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REVIEW ARTICLE

Immune Interventional Strategies against Chronic Infection Diseases and Cancers: Present Challenges and Road Map to Solution

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ABSTRACT

The therapeutic efficacy of antiviral therapy against chronic viral infections and anticancer strategy against cancers is not satisfactory. Most of the antiviral drugs cause reduction of viral replication in chronic virus-infected subjects, however, recovery or cure from diseases does not occur in most cases. Various types of therapeutic approaches, such as ablation of cancer tissues, use of anticancer drugs and radiation therapy, are applied to treat patients with cancers. But, recurrence of cancer is a formidable problem in clinics. Taken together, sustained control of virus replication in chronic viral carriers and control of cancer recurrence in cancer patients are two major challenges. It is now evident that although different factors are responsible for pathogenesis of chronic viral infections and cancers, almost all patients exhibit distorted antiviral and anticancer immune responses. Thus, a new field of treatment of these diseases by immune intervention has been emerged. Immune therapy against chronic viral infections and cancers are in their infancy and facing several challenges. These challenges will be discussed to provide a road map for development of clinically-acceptable and potent immune therapeutic approaches against these diseases, especially in the context of liver diseases.

Abbreviations: HBV—Hepatitis B virus; HCV—Hepatitis C virus; HIV—Human immunedeficiency virus; DC—Dendritic cells.

Keywords: Chronic viral infection, Cancer, Antiviral and anticancer drugs, Immune therapy.

Host Immunity is a Critical Regulator of Pathogenesis of Chronic Viral Infections and Cancers

Some viruses, such as influenza virus, measle virus, hepatitis A virus and hepatitis E virus, usually causes acute and self-limiting infections. On the contrary, hepatitis B virus (HBV), hepatitis C virus (HCV), herpes viruses and human immunodeficiency virus (HIV) are notorious for causing chronic infections. Patients with chronic viral infections exhibit ongoing replications of viruses without (asymptomatic) or with features of inflammations and tissue damages (symptomatic). The mechanisms that regulate the pathogenesis and clinical courses of chronic viral infections are not well understood, however, both viral-derived factors and host-related factors play critical roles in this regard. The nature of viruses, amounts of viruses, genotypes of viruses and routes of infection may be related to viral persistency, however, the role of individual viral-derived factor during establishment of chronic viral infections could not be substantiated. For example, if immune-competent and healthy persons are infected with same sources of HBV, some of them develop acute or self-limiting HBV infection, whereas, others are chronically-infected with the virus. However, once a chronic viral infection is established in a host, either immune-competent or immune-comprised, the hosts usually exhibit distorted immune responses to various viral antigens.[1-3]

The etiological factors, cellular events and molecular mechanisms underlying carcinogenesis are also highly variable. Interestingly, the immune statuses of the cancer-bearing hosts are comparable with those of chronic virus-infected persons. In spite of harboring abundant amounts of cancer cells in all patients with cancers, they show diminished, impaired and distorted anticancer immunities.[4]

The limited therapeutic efficacies of antiviral drugs and anticancer therapeutic approaches against chronic viral infections and cancers, and presence of distorted antiviral and anticancer immunity in these patients have exposed a new field of therapeutic intervention, immune therapy, against these diseases. However, there is no standard or universal regimen of immune therapy because different viruses employ different mechanisms to establish chronic

infections, and similar diversities are prevailing regarding pathogenesis of cancers. The efficacies of antiviral drugs and anticancer therapeutic approaches are also highly variable. Naturally, the challenges of immune therapies against chronic viral infections and cancers are also diverse. Unfortunately, it is not possible to provide any universal road map to address these challenges. In this article, we would provide a general discussion about present challenges of immune therapy. Also, a road map will be given to address these challenges on the basis of present realities and scientific developments. Specific examples about some gastrointestinal diseases, more specifically of liver diseases would be given for better understanding of these factors.

