48-56], mutant ras [57, 58], p53 [59, 60], survivin [61], telomerase [62, 63], and gangliosides [64]. Although immunotherapy of pancreatic cancer based on vaccination with these antigens showed promising effects, the results were of a limited clinical efficacy. Although it is not clear why the induced anti-tumor responses after these peptide-based vaccinations are weak, one possible mechanism could be the low numbers of activated antigen presenting cells in the host. Dendritic cells (DCs), the most professional antigen presenting cells, play a central role in shaping the quantity and quality of the anti-tumor immune responses. The success of DC-based vaccination in several types of cancer encouraged recent studies to use this approach in pancreatic cancer, in particular the number and function of circulating DCs in this group of patients have been found to be impaired [65-67].

4. Potential use of DC-based Vaccination in Pancreatic Cancer

4.1. DCs and Anti-tumor Immunity

DCs are believed to be the professional antigen presenting cell type most adept at activating naive T
cells. DCs express all the molecules required for appropriate co-stimulation of T cells, including CD40, CD80, CD86, MHC, and toll-like receptor (TLRs). DCs are also considered as a potential target for gene therapy, where they are thought to play at least three distinct roles [68]: (1) MHC class II-restricted presentation of antigens secreted by neighboring, transfected cells, (2) MHC class I-restricted "cross" presentation of antigens released by neighboring, transfected cells, and (3) direct presentation of antigens by transfected DCs themselves. A number of trials have demonstrated the potency of DCs as vehicles for delivering antigen and achieving a tumor-specific immune response. In principal, DC-based vaccination is based on the generation of DCs from peripheral blood monocytes in vitro with GM-CSF and IL-4 and subsequent maturation with cytokines or TLR agonists [69-71]. After maturation, these cells are loaded with the target antigens and infused back into the host to stimulate anti-tumor T cell responses [70]. Tumor antigen, can be in different forms, including: 1) whole tumor lysate; 2) tumor-associated protein; 3) deoxyribonucleic acid (DNA) encoding a tumor antigen; or 4) antigenic peptides. Recent studies showed that DCs pulsed with a tumor-associated peptide or lysate are effective in treating metastatic melanoma, renal cell carcinoma, prostate cancer, and advanced breast and ovarian cancers [69, 71-77]. Pulsing DCs with peptides, however, has more advantage over the other forms of antigens because: 1) peptides are easily synthesized; 2) they can be loaded directly onto activated (matured) DCs without a prior uptake and processing; and 3) several tumors share antigenic peptides and can be targeted with vaccination with the same peptide. In case of peptide-based loading of DCs, DCs can be activated in vitro with a TLR agonist to upregulate MHC class-I and class-II to increase the binding of peptide. Then, TLR agonist can also be injected upon DC-based vaccination to license the full maturation of the injected DCs in vivo.

4.2. Altered DC Activities in Pancreatic Cancer

With regard to DCs in patients with pancreatic adenocarcinoma, there is typically a paucity of immune cells within the tumor (particularly DCs), and there is a negative correlation between the numbers of CD4+ and CD8+ T-cells, as well as tumor growth and progression [66]. In addition, DC function is impaired in pancreatic cancer patients and the underlying mechanisms are unknown [65]. In vitro studies showed that medium conditioned by a highly metastatic human pancreatic cancer cell line BxPC-3 [BxPC-3 conditioned medium (BxCMI)] can produce IL-6 and G-CSF that induced suppression of DC differentiation, maturation, and antigen presentation in vitro [66, 78]. Interestingly, the levels of the immunosuppressive cytokines, IL-10 and VEGF have been found to gradually decrease during chemotherapy, coinciding with restoration of the impaired immunity of patients with pancreatic cancer [79]. These studies showed also that the ideal times to collect DCs for immunotherapy is after completing each cycle of chemotherapy.

