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Active and passive immunization for cancer

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Abbreviations: ADC, Antibody Drug Conjugate; ADCC, Antibody Dependent Cell Cytotoxicity; APC, Antigen Presenting Cell; BCG, Bacille Calmette Guerin; CD, Cluster of Differentiation; CDC, Complement Dependent Cytotoxicity; CTL, Cytotoxic T-Lymphocyte; CTLA4, Cytotoxic T Lymphocyte Antigen 4; DC, Dendritic Cell ; ERBB, Erythroblastic Leukemia Viral Oncogene Homolog ; GM-CSF, Granulocyte Macrophage Colony Stimulating factor; HBV, Hepatitis B virus ; HER2, Human Epidermal Growth Receptor 2; HPV, Human Papilloma Virus ; ID, infectious disease; Ig, Immunoglobulin ; IL, Interleukin; MBVs, Mixed Bacterial Vaccines ; MHC, Major Histocompatibility Complex; NK, Natural Killer Cell; TAA, Tumor Associated Antigen; T_H, T Helper Cell; TNF, Tumor Necrosis Factor

Vaccination started around the 10th century AD as a means of preventing smallpox. By the end of the 19th century such therapeutic vaccines were well established with both active and passive preparations being used in clinical practice. Active immunization involved administering an immunogen that might be live/ attenuated, killed/ inactivated, toxoid or subunit in origin. Passive immunization involved giving preformed antibodies, usually to very recently exposed individuals. At about the same time such approaches were also tried to treat a variety of cancers – proof of principle for the protective role of the immune response against malignancy was established by the observation that tumors transplanted into syngeneic hosts were rejected by the host innate and adaptive responses. The impact of these therapeutic vaccination has taken a considerable time to become established - in part because target antigens against which an adaptive response can be directed do not appear to be uniquely expressed on malignant transformed cells; and also because tumor cells are able to manipulate their environment to downregulate the host immune response. Therapeutic cancer vaccines are also divided into active and passive types – the latter being subdivided into specific and non-specific vaccines. Active immunization utilizes an immunogen to generate a host response designed to eliminate the malignant cells, whereas in passive immunization preformed antibodies or cells are administered to directly eliminate the transformed cells - examples of each are considered in this review.

Introduction

Active immunization (or vaccination) as we would recognize today, historically focused on the prevention of specific infectious diseases (ID) starting with smallpox in the late 17th / early 18th centuries. Prophylactic vaccines have proved generally highly effective and currently infants in the UK are protected against 25 different IDs by four months of age. A related procedure, the administration of antibodies (passive immunization) started with diphtheria antibodies (antitoxin), first given successfully on Christmas Day, 1891. (Parrish 1968) The basis for such approaches is to make use of the same host mechanisms that would normally eliminate infection.

Concurrently, similar approaches began for the treatment of cancer. As with IDs they were based on the principle of identifying a difference(s) between tumor and normal cells and using these to facilitate host elimination of the tumor. Although work started in the 18th century, it wasn't until the 20th century that the use of either vaccines or antibody preparations, or combinations, to treat certain cancers became more widespread. Therapeutic immunization anti-tumor approaches form the basis of this review - of considerable importance given that in high income countries slightly more than 12% of all deaths are due to lung, colorectal, breast and stomach cancers: with stomach and lung cancers causing just over 5% of deaths in middle income countries.[24]

Therapeutic vaccines and cancer treatment

The concept that modulation of host response to the tumor might be a potential approach to cancer treatment was recognized at the end of the 19th century when Coley (USA) and Fehleisen (Germany) both independently reported some success in the treatment of malignancy by injecting live or killed bacteria, either into the patient or directly into the tumor.[11,7,8] The approach was based on the clinical observation that some patients post-surgery had an improved outcome if they developed an infection with associated fever. The results, however, were not consistently reproducible and the approach was not widely adopted. Nevertheless, the value of such Mixed Bacterial Vaccines (MBVs) or Coley's Toxins as they were also known, was the stimulus it provided for future research in the area.