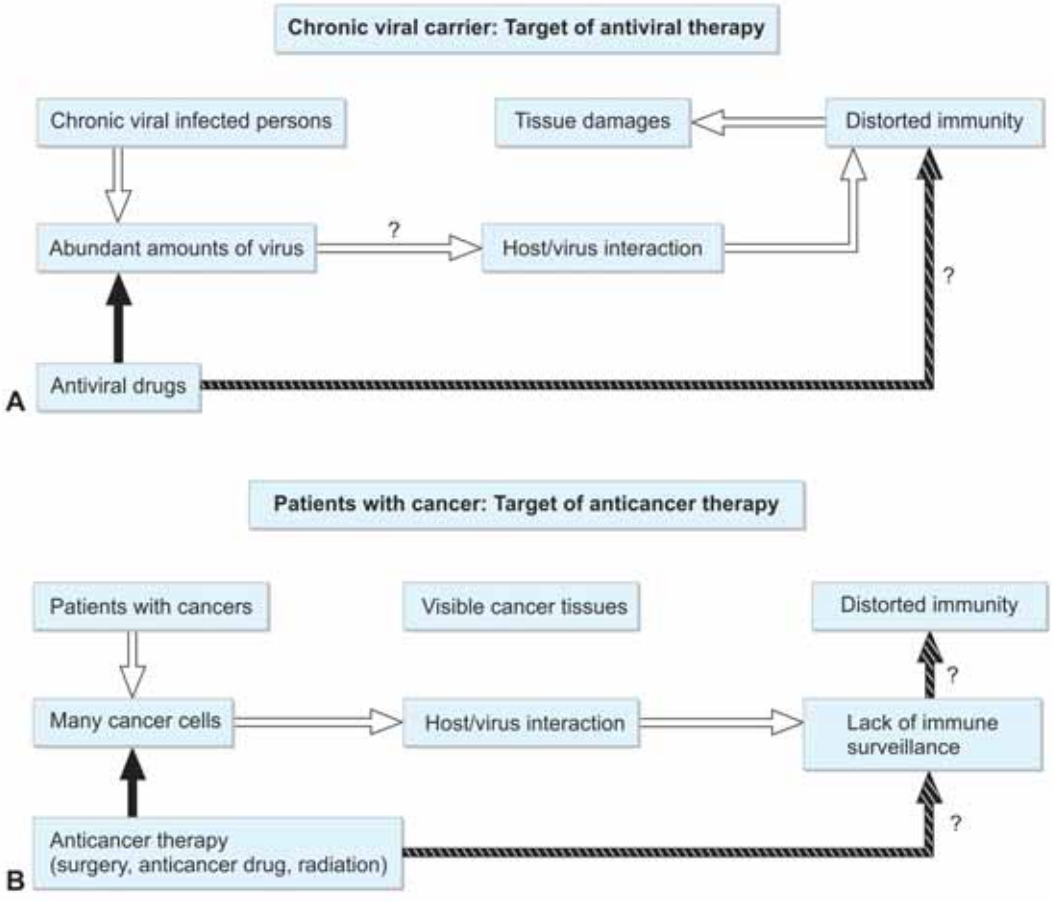
Limitations of Therapeutic Options against Chronic Viral Infections and Cancers

Patients with chronic viral infections are treated by antiviral drugs. These drugs usually reduce the levels of virus replication, but they cannot eradicate the virus completely from chronic viral carriers. Before prescribing antiviral drugs, it is assessed whether (1) these patients exhibit subjective, biochemical or histological features of tissues damages, (2) the diseases are progressive or not and (3) the patients are going to develop complications. At present, treatment is usually recommended for chronic viral carriers with tissue damage, progressive diseases or complications. In fact, antiviral drugs are not effective against asymptomatic chronic viral carriers, and are not capable of eradicating the viruses completely from chronic viral carriers.[5]