4.3. Preclinical Studies Based on DC Vaccines in Pancreatic Cancer

Given the central role of dendritic cells (DCs) in shaping the quantity and quality of the anti-tumor immunity, DC-based immunotherapy could be a promising approach against pancreatic cancer. DC-based vaccination in preclinical studies has shown promising anti-tumor effects against pancreatic cancer using DCs loaded with different strategies including, α-galactosaccharide [80], total tumor RNA [81, 82], tumor lysates [83, 84], tumor lysate and transfection with the recombinant adenoviral vector encoding IL-18 gene [85], UV-irradiated syngeneic pancreatic tumor cells [86], or allogenic GM-CSF-transfected irradiated pancreatic tumor cells [40, 44, 87-89]. Although, the obtained anti-tumor responses in these studies were of a limited efficacy, DC-based vaccination strategy showed promising effects [80, 81, 86, 90-92].

4.4. Clinical Studies Based on DC Vaccines in Pancreatic Cancer

Because of the impairment of the number and function of circulating DCs in patients with pancreatic cancer as discussed above [65], vaccination with ex vivo generated autologous DCs is a potential therapeutic approach in this group of patients. Indeed, clinical studies showed promising anti-tumor effects after vaccination with ex vivo generated DCs without toxicity [90, 93]. For instance, a complete remission of the liver metastases of pancreatic cancer was observed in a patient whose cancer was refractory to chemotherapy with gemcitabine and endured for 8 months following vaccinations with survivin peptide-loaded DCs [61]. In another study that involved 20 patients with cancer, including pancreatic, hepatocellular, cholangiocellular, and medullary thyroid carcinoma with stage IV disease, were vaccinated in 3-week intervals with immature DCs that were pulsed with autologous tumor lysate and matured with TNF-α [94]. The vaccination was followed by the administration of the adjuvant IL-2 (20,000 U/kg) daily, for 12 days. The vaccination was well tolerated with no physical signs of autoimmunity. DC vaccination induced delayed-type hypersensitivity reactivity in 18 patients and IFN-γ+ T cells were observed in 3 patients, where the objective changes in measurable lesions or tumor markers were evident in 7 of 20 assessed patients. Vaccination with allogenic GM-CSF-secreting tumor alone or in sequence with cyclophosphamide for metastatic pancreatic cancer resulted in significant tumor-specific immune responses without toxicity [95].
Antigen-specific T cells were demonstrated in another study of patients with pancreatic cancer whose T cells were stimulated with autologous matured DCs transfected with total tumor mRNA [81]. Vaccination with DCs loaded with MUC-1 peptide has also been applied as adjuvant therapy in patients with resected pancreatic and biliary tumors [96-99]. Adoptive therapy of in vitro antigen-activated T cells was found to augment the efficacy of vaccination of pancreatic cancer patients with MUC-1-pulsed DCs [100].

Although the obtained anti-tumor responses in these studies were of a limited efficacy, they indicate that DCs loaded with different forms of tumor antigens is a potential immunotherapeutic approach in pancreatic cancer. Several of clinical studies in different clinical setting indicate to the safety of intravenous or subcutaneous administration of immature or mature DCs pulsed with or without different forms of antigens, including peptides or tumor lysates [72, 76, 98, 101-108]. DC vaccination utilized in these studies was safe and well tolerated with minimal toxicity, including mild and self-limiting, grade 1 myalgia, low-grade fever, nausea and vomiting. No grade 3 or4 toxicity was observed in any patient. Importantly, there was no hepatic toxicity nor de novo autoimmune formation was observed, indicating that vaccination with autologous tumor-pulsed DCs generated from peripheral blood is safe and can induce tumor-specific cellular cytotoxicity with achievable clinical responses even in patients with advanced disease.