In 1884, Nuttall in collaboration with Flugge suggested that protection against particular pathogens was due to chemicals released by cells present in blood.[2] These "antidotes" (synonym opsonins or bacteriotropins) were identified and successfully used to treat a number of infections including diphtheria and

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pneumococcal disease. The same approach was subsequently applied to cancer, with different animal species being immunized with malignant cells in the expectation that the resultant antisera could be used to treat human disease: the results, however, were uniformly unsuccessful.

Support for cancer treatment by vaccination did however come from the later observation that tumor cells transplanted into a different host do not multiply but are killed by host defenses. That this was not rejection of "foreign" tissue by cytotoxic T lymphocytes (CTL) cell activity due to major histocompatibility complex (MHC) mismatching, but rather recognition (and elimination) of the expressed cancer associated immunogens in the transplanted tumor cells, was due to the transplantation being performed between genetically identical (syngeneic) animals.

Infectious disease immunity induced by active/passive immunization

Active immunization involves administering the pathogen, or a part of the pathogen (a Pathogen Associated Molecular Pattern - "an immunogen"), which is then recognized by an Antigen Presenting Cell (APC), usually a Dendritic Cell (DC) either through surface or endosome expressed receptors (Pattern Recognition Receptors). Where the immunogen is recognized by surface receptors (for example Toll-like receptor 4) it is taken into the DC through receptor-mediated endocytosis; when it is taken up by micropinocytosis, intracellular receptors (eg Nucleotide Oligomerisation Domain Proteins) are involved. By whichever mechanism cell entry is affected, the immunogen is then degraded into small peptide[a] fragments either in the phagolysosome or the cytosol – how the peptide fragments are then further processed depends on the site of degradation.

Peptide fragments generated in the phagolysosome are bound there to (MHC) II molecules and the MHC II-peptide complex then migrates through the cytoplasm to the cell surface: a similar process occurs with cytosolic processed peptide fragments but here the peptide fragments are bound to MHC I molecules.

Immunogen recognition and processing by either mechanism meanwhile activates the APC causing it to migrate to local peripheral lymphoid organs (e.g., draining lymph nodes or gut associated lymphoid tissue) where the MHC-peptide complex is presented to naïve T cells. This process is enhanced by the use of adjuvants, which may be based on depot adjuvants (for example alum), DC activators (for example MonoPhosphoryl Lipid) or Proinflammatory molecules (for example MF59).

Simultaneous delivery of MHC II-peptide complex together with both co-stimulatory and cell-cell adhesion molecules by the APC to the T cell receptor and the associated CD3 complex of membrane proteins activates the naive T helper (T_H) cell, which then secretes Interleukin (IL) 2 causing the same T helper cell to differentiate into an effector T helper cell and then undergo proliferation through clonal expansion with some cells also becoming memory cells.

Effector T helper cells become either T_H1 or T_H2 cells, identifiable because of their $CD4^+$ surface glycoprotein. The former are induced when the APC presents peptide associated with MHC II molecules in the presence of IL-12, whereas the latter require MHC II peptide presentation in the presence of IL-4 and IL-2.

T_H1 cells exhibit several functions – they activate macrophages to kill pathogens they have internalized, they secrete cytokines that activate cytotoxic T cells, they induce B cells to change the type of immunoglobulin (Ig) G molecule they secrete ("class switching"), and they assist the recruitment of leucocytes to the site of an inflammatory process. T_H2 cells promote the differentiation of naïve T cells down the T_H2 pathway, while inhibiting them entering the T_H1 pathway: they also cause class switching in B cells and are involved in IgE secretion.

CTLs, identifiable by their $CD8^+$ surface molecule, are activated through their T cell receptor by APCs presenting peptide in conjunction with MHC I molecules – this is analogous to activation of T helper cells. Cells that recognize specific peptides undergo clonal expansion and some will become long-lived memory cells. Any infected cell that subsequently presents the same peptide together with MHC I will then be induced to undergo programmed cell death (suicide, synonym apoptosis). CTLs provide protection against intracellular infections (e.g., viruses), tumor cells and mismatched transplanted tissues.

