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REVIEW | OPEN ACCESS

Vaccines targeting the neovasculature of tumors

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Abstract

Angiogenesis has a critical role in physiologic and disease processes. For the growth of tumors, angiogenesis must occur to carry sufficient nutrients to the tumor. In addition to growth, development of new blood vessels is necessary for invasion and metastases of the tumor. A number of strategies have been developed to inhibit tumor angiogenesis and further understanding of the interplay between tumors and angiogenesis should allow new approaches and advances in angiogenic therapy. One such promising angiogenic approach is to target and inhibit angiogenesis with vaccines. This review will discuss recent advances and future prospects in vaccines targeting aberrant angiogenesis of tumors. The strategies utilized by investigators have included whole endothelial cell vaccines as well as vaccines with defined targets on endothelial cells and pericytes of the developing tumor endothelium. To date, several promising anti-angiogenic vaccine strategies have demonstrated marked inhibition of tumor growth in pre-clinical trials with some showing no observed interference with physiologic angiogenic processes such as wound healing and fertility.

Introduction

Cancer mortality is related to the spread of neoplastic cells to distant loci where the cells, supported by existing blood vessels and angiogenesis, proliferate and give rise to secondary tumors. Tumor angiogenesis is up-regulated by a number of conditions including hypoxia, hypoglycemia, mechanical disruption, and genetic and inflammatory alterations [1] that lead to activation of growth factors and pro-angiogenic genes [2, 3]. The stringent regulation of angiogenesis in normal tissues is often lacking in tumor angiogenesis, resulting in immature and leaky tumor vessels. Furthermore, compared to the tissue-vessel distribution in normal tissue, there is an uneven distribution of vessels within tumors, leading to tumor hypoxia and inefficient transport of chemotherapeutic drugs. In contrast to normal endothelial cells, in which the vast majority are quiescent, tumor endothelial cells actively proliferate, driven by hypoxia and increased levels of angiogenic factors and their cognate receptors. These differences between quiescent and angiogenic endothelial cells resulted in the first clinical anti-angiogenesis trial on human cancer two decades ago. There are now several anti-angiogenic therapies that have received FDA approval including sunitinib, sorafenib, and bevacizumab; and with more than 40 anti-angiogenic drugs in clinical trials [4], further advances are anticipated [5– 11].

Differences among tumor endothelial cells and non-malignant endothelial cells may not only be quantitative but in some instances may also be qualitative. With serial analysis of gene expression, investigators compared gene expression from endothelial cells isolated from normal or malignant tissue, and found that several transcripts (e.g., CD276) were specifically elevated in the tumor endothelium [12, 13]. Although most receptors/proteins that are increased in the tumor endothelium are also up-regulated in physiologic angiogenic processes, CD276 is not increased in the vessels of wounds or the corpus luteum [13]. Nevertheless, CD276 is not completely specific for the tumor endothelium because its expression may be induced by cytokines on the cell surfaces of B cells, T cells, and dendritic cells. There are also many proteins/receptors in tumor endothelial cells that are overexpressed (such as VEGFR2 and survivin) compared to expression in quiescent endothelial cells. Proteins differentially expressed on tumor endothelial cells or the supporting matrix are attractive targets for vaccine strategies, with the goal of breaking tolerance to self-antigens.

Targeting the tumor vasculature with vaccines as well as with other immunotherapies may have several potential advantages over targeting tumor cells. First, tumor endothelial cells are more accessible to the immune system than are tumor cells at a distance from the vessels. Second, endothelial cells of the tumor are usually more stable genetically than tumor cells, thereby reducing the risk of resistance developing to immunotherapies [14, 15]. Chromosomal abnormalities, however, have been identified in endothelial cells of solid tumors [16, 17], and in glioblastomas, the tumor cells and its endothelium are derived from common cancer stem-like cells [18, 19]. Third, down-regulation of MHC I in tumor cells occurs less frequently in tumor endothelial cells, thereby leading to a more potent CD8+-mediated response. Fourth, since inhibition of a single endothelial cell can inhibit up to 100 tumor cells [20, 21], immunotherapies directed toward tumor endothelial cells have the potential of an amplifying inhibitory effect.

As a result of these putative advantages and differentially expressed proteins in the tumor endothelium, a number of immunotherapeutic strategies have targeted angiogenesis, including monoclonal antibodies, vaccinations, and adjuvant co-

stimulatory therapies [1]. The most successful of these approaches, thus far, has been passive immunotherapy by utilizing monoclonal antibodies. In 2004, the monoclonal antibody bevacizumab which targets angiogenesis through VEGF received approval for treatment of colorectal cancer [22]. Bevacizumab has also shown efficacy against other cancers including lung, renal, and breast cancers [23, 24]. It is likely that the success and ability of bevacizumab to selectively target tumor endothelial cells has provided impetus to development of other forms of angiogenic immunotherapies. Several promising preclinical studies of tumor endothelial vaccines have led to clinical trials that are primarily in phase I. In the burgeoning field of tumor immunotherapies, we will focus on tumor vaccines that have a major anti-angiogenic component.