The principle of treatment of chronic viral carriers by antiviral drugs has been summarized in Figures 1A and B. Antiviral drugs are capable of reduction of viral replication in most patients with chronic viral infection (shown by black arrow). It is expected that reduction of virus replication will be followed by restoration of antiviral immunity and control of tissue damages. However, antiviral drugs induce sustained control of virus in only few patients. Accordingly, restoration of host immunity and control of tissue damages are not accomplished by antiviral therapy in most chronic viral carriers (shown by hatched arrow). Highly potent antiviral drugs are available due to better understandings of viral life cycle and tremendous development of medicinal chemistry. For example, type 1 interferon has been used for treating chronic HBV and HCV infections for more than two decades. Interferon induces antiviral microenvironments in liver tissues, however, their direct antiviral potentialities are not clear. At present, true antiviral drugs are available against various viruses. Patients with chronic HBV infection are now treated by nucleoside analogs. Some of these drugs are phosphorylated to the triphosphate and competes with dCTP for incorporation into growing DNA chain causing chain termination of the replicating HBV. This may occur during reverse transcription of the first strand of HBV DNA, and during synthesis of second strand of HBV DNA.[6,7] For treating HIV-infected persons, most therapeutic regimens are combinations of inhibitors of viral enzymes—reverse transcriptase and protease. In addition, newer drugs that target viral entry into the cells have been developed as antiviral drugs against HIV.[8] However, administration of nucleoside analogs or enzyme inhibitors usually fails to induce sustained control of viral replication in majority of patients.

The presently-available therapies against cancers are directed to (1) destruction of cancer tissues by surgery or other ablation techniques, and (2) destruction of cancer cells by anticancer drugs or radiation therapies.[9,10] The therapeutic efficacy of these approaches is highly variable and depends on: (1) The nature of cancer, (2) the type of cancerous tissue, (3) presence or absence of metastasis and (4) the nutrition statuses of the patients. If a cancer is detected in its early stage, the cancer tissues can be destroyed almost completely by these therapeutic approaches. However, after successful removal of cancer tissues by surgery or ablation techniques or destruction of cancer tissues by anticancer agents or radiations, the cancer may relapse at the original site of cancer or in another site. As shown in Figure 1B, it is expected that if cancer burden of a cancer-bearing host is diminished by anticancer therapeutic approaches, the persons will restore the immune surveillance system against cancer cells. However, it is not guaranteed, rather restoration of immune surveillance is an unexpected event in most cancer patients. Accordingly, recurrence of cancer is a common feature of cancer patients treated by conventional anticancer therapies.

Commercially-available antiviral drugs and conventional anticancer therapeutic approaches may be regarded as first line of therapeutic approaches against chronic viral infections and cancers respectively. These therapeutic approaches are endowed with capacities to transient reduction of viruses and reduction or eradication of cancer tissues. However, control of tissue damage and sustained control of viral replication is not achieved by antiviral drugs in most patients with chronic viral infections. Again, immune surveillance mechanism is not properly induced and maintained in most patients with cancers by conventional anticancer therapeutic approaches. Thus, second line of therapeutic approaches is needed to induce and maintain sustained control of virus in chronic viral infections and proper induction and maintenance of



Figs 1A and B: The limitations of antiviral and anticancer therapies in patients with chronic viral infections (A) and cancers (B) are shown. (A) All patients with chronic viral infections harbor abundant amounts of virus and also exhibit distorted antiviral immunity. Antiviral drugs usually reduce viral replication but restoration of immunity (shaded lines) may or may not be achieved. (B) Anticancer approaches reduce cancer burden, but anticancer immune surveillance system is not usually induced by conventional anticancer therapeutic approaches

anticancer immune surveillance system in patients with cancers. One way to accomplish this is dependent on further developments of medicinal chemistry because if more potent antiviral drugs can eradicate the virus completely from chronic viral carriers, sustained antiviral responses will be attained by antiviral drugs. Regarding treatment of cancers, the possibility of control of cancer recurrence is not so encouraging. Relapse of cancer cells may start even after complete eradication of cancer cells from the hosts because several factors induce carcinogenesis and many of these factors are not controllable *in situ*.

In this context, immune therapy may represent an alternative therapeutic approach or a second line of therapeutic option against chronic viral infections and cancers.