5. The Potential use of TLR Agonists to Augment DC Vaccines in Pancreatic Cancer

5.1. Limitation of DC-based Vaccination

Although DC-based vaccination of pancreatic cancer as discussed above appears to benefit this group of patients, the obtained results were with limited efficacy. To be capable of killing target tumor cells and exert anti-tumor activity, cytotoxic CD8+ T cells need to recognize antigens by matured DCs, which also provide help after interaction with CD4+ helper T cells [109, 110]. Immature DCs, however, are unable to stimulate T cells and induce tolerance because they lack the co-stimulatory signals required for T cell activation [111]. Although preclinical and clinical studies have shown measurable anti-tumor immune responses after vaccination with exogenous antigen-loaded DCs against pancreatic cancer [80, 81, 90, 91, 112], the results were of a limited efficacy. Migration of ex vivo DCs to lymph nodes is a critical process for efficient antigen presentation and initiation of immune responses. A rapid activation of DCs upon their injection favors their migration to lymph nodes draining the tumor site and facilitates the generation of a measurable anti-tumor responses. Induction of inflammatory cytokines is a prerequisite step for the activation of DCs and their subsequent migration to lymph nodes [113]. Therefore, one reason for the limited anti-tumor efficacy of DC-based vaccination could be attributed to the use of immature or semi-mature DCs and the absence of a potent adjuvant capable of maturing DCs upon their injection.

One of the concerns relating to ex vivo generated DCs, however, is how to ensure effective migration to the T cell areas in the lymph nodes. The migration of DCs from the tissues to the lymph nodes is tightly controlled and involves many different mediators and their receptors. One potential approach to enhance migration of ex vivo generated DCs could be by co-administration of a potent adjuvant such as inflammatory cytokines or TLR agonists [70, 71]. Another approach is the enhancement of migration of ex vivo generated DC vaccines by preconditioning the patient with inflammatory cytokines or TLR agonists.

5.2. Targeting Activation of DCs in vivo by TLR Agonists

DCs are equipped with receptors that sense different microbial products “danger signals” such as TLR agonists [114]. So far about 13 TLRs that can sense different classes of TLR agonists that have been characterized [115]. TLRs are members of a family of transmembrane proteins with an extracellular leucine-rich domain and a conserved cytoplasmic domain homologous to that of the interleukin-1 receptor (IL-1R), termed the Toll/IL-1R homology (TIR) domain [116, 117]. This structure allows TLRs to recognize their specific TLR agonists and activate, via the TIR domain, a series of downstream pathways that result in immune and inflammatory responses [118]. After binding to their specific ligands on innate immune cells, TLRs dimerize and undergo conformational changes which are required for the recruitment of adaptor molecules to the TIR domain [116, 119]. Once the adaptors are recruited, a complex of IL-1R-associated kinases (IRAKs), TRAF6 and IRF-5 is formed that results in the downstream phosphorylation of IκB which in turn frees NF-κB. Unbound NF-κB translocates into the nucleus where it directly regulates the transcription of pro-inflammatory genes. When triggered, TLR signaling induces pro-inflammatory mediators, including cytokines and chemokines, and maturation of DCs [120-122]. These mediators in combination with matured DCs, activate cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, promoting adaptive immunity [117, 121, 123-125].

In our own experience, we have demonstrated in a series of our recent studies the potent adjuvant effects
of the TLR3 agonist poly(I:C) to post vaccination CD8\(^+\) T cell responses to self and non-self antigens and generation of a robust anti-tumor immunity against melanoma and lymphoma [126, 127]. The adjuvant effects of poly(I:C) were more pronounced when the host was pretreated with chemotherapy (cyclophosphamide) [128]. These adjuvant effects of poly(I:C) was mediated by a rapid induction of a plethora of inflammatory cytokines (IL-6, TNF-α, MCP-1 (CCL-2), IFN-γ, IL-12, and IFN-α) coincided with activation of NK cells and DCs [127]. Importantly, these studies demonstrated that depletion of DCs from the host before vaccination with antigen plus poly(I:C) resulted in significant decrease in the antigen-specific CD8\(^+\) T cell responses [129], indicating to the critical role of poly(I:C)-activated DCs in mediation of its adjuvant effects. We found further that the TLR3 agonist can also directly act on T cells [130]. Previous studies have also established the adjuvant effects of several TLR agonists, in particular, TLR3 (poly(I:C)), TLR7/8 agonist (imiquimod), and TLR9 agonist (CpG) agonists, to the anti-tumor CD8\(^+\) T cell responses [122, 127-138]. These beneficial effects of TLR agonists to immunotherapy could be because of their induction of maturation of resident immature DCs at the site of vaccination and their subsequent migration to the draining lymph nodes [139-144].