Delivery Systems of Tumor Endothelial Vaccines

As this review will highlight, there are many promising tumor endothelial vaccines with demonstrated efficacy in various animal models. These vaccines have been delivered by different approaches/vectors, including direct inoculation of peptides or "naked DNA", gene gun with gold particles, intradermal electroporation, tumor or dendritic cell-based vectors, and attenuated live bacteria vectors. The particular delivery system for anti-angiogenic vaccine therapy is selected at least in part based on whether immunizations are comprised of peptides/proteins, DNA, or RNA. For peptide delivery systems, the peptide can be inoculated directly into the animal model along with an adjuvant, or dendritic cells can be pulsed with the peptides before their inoculation. For gene therapy vaccine approaches, recombinant DNA may be delivered alone ("naked DNA"), by non-viral and viral carriers, or by eukaryotic and prokaryotic cells. Although delivery systems for vaccines targeting tumor endothelial cells generally mirror those targeting tumor cells [25– 29], there are exceptions such as the infrequent use of viruses with tumor-endothelial vaccines. Nevertheless, we see no contraindication to using modified herpes simplex or vaccinia viruses to augment the immune response of endothelial vaccines as in tumor cell vaccines.

To date, plasmids encoding angiogenic self-antigens are the most common forms of nucleic acid to demonstrate an anti-angiogenic effect in mouse models. Moreover, bacteria have been the most frequently used delivery system for plasmid-based vaccines (see reviews of [30, 31]). Of the 32 vaccines with specific targets covered in this review, bacteria were the primary delivery vector in 11 studies, whereas direct inoculation of "naked" plasmid DNA was the primary delivery system in 6 studies (see Table 1). Several animal studies have demonstrated that orally administered bacteria-based vectors with attenuated, nonreplicating strains of *Listeria* or *Salmonella* have the potential to prevent and treat cancer through inhibition of angiogenesis [32– 35]. Although safety concerns are a factor in considering these bacterial delivery systems, it is of note that one *Salmonella enterica* strain has been approved by the FDA for vaccine use [30, 36]. Moreover, several bacteria-based vaccines that had marked anti-angiogenic and anti-tumor activity showed little to no autoimmune response, at least in the animal studies. Electroporation is also an appealing approach that has been used with DNA or RNA vaccines that target the tumor endothelium [37, 38]. Because of the high number of antigen presenting cells, the skin is a common route of delivery for varied delivery systems including electroporation. The intradermal DNA vaccination approach enables long-term immune protection against tumor angiogenesis and growth. Although electroporation has been used less frequently than direct inoculation of plasmid DNA, it may be more effective. For example, intradermal electroporation of "naked DNA" gave a much stronger anti-angiogenic and anti-tumor immune response to survivin compared to intramuscular DNA injection [37, 39, 40].

Table 1

Different Strategies Utilized With Tumor Endothelial Vaccines

TARGET	FORM OF THE VACCINE	TUMORS	Vector/Route	MECHANISMS	Other Comments	REFERENCE
Endothelial Cell Targets						
VEGFR2	mVEGFR2-AP fusion protein	Melanoma and lung carcinoma	DC pulsed	Ab, CTL Primarily CD8+	P	Li Y et al., 200 [45]
	Autologous DNA vaccine-full-length mVEGFR2	Melanoma, colon carcinoma, non-small cell lung carcinoma, hepatoma	*S. typhimurium* , oral	CTL	Modest delay in wound healing P, T	Niethammer A et al., 2002 [59]
	Xenogeneic DNA vaccine	Murine melanoma, carcinoma, fibrosarcoma, lyphoma	"Naked" DNA, SC	Ab, CTL, CD4+ (Th1)-mediated	Quail VEGFR2 vaccine Increased levels of IgG2a and 2b P, T	Liu, J-Y et al. 2003 [130]