Immune Therapy against Chronic Viral Infections and Cancers

Major immune interventional approaches against patients with chronic viral infections and cancers have been shown in Figure 2. Initially, cytokines, such as interleukin-2, interleukin-12 and interferon-gamma, have been administered to patients with chronic viral infections to upregulate host immunity. Various growth factors have also been used as immune therapeutic agents. Most of these studies were done as pilot study or open clinical trials. Some studies have shown that administration of polyclonal immune modulators caused subjective improvements of

Immune interventional strategies against chronic viral infection and cancers

Nonantigen-specific immune modulators:
1. Cytokines
2. Growth factors

Antigen-specific immune intervention:
1. Antigen-based vaccine therapy
2. Epitope-based vaccine therapy
3. DNA-based vaccine therapy

Cell-based immune therapy:
1. T cell-based immune therapy
2. Dendritic cell-based vaccine therapy

Fig. 2: Cytokines, growth factors and antigen-specific immune interventional strategies are now used for treating patients with chronic viral infections and cancers

these patients, however, real efficacy of these therapeutic approaches have remained questionable due to lack of randomized controlled trials (immune interventional strategies against chronic HBV infection).[11] In addition, the doses of these immune modulatory agents, duration of therapy, therapeutic protocols have not been optimized for different chronic viral infections.

When clinicians were trying to develop immune therapy against chronic viral infections and cancers by polyclonal immune modulators, it became evident that administration of polyclonal immune modulators may be detrimental for patients with chronic virus infection. Studies have revealed that nonantigen-specific immune responses are related to tissue damages, whereas, antigen-specific immunity is needed for control of viral replication and also reduction of tissue damages in many chronic viral infections.[12,13] This opened a new field of clinical applications of immune therapy for patients with viral infections and cancers. In order to induce antigen-specific immunity in chronic viral carriers and cancer patients, viral-related antigens or tumor-associated antigens have been used.[14-16] This therapeutic approach has been regarded as vaccine therapy. In addition to antigen-based vaccines, epitope-based vaccines and DNA vaccines have also been used to induce viral or cancer-specific immunity.[17,18] In general, these therapeutic approaches are safe, but mixed signals have been found regarding their efficacies. In some studies, vaccine therapy has shown antiviral as well as immune modulatory potentials. On the other hand, the efficacy of vaccine therapy is not so promising in other clinical trials.[19,20]

In the mean time, the concept of cell-based immune therapy originated. Initially, T-cell-based immune therapies have been applied in patients with cancers.[21-23] Due to better understandings about cellular and molecular events regarding induction and maintenance of antigen-specific immunity, it became evident that antigen-presenting dendritic cells (DCs) are critical regulators of immunity.[24,25] Different preclinical trials also revealed that antigen-specific immunity can be induced and maintained in chronic viral carriers and cancer patients by administrating antigen-pulsed DCs.[26-28] The first report about safety and efficacy of antigen-pulsed DC vaccine in patients with cancer has been published by Hsu et al in 1996.[29]

Limitations of Immune Therapy against Chronic Infections and Cancers

Different types of immune therapies have been applied in patients with chronic viral infections and cancers during last three decades (Fig. 2). Thousands of publications are available about immune responses of these patients, however, few immune therapeutic approaches have received a general acceptance as therapeutic approaches in clinics. Immune therapeutic approaches against chronic viral infections and cancers are facing several challenges (Fig. 3) and these will be described first to provide a road map for solution.

Fundamental Differences between Animal Models of Human Diseases and Patients with Chronic Viral Infections and Cancer

Due to ethical and scientific limitations, the concept of immune therapy usually originates from animal studies and the therapeutic regimen is first optimized in animal models of human diseases. After assessing safety and efficacy of these maneuvers in normal volunteers, clinical trials are conducted in patients. Animal models of human diseases provide important information when critical cellular and molecular mechanisms about host/virus or host/cancer cell interactions cannot be studied in details in human. However, there are fundamental differences regarding pathological processes in human diseases and animal models of human diseases. This has become an important issue in the context immune therapy against chronic viral infections and cancers. Due to tremendous development of molecular and cellular biology, it is now possible to produce transgenic mice that represent an animal model of chronic viral infections. Also, availability of tumor cell lines allows production of animal models of cancers. Various immune therapies, such as polyclonal immune modulators, vaccine therapy and DC-based vaccines, have been applied in animal model of human diseases with excellent therapeutic outcome. However, when similar types of immune therapeutic approaches are applied in patients with chronic viral infections and cancers,