Thus the type of MHC molecule presenting the pathogen-derived peptide determines the response – MHC I molecules activate CTLs, whereas MHC II molecules activate B cells, T_H1 and T_H2 cells. All nucleated cells in the body express MHC I molecules but only APCs (macrophages, dendritic cells and B cells) have MHC II molecules.

Passive immunization is based on administering pre-formed antibodies, which are obtained from a convalescent donor or in the case of respiratory syncytial virus, are commercially prepared. The same process provides the basis for natural acquired immunity from mother to child either transplacentally or through breast milk.

Antibodies whether induced by active immunization or passively acquired exert their prophylactic ID effects by blocking a pathogen attachment molecule or secreted toxin (neutralizing antibodies), activating complement through the classical pathway (Complement Dependent Cytotoxicity, CDC), or facilitating antibody dependent cell cytotoxicity (ADCC). ADCC involves natural killer (NK) cells, macrophages, neutrophils or eosinophils recognizing an Fc receptor on an infected cell bound with IgG molecule, for example FcγRIII, ligating to it and then inducing cell lysis. The downstream signaling effects of the antibody-receptor ligation are important.

Cell mediated immunity involves either inducing apoptosis of infected cells by CTLs, upregulation of intracellular killing mechanisms by T_H1 cells, or facilitating the activities of other T cells (T_H2 cells).

For both antibody and cell mediated immunity the immune response is specific to the immunogen(s).

Table 1. Therapeutic Cancer vaccines

Approach to Immunization	Target	Subtype	Example	Comment
Active				
	Specific	Whole (irradiated) cell	GVAX prostate	Immunogen is irradiated autologous malignant pancreatic cells: also contains GM-CSF transfected gene and ipilimumab
		Component cell vaccine	Peptide, protein, tumor lysate and shed antigen vaccines have been developed	Non licensed as of May 2014
	Non-specific	Live, attenuated vaccine	BCG vaccine	Local tumor instillation (eg bladder cancer) enhances immune response
Passive				
	Specific	Antibody	trastuzumab	Blocks Human Epidermal Growth Receptor 2
		Antibody Drug Conjugate	brentuximab vedotin	Antibody targets malignant cell releasing the fused antineoplastic drug
		Autologous or allogeneic T cells	Tumor invading lymphocytes, CTLs, T_H and T regs cell vaccines developed	Termed adoptive T cell therapy – non licensed (May, 2014)
	Non-specific	Antibody	ipilimumab	CTLA4 blocking antibody
		Autologous or allogeneic T cells	Tumor invading lymphocytes, CTLs, T_H and T regs cell vaccines developed	Termed adoptive T cell therapy – non licensed (May 2014)

[a] This discussion relates to a peptide immunogen only.

Tumor immunity induced by active/ passive immunization

As the lifetime risk of developing a tumor in the UK is just under 50%, presumably up to half the population may have an immune response that can eliminate malignant cells. In the other half, some individuals with particular malignancies may have both lymphocytes and antibodies directed against tumor cells – the former are able to activate cell-mediated immune responses, while the latter can bind to malignant cells; however, this doesn't necessarily result in tumor eradication because either the tumor suppresses the normal host adaptive immune response that would be expected to eradicate the "abnormal" malignant cells, or the tumor cells are sufficiently indistinguishable from normal tissue that the host adaptive immune response to the abnormal cells is insufficient to eliminate the tumor. Such downregulation of the host response to malignancy is paralleled by ID pathogens, which are able to evade host innate and adaptive responses through a variety of mechanisms – *Staphylococcus aureus* for example secretes Protein A that binds to IgG so preventing its action, and the influenza virus attachment molecule, haemagglutinin, undergoes antigenic drift.

Two key functions of either the active or passive immunization approach are to first present the tumor immunogen in such a way that an appropriate adaptive immune response is generated, and second to modulate the tumor cells' ability to suppress the host response. While progress in these two areas is happening as discussed below, it is slow and incomplete so that at present cancer vaccines (active) and/or antibodies (passive) are only used as an adjunct to conventional treatments where disease outcome is poor or recurrence rates are high.