Taken the above studies together, it appears that TLR agonists are a potential approach to induce activation of immature DCs and maximize their contribution to enhanced T cell responses. Therefore, it is possible that treatment of a host with pancreatic cancer with TLR agonists, in particular the TLR3 agonist poly(I:C), the TLR9 agonist CpG ODN, and the TLR7/8 agonist imiquimod, concomitantly with vaccine with DCs pulsed with single or multiple peptides can induce the maturation of the injected DCs and their migration to draining lymph nodes where effective antigen presentation can occur, resulting in efficacious anti-tumor immunity. Meanwhile, administration of a TLR agonist would also elicit the activation of endogenous NK cells and DCs and their production of inflammatory cytokines, resulting in a beneficial microenvironment that will further enhance the overall anti-tumor immunity. These events may lead to significant clinical responses.

5.3. TLR Agonists as Adjuvants to DC Vaccines Against Pancreatic Cancer

The use of TLR agonists as a potent stimulator of DC-based vaccination in pancreatic cancer as discussed above is likely to be a working hypothesis since treatment of this cancer with other TLR agonists has been found to induce significant anti-tumor effects even in absence of active vaccination. For instance, intratumoral or systemic administration of the TLR2/6 agonist 'macrophage-activating lipopeptide-2' resulted in induction of infiltration of lymphocytes in the pancreatic tumor bed with significant tumor suppression [145]. These studies led to a clinical trial based on the intratumoral injection of this Toll-like receptor-2/6 agonist in patients with pancreatic carcinoma. This treatment resulted in the induction of influx of lymphocytes and monocytes in the tumor, and abolishment of inhibition of NK activity [146]. Furthermore, treatment with the TLR9 agonist CpG-ODN in an orthotopic murine model of human pancreatic cancer induced an improvement of survival of the tumor-bearing mice [147]. These induced anti-tumor effects after treatment with these TLR (TLR2/6 and TLR9) agonists were more effective in combination with the chemotherapeutic drug gemcitabine, the drug of choice in pancreatic cancer. Taken the adjuvant anti-tumor effects of these TLRs with the adjuvant anti-tumor effects of vaccination with antigen-pulsed DCs, it can be suggested that combination of these two modalities would induce higher anti-tumor responses than the use of either of them alone. Although activation of DCs with TLR agonists in vitro is as, previous studies have shown that this in vitro maturation alone is not sufficient to induce therapeutic anti-tumor effects against an advanced bulky tumor and that in vivo adjuvants are a prerequisite to establishment of anti-tumor responses [122, 148, 149]. The advantage of administration of TLR agonists is to induce the contribution of the endogenous innate immune cells and their cross talk to the exogenous DCs. These events can overcome the immunosuppressive effects in the tumor-bearing host and lead to effective antigen-specific immune responses. The application of TLR-based therapy in the clinical setting can open new avenues for cancer immunotherapy, in particular the agonists for TLR3 (poly(I:C)), TLR7/8 (imiquimod), and TLR9 (CpG) have just ranked as a potential adjuvant for cancer immunotherapy among the 12 agents listed by the Immunotherapy Agent Workshop held at NIH, July 2007 [150]. Taken together, these studies suggest that co-administration of a TLR agonists with DCs loaded with multiple epitopes would lead to an effective immunotherapeutic regimen in pancreatic cancer.