Causes underlying low efficacy of immune therapy

1. *Limitation of translation of immune therapy from mice to man:* Human is the only therapeutic model of human diseases
2. *Improper conception of immune therapy:* Immune therapy is not a replacement therapy
3. *Misunderstanding about nature of immunity:* Diminished immunity and distorted immunity
4. *Improper selection of immune interventional strategies:* Innate immunity or adaptive immunity
5. Restricted information about nature of antigen and epitope: Immunogenic or tolerogenic antigens
6. *Lack of proper protocol of cell-based therapy including dendritic cell-based therapy:* Study in patients with advanced diseases. Improper insights about antigen and method of preparation of antigen-pulsed dendritic cells
7. Restoration of immunity is not committed to therapeutic efficacy

Fig. 3: Major challenges about immune therapy in patients with chronic viral infections and cancers

the therapeutic efficacy is negligible. For example, different cytokines have shown potent antiviral effects in HBV-transgenic mice,[30,31] but not in patients with chronic HBV infection.[11] In HBV-transgenic mice, the replication cycle of the virus is completely different from that of patients with chronic HBV infection. Moreover, there are no liver damages in HBV transgenic mice, however, patients with chronic HBV infection exhibit variable degrees of liver damages. Finally, huge amounts of cytokines are given to mice, but that amount cannot be given in patients with chronic HBV infection due to concern about safety of patients.

In the context of cancer, animal models of cancers are developed by implantation of cancer cell lines in normal mice or by administration of some carcinogenic agents. Cancer develops in these animals in a short time. On the contrary, cancer development is a time-consuming matter in human. It takes several years for cancer development and the architecture of cancer tissues is altered. Moreover, cancers in human may have capsule, which hinders entry and activity of immune modulators. In line of this, the efficacy of immune therapy is excellent in animal model of human diseases, but it is extremely difficult to reproduce this in patients with cancers.

Challenges Related to Concept of Immune Therapy: Immune Therapy is not a Supplementary Therapy or Replacement Therapy

Studies have shown that the functions of different immunocytes, such as T-cells, B-cells, monocytes/macrophages and DCs, are diminished in patients with chronic viral infections and cancers. Some subjects also exhibit decreased levels of cytokines. Based on these findings, the strategy of immune therapy has previously been developed to upregulate the functions of different immunocytes or immune modulators. This principle of therapy may be followed during supplementary and replacement therapies. The immune intervention strategies should be designed in a manner so that a series of complex interactions among immunocytes, cytokines, chemokines and several other immune-related mediators occur *in vivo* without tissue damages.

Differences between Diminished and Distorted Immune Responses

There are some misconceptions about immune responses of patients with chronic viral carriers and cancers. It is usually noted that the immune responses of these subjects are diminished. This is not true. The immune responses of these patients are distorted. In most cases, the viral-specific and cancer-specific immune responses are diminished, whereas, antigen nonspecific immunity is exacerbated in these patients. Even, antigen-specific immunity to all types of antigens of the virus or cancers is not diminished. Accordingly, it becomes extremely difficult to design immune therapy in these diseases. If the immune responses are diminished in subjects with chronic infections and cancers, the target of immune therapy is simple because upregulation of host immunity will be the primary aim of this therapy. However, reshaping of distorted immune responses of patients with chronic viral infections and cancers is extremely difficult.

Selection of Interventional Strategies of Immune Therapy

Both innate and adaptive immunity can be activated by immune therapy. If the target of immune therapy is to activate one or more immunocytes, that can be accomplished by activating only innate immunity by immune modulators, like cytokines and growth factors. However, to have sustained antiviral and anticancer immune responses, immune therapy should induce long-lasting immunity and immune surveillance systems. This can be accomplished in chronic viral carriers and cancer patients by inducing optimum levels of adaptive immunity.

Limitations of Antigen-based or Epitope-based or DNA-based Vaccine Therapies

As it became evident that antigen-specific immunity has antiviral, anticancer as well as immune surveillance properties in virus-bearing and cancer-bearing hosts, the purpose of immune therapy is to induce antigen-specific immunity in these patients by antigen-based vaccines or epitope-based vaccines or DNA vaccines. Proper evaluation of these therapies has not been done yet. In fact, little is known about appropriate antigens, dose of antigen, and duration of vaccinations and route of vaccination. Application of immune therapy in more and more patients and randomized controlled-trials are needed to develop insights about the scopes and limitations of these approaches.