It is believed that similar mechanisms in part explain the anti-tumor effects of antibodies induced by therapeutic cancer vaccines – that is blocking a receptor ligand interaction, CDC or ADCC.[20] However, additional effects of antibodies may be mediated through effects on tumor vasculature or stromal tissue, agonist effects on the receptor, and use of the antibody to deliver a drug to the malignant cell: antibody preparations that modulate the host's immune response to the tumor have also been developed.

There appear to be at least four mechanisms to explain the effectiveness of active immunization with tumor vaccines – first antibody generation as with the passive immunization approach discussed above: second anti-tumor CTL activity: third using the vaccine to deliver immunomodulatory molecules to the tumor environment (ADC as discussed previously) and finally a non-specific enhancement of the host immune response.

The final step in the pathway, namely tumor cell lysis occurs through a cell mediated immune response that involves both Natural Killer (NK) and CTLs – evidence for this is based on the increased incidence of malignancy in both immunodeficient and T cell deficient individuals.[22]

Prophylactic vaccines and cancer prevention

Although not used for cancer treatment it is important to mention two prophylactic ID vaccines, which prevent infection

and stop subsequent cancer development. The hepatitis B virus (HBV) vaccine has shown proven efficacy in the prevention of HBV associated hepatocellular cancer, and there are similar high expectations that the bivalent and quadrivalent first generation adjuvanted Human Papilloma Virus (HPV) vaccines (Cervarix and Gardasil respectively) will have a similar impact on cervical cancer. It is believed that the effectiveness of both HPV vaccines is based on their generating a B cell associated adaptive humoral response to the L1 immunodominant molecule with HPV specific antibodies in cervical mucus preventing virus cell entry through a neutralizing antibody response. This then prevents the subsequent changes to the cell replication cycle induced by the virus that lead to cervical or other ano-genital malignancies.[6,5,4] The use of an aluminum adjuvant with Gardasil and a DC activator adjuvant with Cervarix is key to their effectiveness.

Therapeutic vaccines and cancer treatment

Both active and passive immunization approaches have been applied to cancer treatment. Passive immunization involves the administration of either an antibody against a defined antigen (s), or a reactive lymphocyte that recognizes the malignant tumor cell. Furthermore, passive immunization may be non-specific where the aim is to activate a generalized host adaptive immune response, or specific when the objective is a targeted response against a particular malignant cell. Passive immunisation can also be used to deliver a drug to a defined (malignant) cell whereby antibodies against a cell antigen are used for targeting and delivering the drug. See **Table 1**.

Active immunization similarly can be non-specific or specific with the same expected outcomes as for passive immunization i.e., a non-specific vaccine is administered in the expectation that the resulting generalized activation of the host adaptive immune response will eliminate the malignant cells. In contrast a specific vaccine is based on administering an antigen (or more accurately an immunogen) to an individual with a malignancy in the expectation that they will develop an antibody, a CTL, or combination response, which will then target a defined tumor associated antigen(s) (TAA) and eliminate the malignant cell - an active cancer vaccine may be constructed from a component(s) of the cell or the whole cell, rather like the subunit and whole cell ID vaccines respectively. More complex vaccines that use both specific and non-specific components have also been developed – for example GVAX Prostate, see below.

Passive immunization and cancer treatment

Passive immunization for cancer involves administering either antibodies or CTLs; for antibodies they can act in a non-specific or specific manner as discussed below.

Antibody based: non-specific

Many tumors have the ability to downregulate the host immune response and enable their survival and continuing growth; preformed antibodies may therefore be administered with the aim of modulating the tumor immune environment in favor of the host. One example of such an approach relates to the process of APC antigen presentation to a T lymphocyte where activation of this latter cell requires that the MHC-TAA complex is presented with the co-stimulatory molecule CD28, which ligates with B7 facilitating activation of the T cell and initiating the adaptive host response – in the context of an infection, then after the pathogen had been eliminated, the activated clone of T cells would secrete CTL Antigen 4 (CTLA4) which would be transported to the APC-T cell synapse to bind with high affinity to the B7 molecule so limiting T cell activation and terminating the infectious response.