5.4. TLR Agonists can Enhance DC-based Vaccination Against Pancreatic Cancer by Interfering with Regulatory T (Treg) Cells

\(T_{reg}\) cells exist naturally in the steady state and constitute about 5-10% of CD4\(^+\) T-cells [151]. Conventional CD4\(^+\) T cells can also convert into \(T_{reg}\) cells upon certain antigen recognition [151].
Phenotypically, T_{reg} cells constitutively express the high affinity α-chain of the IL-2 receptor (CD25), glucocorticoid-induced tumor necrosis factor receptor (GITR) and cytotoxic T lymphocyte-associated antigen (CTLA-4) and Forkhead box P3 (Foxp3), a transcription factor required for T_{reg} cell development and function. They are functionally characterized by their secretion of the suppressive cytokines IL-10 and TGF-β and the capability to suppress T cell responses directly or indirectly by inhibiting the functions of DCs [152]. Indeed, preclinical and clinical studies demonstrated increased frequencies of T_{reg} cells in hosts with the promotion of the pancreatic tumor, where depletion of T_{reg} cells promoted tumor-specific immune responses in pancreas cancer-bearing mice [36, 37, 153-155]. DC- T_{reg} cell crosstalk is critical in shaping the immune response, where T_{reg} cells inhibit DC activation and activated DCs inhibit the suppressive effects of T_{reg} cells [156].

Recent studies demonstrated that T_{reg} cells express TLRs and those TLR agonists have the capacity to directly regulate T cell responses and modulate the suppressive activity of T_{reg} cells [157-161]. For instance, TLR9 agonist CpG can synergize with anti-CD3 to induce partial abrogation in the suppressive activity of T_{reg} cells [162, 163]. The TLR2 agonist Pam3Cys was also found to directly act on purified T_{reg} cells, and when combined with TCR stimulation, TLR2 triggering augmented T_{reg} proliferation in vitro and in vivo and resulted in a temporal loss of their suppressive effect [164]. Synthetic and natural agonists for human TLR8 can also reversed T_{reg} cell function independent of DCs [165]. A problem with TLR agonists that has not been fully appreciated is that they can generate suppressive as well as inflammatory responses in T_{reg} cells [166]. For instance, costimulation of T_{reg} cells with the TLR5 agonist flagellin potently increased their suppressive capacity and enhanced expression of FOXP3, the surrogate marker for T_{reg} cells [167], may be inducing the regulatory molecule SOCS-1 (suppressor of cytokine signalling-1) [168]. These data indicate that the quality of the T cell response depends on what type of TLR is triggered. Therefore, the nature of TLR/TLR agonist signaling pathway should be carefully considered during application of TLR-based stimulation of innate or adaptive immunity.

CONCLUSION

Although application of vaccination with ex vivo DCs loaded with different forms of tumor antigens has been found to induce favorable anti-tumor responses against pancreatic cancer, these responses were of limited efficacy. Co-administration of TLR agonists with this DC-based vaccination would significantly improve the immune responses and anti-tumor efficacy against pancreatic cancer. Under this setting, DCs can be generated from autologous peripheral blood mononuclear cells, matured with a TLR agonist or an inflammatory cytokine (e.g. TNF-α) and then loaded with the target peptide. This maturation process is required to upregulate the expression levels of MHC class-I and class-II and thus enhance their binding efficiency to the loaded MHC class-I and class-II-restricted peptides, respectively. Given several TLR agonists are FDA approved for clinical application, combination of TLR agonists and DC vaccine would lead to a new therapeutic intervention to treat pancreatic cancer patients in future studies.

REFERENCES

The Potential use of Dendritic Cell-based Immunotherapy


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[128] Salem, M.L.; Kadima, A.N.; El-Naggar, S.A.; Rubinstein, M.P.; Chen, Y.; Gillanders, W.E.; Cole, D.J. Defining the ability of cyclophosphamide preconditioning to enhance the antigen-specific CD8+ T-cell response to peptide
vaccination: creation of a beneficial host microenvironment involving type I IFNs and myeloid cells. J. Immunother., 2007, 30(1), 40-53.