Limitations of Cell-based Therapy

To induce antigen-specific immunity in patients with chronic viral infections and cancers, mere administration of antigens or epitopes may not be effective. These patients have shown impaired functional capacities at all levels of immune cascades, such as at the level of antigen priming (antigen-presenting cell levels) and also in the context of functioning of effecter cells (T-cell and B-cell levels). Moreover, these patients harbor abundant amounts of antigen and basically

tolerant to virus-related and cancer-related antigens. Accordingly, antigen-based therapy and epitope-based vaccine therapy are not supposed to induce proper virus-specific and cancer-specific immunity in patients with chronic viral infections and cancers because the injected antigens or epitopes are not likely to be properly processed and presented for activation of T-cells and B-cells. These limitations can be overcome if cell-based therapy is employed. Adaptive transfer of activated T-cells has been used in several cancer patients to kill cancer cells. Although these T-cells can kill some cancer cells, they are unable to block growth of cancer cells and they can not induce anticancer immune surveillance mechanism.

Limitations of DC-based Therapies

Although little has been done to treat patients with chronic infection by antigen-pulsed or peptide-pulsed DCs, many clinical trials are going on regarding the utility of antigen-pulsed DCs and epitope-pulsed DCs in cancer patients. Meta-analyses have shown that the present regimen of DC-based therapy, in which antigen or epitope-loaded DCs are administered to these patients, has only limited therapeutic efficacy.[32] However, studies in animal models of human diseases and also in patients indicate that if these therapeutic approaches can be properly designed, their efficacies can be increased in patients with chronic viral infections and cancers.

The limited efficacy of DC-based therapy is related to improper understandings about (1) DCs that should be used (blood or bone marrow or lymph node derived), (2) antigens that should be chosen, (3) method of loading DCs with antigen, (4) method of administration of antigen-pulsed DCs (intradermal or subcutaneous or intramascular, or intravenous) and (5) characterization of antigen-pulsed DCs before administration to patients.

Induction of Immunity may not be Reflected in Therapeutic Efficacy

Immune therapy has been designed to treat patients with chronic viral infections and cancers by restoration of host immunity. These patients harbor abundant amount of viruses or cancer cells, they are tolerant to these antigens, exhibit tissue damages and complications. Immune therapy is targeted to induce and sustain immunity in these subjects. However, due to multifactorial problems of these patients, some patients may not exhibit therapeutic efficacy of immune therapy even if proper immunity is induced and sustained by immune therapeutic approaches.

ROAD MAP TO SOLUTION

The main purpose of immune therapy is to develop an immune surveillance mechanism in patients with chronic viral infections and cancers. The target of immune therapy in chronic viral carriers is to achieve sustained control of viruses with restoration of antiviral immunity. In patients with cancer, restoration and functioning of immune surveillance system is the principle aim of immune therapy.

We have discussed about the limitations of ongoing immune therapeutic approaches against chronic viral infections and cancers. Next, we will discuss how these problems can be solved (Fig. 4).

Re-evaluation of Immune Responses in Patients with Chronic Viral Infections and Cancers

Although important information about pathogenesis of disease processes and scope of immune therapy can be gathered by conducting experiments in animal models, the utility of these therapies can only be assessed by conducting investigations in patients with these diseases. In addition, it is unlikely that there is any universal immune therapeutic approach for all types of chronic viral infections and cancers. Accordingly, the interventional strategies should be ascertained on a case by case basis. In future, it may be