The survival mechanism for certain tumors is to promote their growth and metastasis by encouraging CTLA4 production and so downregulating the T cell activity, that would normally be directed against the malignant cells.(Quezada 2013) A passively administered antibody that blocked CTLA4 would therefore be expected to maintain T cell activation against tumor cells, and clinical trials with the anti CTLA4 monoclonal antibody, ipilimumab have demonstrated the benefit in terms of extended survival in for example patients with metastatic malignant melanoma.[15] One particular problem with this approach, however, is that the generalized T cell activation caused by ipilimumab may lead to immune adverse events particularly in the skin and gastro-intestinal tract.

Antibody based: specific

Despite the earlier treatment failures with antibodies raised in animal models as previously discussed, technological advances in the late 20th century led to the recognition of the complexity and large number of molecules expressed on cell surfaces, generating renewed interest in developing antibody directed cancer treatments that might block specific tumor molecules or facilitate antibody dependent cell cytotoxicity (ADCC). Cell surface molecules may be categorised as somatic tissue derived (ie those antigens expressed on normal adult tissues), developmentally derived (ie those expressed on fetal cells), and in the case of tumors, neoplastic tissue derived (ie those expressed on cells that have undergone malignant transformation – these vary with the tumor type).[19]

The objective of the specific passive immunization approach is to administer an antibody, usually IgG, that is specific to a surface molecule(s) expressed uniquely on a tumor cell (TAAs), and not on other cell lineage lines, and which in addition does not cross-react/ recognize surface molecules on "normal, non-cancerous" cells. Furthermore, both the antibody pharmacodynamics and pharmacokinetics are important to a successful product – for example a cell surface expressed TAA that is also secreted into plasma would be expected to reduce treatment efficacy due to a reduction in available antibody concentration at the cell surface level.

The identification of such unique TAAs has so far proved elusive largely because the expressed tumor surface antigens are also found on normal cells. However, in particular tumors these TAAs, while not unique, are overexpressed, and (specific) monoclonal antibody vaccines have been developed and licensed with

their effectiveness being largely explained on the basis of their preferential activity against these overexpressed TAAs.

An example of this approach is the monoclonal antibody trastuzumab, directed against the Human Epidermal Growth Receptor 2 (HER2), which is overexpressed in 25–30% of females with metastatic breast cancer. Studies have shown that breast cancer patients whose tumors overexpress HER2 have a shortened disease-free survival compared with patients whose tumors do not overexpress HER2. Blocking this receptor by antibody retards malignant cell proliferation and as part of a multimodality treatment approach has been shown to delay disease progression.[21] That the action of trastuzumab is, however, more complex than receptor blockade is evident from the observation that ADCC is more likely to occur in malignant breast cells overexpressing HER2 than in cells that do not overexpress HER2.

HER2 is a member of the Erythroblastic Leukemia Viral Oncogene Homolog (ERBB) family of growth factors, and a group of monoclonal antibodies (including Cetuximab) directed against the highly related Epidermal Growth Factor Receptor (EGFR) have been approved in the US for treatment of a number of solid tumors including lung and colorectal cancers.[25,17]

Currently 12 therapeutic monoclonal antibody preparations have been licensed by the US Federal Drug Agency as adjunctive therapies in the treatment of certain hematological malignancies and solid tumors.[20] Such monoclonal antibodies were first developed in the mouse model, but cross reactivity between mouse proteins and human proteins led to the development initially of chimeric mouse-human monoclonal antibodies where the constant part of the Ig molecule was human and the variable part mouse-derived, and subsequently to a fully humanized monoclonal Ig molecule.