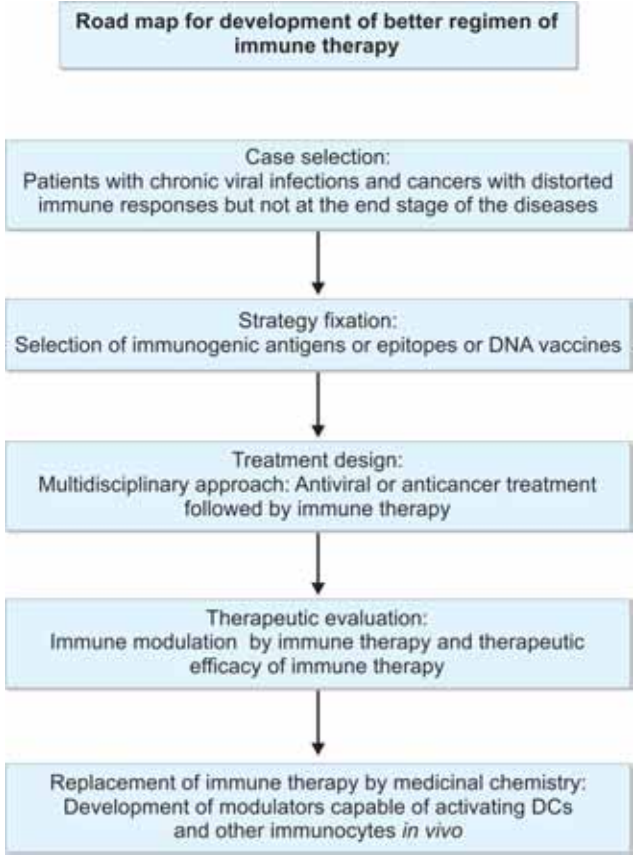


Fig. 4: Road map to develop better and effective regimen of immune therapeutic approaches against chronic viral infections and cancers

possible to get some common facts that will allow development of immune therapy for certain diseases. Also, it may be possible to assess the prognosis of immune therapy from the clinical background of these patients.

Case Selection for Immune Therapy

It is needless to say that no therapeutic approach can be available that is effective in all patients with chronic viral infections and cancers. In the context of antiviral therapy, all patients with chronic HBV infection without liver damages are not given any antiviral drugs because these patents do not respond to these drugs. In case of cancers, different types of therapeutic approaches are not given to patients with advanced cancers. Unfortunately, immune therapy has mainly been applied in patients with advanced cancer. This is not an exception because any new type of therapy is done in these types of patients due to concern of safety. All patients with advanced cancers are immune compromised. Accordingly, immune therapy is unlikely to achieve its goal in such patients. Due to safety concern, there are few studies with DC-based immune therapy in patients with chronic viral infections. As immune therapy is in its infancy, the real potentials of this therapy should be assessed in immune competent patients with cancers and in patients with chronic infection without complications. It would be non-scientific if we conclude about the efficacy of immune therapy without performing clinical trials in proper subjects.

Strategy of Immune Therapy

Induction of innate immunity can be counter productive as a therapeutic approach in these patients because this can induce inflammation in patients with chronic viral infections and cancers. When a chronic viral infection is established or a cancer is clinically detected, it means that the innate immunity of these subjects could not inhibit the disease processes. Attempt should not be taken to induce innate immunity in these patients. On the contrary, adaptive immunity can kill virus infected cells and cancer cells by a noncytopathic mechanism. Thus, the possibility of tissue destruction is minimized. Accordingly, the purpose of immune therapy should be to induce adaptive immunity.

Selection of Antigens

In all types of viruses and cancers, there are several virus-related antigens and cancer-related antigens. However, the functions of these antigens differ considerably. Some of these antigens are immunogenic, whereas, others may be tolerogenic. For example, many antigens of HBV or HCV down regulate host immunity. Thus, immunogenic antigens should be selected for immune therapy. Again, some antigens may induce T helper 1 immunity, whereas, others can induce T helper 2 immunity. Some antigens may induce humoral immunity, whereas, others can give a cytotoxic T cell response. Based on the virological and immunological status of the patients, antigens should be carefully selected for successful immune therapy.

Production of Immunogenic Antigen-Pulsed DCs

Antigen-presenting DCs loaded with antigen (antigen-pulsed DCs) are now used for treatment of cancers[32] and their safety has recently been confirmed in noncancerous subjects.[33] Extensive use of antigen-pulsed DCs is expected in cancer patients as well as in chronic viral infections in near future. There are major limitations regarding the protocol of production of antigen-pulsed DCs or epitope-pulsed DCs. Antigen-pulsed DCs should be prepared by culturing DCs with immunogenic antigens. Now, it is prepared by culturing DCs with whole tumor products or tumor RNAs or exosomes. The immunogenic nature of these products is not clear. Whole tumor may contain immunogenic and tolerogenic antigens and it is really elusive if the injected DCs would induce immunity or tolerance. Viral antigen-pulsed DCs have mainly been administered to animals with chronic viral infections. Many viral antigens are not immunogenic, rather, they suppress immune responses. The protocol for preparing immunogenic antigen-pulsed DCs should be confirmed by conducting preliminary studies in man and mice.