The final passive antibody approach uses specific antibody as a vehicle to deliver drugs to tumor cells – termed an antibody drug conjugate (ADC). This approach developed as a mechanism to reduce drug toxicity by directing drug activity to tumor cells and avoiding bystander effects on normal tissue. Proof of principle was demonstrated by enclosing doxorubicin in liposomes coated with specific antibody against mouse squamous cell carcinoma cells, and then administering them to affected mice with resulting tumor eradication/ reduction in tumor mass.[1] Doxorubicin conjugates, however, had very limited clinical efficacy in humans and more potent ADCs were subsequently developed with two currently licensed for use in the US. One example is brentuximab vedotin, which has a chimeric antibody directed against CD30 (expressed on both Hodgkin's and large cell lymphomas, and embryonal carcinomas) conjugated with the antineoplastic compound monomethylauristatin E – when administered to patients with resistant/ refractory Hodgkin's lymphoma, efficacies in excess of 85% have been reported.[13,12]

T Cell-based specific/ non-specific

Various approaches to administering different T cell types (CTLs, tumor infiltrating lymphocytes [TILs], T_H and Tregs) for cancer treatment have been trialled since the mid-20th century. See **Table 1**. The immunological basis for T cell therapy is evident from the significantly improved survival in patients with colorectal cancer whose tumors show high levels of TILs compared with those patients with low level TIL infiltration. Although there are a large number of TAAs against which T cell activity might be directed, the process, also termed adoptive T cell transfer, has not yet resulted in any licensed (passive) vaccines. Proof of principle of the antitumor effects of administered CTLs has, for example, been demonstrated in patients with malignant melanoma where T cell infiltration of tumor occurred although its clinical impact was limited. The use of TILs isolated from patient tumor specimens has also been generally unsuccessful.[14] Of concern has been the emergence during treatment of tumor escape variants presumably indicating the need for CTLs, and hence TAAs, to comprise a broad range of epitopes, this would appear to be similar to the postulated emergence of a mumps vaccine escape variant against which the current Jeryl Lynn strain is not effective.

Active immunization with cancer vaccines

Active immunization for cancer involves administering a cell component (s) or whole cell, which can act in a non-specific or specific manner as discussed below. See **Table 1**. ID vaccines generally contain a number of different excipients that either enhance the host immune response or maintain vaccine effectiveness in a range of environmental conditions – the former include adjuvants that are included in many cancer vaccine preparations.

Non-specific

A non-specific vaccine is used to generate a host cell response that eliminates the cancer through a generalized, non-specific immune stimulant effect, rather like the MBVs/ Coley's toxins described previously. These vaccines may use additional approaches – for example they can also be used as a vehicle to deliver immunomodulatory molecules to the tumor environment.

The first vaccine used in this way was Bacille Calmette Guerin (BCG) that traditionally was developed to protect against hematogenous Tuberculosis. In 1976 Morales et al. reported on the use of intravesical BCG to successfully treat superficial bladder cancer and prevent disease recurrence. The response involves both a cell mediated and humoral response to the vaccine. The former on the basis of granulocyte infiltration of the tumor, followed by macrophages and T_H lymphocytes, and the latter because of the observed cytokines identified in urine of patients administered intravesical BCG, which Bohle et al. suggested represented a predominant T_H1 response – TNF-α, IL-1, IL-2, IL-6, IL-8, IL-12 and IL-18. The T_H2 cytokines IL-5 and IL-10 were also detected, as were GM-CSF, IFN-γ and IL8 which are neither T_H1 or T_H2 cytokines – the authors did, however, acknowledge some considerable variability in cytokine excretion by patient.[3] This non-specific effect of BCG has previously been used to treat leukemia, melanoma and prostate cancer where a small but non-significant improvement in outcome was observed.[9]

Specific

This approach uses a TAAs-based vaccine to generate an adaptive anti-tumor response that subsequently eliminates the cancer

cell. The vaccine may be based on single or multiple antigens or a whole cell preparation can be used – for the latter the cells may be either autologous (same host) or allogeneic (same species different host). The former are more difficult to obtain and prepare, and as a consequence established allogeneic cell lines have been frequently used to develop vaccines (see GVAX below) – although usually MHC matched prior to use it is possible that a "graft versus host response" may explain some of the observed anti-tumor activity. Furthermore, transfection of the allogeneic cell line with proinflammatory cytokines (for example Granulocyte Macrophage Colony Stimulating Factor [GM-CSF]) has been used to enhance the response. Intradermal vaccine administration with multiple dose protocols appears to be the preferred option.[9]

The single or multiple antigen cancer vaccine is equivalent to the subunit ID vaccine. Various approaches to developing these vaccines have been utilized – peptide, protein, tumor lysate and shed antigen vaccines – but none has successfully passed clinical studies to licensing. Given the postulated importance of a cell mediated immune response in eliminating malignant cells, it would not be expected that such antigen vaccines on their own, that generate a primarily B cell response, would be clinically effective. These have been reviewed elsewhere.[10]

GVAX Prostate is an example of the whole cell vaccine approach – this uses an irradiated prostate allogeneic tumor cell line as the "immunogen" combined with GM-CSF in individuals with hormone resistant prostate cancer. The use of the whole cell as the vaccine immunogen results in multiple tumor antigens being presented to host dendritic cells, irradiated cells are unable to replicate and therefore do not constitute a tumor risk to the host. The fact that the vaccine also expresses GM-CSF is believed to optimize immune cell recruitment at the injection site. Clinical trials have been successfully undertaken to demonstrate safety and toxicity, clinical trials to determine clinical benefit need to now be performed.[23] There is also a similar GVAX irradiated pancreas tumor cell line vaccine.

Summary

Malignancies are an important cause of morbidity and premature mortality in middle and high income countries where as many as 10% of deaths result from lung, breast or gastro-intestinal malignancies. Vaccines to treat these cancers effectively would therefore be of considerable importance, but require an in-depth understanding of the interaction between the tumor and the host immune response, including how individual tumors are able to modulate this host response to enhance their survival chances.

Two vaccine programmes to prevent cancer have been successfully developed and implemented for HBV-associated Hepatocellular and HPV-associated cervical cancer. Given that both HBV and HPV immunology is relatively simple with disease prevention associated with a neutralizing antibody response, the traditional approach to immunization used for many vaccine preventable infections has been applied for these two infections – namely a simple peptide antigen (s), an adjuvant and various excipients including preservatives, buffers and diluents.

In contrast the progress in developing therapeutic vaccines to treat malignant disease has been much slower and reflects the complexity of the host/ tumor interaction, with the need to generate a cell mediated response apparently more important than the simple antibody response that is so effective for a number of vaccine preventable infections. This necessary understanding informs the selection of tumor vaccine antigen/ immunogen, the mechanism (s) for involving DCs in uptake, processing and presentation of these tumor components, and delivery approaches that involve route of vaccine administration and schedule, making the construction of therapeutic cancer vaccines inevitably far more complex than their ID equivalent.

As knowledge of tumor host interaction has expanded so the use of such preparations has accelerated over recent years; like ID vaccines they can be divided into active and passive types, with both being subdivided into specific and non-specific vaccines based on their mode of action. Passive types are based on the administration of preformed antibody or T lymphocytes: active immunization may be designed to eliminate the malignant cell, or enhance the host immune response in a more general manner.

It is evident, however, that future effective cancer vaccines will not be as easily categorised as active/ passive and specific/ non-specific but will contain a number of separate components based on an in-depth understanding of tumor host immunology. Thus the immunogen is likely to have multiple epitopes, in part to prevent the emergence of escape variant malignant cells – specific active immunization. A means of enhancing the host response may be included for example, a transfected proinflammatory cytokine gene (s) – non-specific active immunization. Incorporating a means of overcoming tumor downregulation of the host response may also be a necessary feature, for example blocking T cell suppression – non-specific passive immunization. And finally the vaccine may directly target transformed cells using monoclonal antibodies – specific passive immunization.

For the foreseeable future, these vaccines will not be used for treatment alone but will be part of a therapeutic approach that involves traditional modalities. It would be expected, however, that as tumor immunology understanding increases their impact will become increasingly more effective.

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