Immune Therapy as a Multidisciplinary Approach

The utility of immune therapy as an independent therapeutic approach against chronic viral infection or cancer is not so inspiring at this point. This is mainly because it is extremely hard to induce and sustain antiviral immunity in subjects with chronic viral infection with very high viral load. Also, antitumor immunity may not be induced in patients with cancers with abundant amounts of cancer cells. Abundant amounts of viruses and cancer cells induce immunogenic tolerance in these patients. Antigen excess always hinders induction of antigen-specific immune responses**.** To address this issue, immune therapy may be applied after decreasing the amounts of virus and cancer cells. This can be done by treating patients with chronic viral infections by antiviral drugs and patients with cancers by conventional antitumor therapeutic therapies. These therapeutic approaches would reduce viral and cancer burden and thus a file may be prepared for proper activity of immune therapy. In fact, combination of antiviral and immune therapy has shown potent therapeutic effect compared to monotherapy with

either antiviral drugs or with only immune therapeutic approach.[34] Studies have shown that immune therapy is effective in cancer patients after ablation of cancer mass.

Replacement of Immune Therapy by Medicinal Chemistry

The purpose of immune therapy is noble, induction and maintenance of immune surveillance mechanisms against viruses and cancer cells. Vaccine therapy and DC-based vaccine therapy seems to be safe therapeutic approaches and capable of inducing the proper therapeutic efficacy against chronic viral infections and cancers, if applied after conventional therapeutic approaches. However, all types of cell-based therapy, including DC-based therapy, need special techniques, trained manpower and highly sophisticated facilities. These types of therapies can be effective but their mass usage is not expected. DCs are basically adjuvants that allow antigens to be properly presented to T-cells and B-cells. Antigen-pulsed DCs carry immunogenic forms of the antigens and directly stimulate the immunocytes for induction of antigen-specific immunity. Studies with DC-based vaccines for more than a decade in cancer patients have provided important insights about the method of induction of antigen-specific immunity. Now, it is known that antigen-pulsed DCs cause activation of cytokines and chemokines *in vivo*. Also, they ensure inflammatory microenvironments for immune responses.

The time is mature to start investigations about the methods of replacing DC-based vaccines by products of medicinal chemistry. The key factors that antigen-pulsed DC provides *in vivo* should be identified and characterized. It may be possible to active DCs of patients with chronic infections and cancers by administrating products of medicinal chemistry. Further development of medicinal chemistry can replace a cell-based therapy with drugs.

Understanding of philosophy and strategy of immune therapy and collaboration between immunologists and scientists of medicinal chemistry may lead to the development of magic bullets for treatment of chronic viral infections and cancers in near future.

CONCLUSION

Immune therapy, especially DC-based therapy seems to be an alternative therapeutic approach for treating patients with chronic viral infections and cancers. Immune therapies have mainly been started as pilot study and open clinical trials have shown that these types of therapies can be adopted in future. Recently only, antigen-pulsed DCs have been used in noncancerous human. The safety of antigen-based vaccine therapy and DC-based vaccine therapy has been confirmed in several studies. Now, there is a need to increase their efficacy. More and more clinical trials should be conducted in these patients. Especially, immune therapy should be done at the primary stages of the diseases to assess the real efficacy of this therapy. The real therapeutic potentiality of immune therapy is yet unknown because immune therapies have been applied mainly in patients with advanced diseases and also, there is no appropriate therapeutic protocol of immune therapy. It seems that immune therapy should be conducted as part of multidisciplinary therapeutic approaches. Finally, immune therapy should be replaced by products of medicinal chemistry. However, further progress of immune therapy is dependent on proper understandings about immune pathogenesis of different diseases and also on development of proper interventional strategies.

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