TARGET	FORM OF THE VACCINE	TUMORS	Vector/Route	MECHANISMS	Other Comments	REFERENCE
Endothelial Cell Targets						
	Autologous DNA vaccine-mVEGFR2 fragment	Breast tumor-rat *Her2* expressing carcinoma; murine p53-deficient breast carcinoma	*L. monocytogenes*, oral	CD8+ mediated Inf-γ Elispot	Encodes listerolysin-VEGFR2 fragment; No effect on wound healing or pregnancy P, T	Seavey MM e al., 2009 [32
	Autologous DNA minigene	Murine breast and colon carcinomas	*S. typhimurium*, oral	CTL	Encodes H-2Kd or H-2Dd restricted peptides P	Luo Y et al., 2007 [63]
	Autologous DNA minigene	Murine lung, prostate, and breast cancers	*S. typhimurium*, oral	CTL	Plasmid also encodes HIV-TAT peptide P	Zhou H et al. 2005 [61]
	$H\text{-}2D^b$ - restricted Peptides	Murine colon carcinomas	SC	CTL	adjuvant (GM-CSF, CD40 Ab); T	Dong Y et al. 2006 [62]
	HLA-A2 or-A24 restricted hVEGFR2 Peptides	Mouse melanoma and colon carcinomas	ID	CTL	HLA-24 restricted Peptide 169 (RFVPDGNRI) induced human PBMC-CTL lysis of endothelial cells	Wada S et al. 2005 [43]
	VEGFR2 Peptide 169 + gemcitabine	Pancreatic cancer (Phase I)	SC	CTL; Reduced Treg cells	Adjuvant (IFA)	Miyazawa M. al., 2009 [66
	Xenogeneic DNA vaccine	Murine breast and colon carcinoma	Cationic liposomes, IV	Ab, CTL	Human VEGFR2; P, T	Xie K et al., 2009 [65]
	Autologous DNA vaccine (VEGFR2 fused with β-defensin 2)	Murine lung and colon cancer	Cationic liposomes, IM	Ab, CTL	Antitumor and anti-angiogenic synergy between VEGFR2 and β-defensin-2; P, T	Wang YS et al 2007 [64]
	Autologous DNA vaccine-Extracellular Domain	Murine Lung	*S. typhimurium*, oral	Ab, CTL CD4+ (Th1), C8+ mediated	Increased levels of IgG2a and 2b P	Zuo SG et al. 2010 [67]
VEGF	Xenogeneic DNA vaccine	Fibrosarcoma, breast cancer, hepatoma	"Naked" DNA, IM	Ab CD4+-mediated	Xenopus VEGF has about 75% homology with humans and mice P, T	Wei YQ et al. 2001 [58]
	Autologous or xenogeneic protein	Murine and human colon caricinoma; human rhadosarcoma	IM	Ab;	h- or mVEGF conjugated to KLH P	Rad FH et al. 2007 [73]
FGFR-1/bFGF	Autologous bFGF peptide	Murine melanoma and lung carcinoma	Lipid A containing liposomes IM	Ab	Effective vaccine against the 44 aa segment of the heparin binding domain; No effect on wound healing or pregancy P	Plum SM et al 2000 [76] Plu SM et al., 200 [77]

TARGET	FORM OF THE VACCINE	TUMORS	Vector/Route	MECHANISMS	Other Comments	REFERENCE
Endothelial Cell Targets						
	Xenogeneic DNA vaccine	Murine fibrosarcoma, hepatoma and breast cancer	"Naked" DNA, IM	Ab	FGFR-1 from Xenopus laevis Delayed wound healing P, T	He QM et al. 2003 [78]
TEM8	Autologous TEM8 with rat Her2 or human tyrosinase-related protein1 DNA vaccine	Rat Her-2 expressing breast carcinoma; Murine melanoma	Gold-particle gene gun	No Ab or CTL response with TEM8 vaccine alone	Synergy observed P	Felicetti P et a 2007 [82]
	Xenogeneic DNA vaccine	Murine melanoma	*S. typhimurium* oral	CTL;	Human TEM8 No effect on wound healing T	Ruan Z et al. 2009 [83]
ENDOGLIN (CD105)	Xenogeneic protein	Murine lung, melanoma, colon carcinoma, fibrosarcoma	SC	Ab;	Synergy with cis-platinum; adjuvant (alum) P, T	Tan GH et al. 2004 [87] Ta GH et al., 200 [88]
ANGIOMOTIN	Xenogeneic DNA vaccine, full-length	Her-2 expressing breast cancer in transgenic mice	Electroporation, TC	Ab	Human angio-motin and Her-2; antitumor synergy when combined with Her-2 DNA vaccine	Holmgren L e al., 2006 [38
TIE2	Xenogeneic protein vaccine	Murine hepatomas and melanomas	SC	Ab	Chicken Tie2 P, T	Luo Y et al., 2006 [94]
	DNA vaccine encoding HLA-restricted peptides	*In vitro* lysis of endothelial cells expressing Tie-2; Tumor response not tested	Gold-particle gene gun	CTL	HLA-A*0201/Kb transgenic mice; the epitope (FLPATLTMV) had the highest CTL response;	Ramage JM e al., 2004 [95
HP59/SP55	Xenogeneic peptides	Murine lung carcinoma	Not stated	Ab	HP59 and SP55 peptide mixture P	Fu C et al., 200 [96]
Pericyte Targets						
HMW-MAA	Xenogeneic DNA vaccine, HMW-MAA fragment	Murine melanoma, renal carcinoma, Her-2 transgenic mice	*L monocytogenes* IP	Ab, CTL	HMW-MAA (2160-2225 aa) fragment fused to LLO T	Maciag PC et al., 2008 [33
PDGFRβ	Autologous DNA vaccine, full-length	Murine colon, breast, lung carcinoma	*S. typhimurium* oral	CTL	Also, targets activated fibroblasts P, T	Kaplan CD et al., 2006 [34
Combined Targets						
SURVIVIN	Xenogeneic DNA vaccine	Murine melanoma	Electroporation, ID	CTL	Human survivin vaccine P	Lladser A et al 2010 [37]
	Survivin/CCL21 DNA vaccine	Murine lung carcinoma	*S. typhimurium* , oral	CTL	Mouse survivin; no effect on wound closure or fertility P, T	Xiang R et al. 2005 [35]

TARGET	FORM OF THE VACCINE	TUMORS	Vector/Route	MECHANISMS	Other Comments	REFERENCE
Endothelial Cell Targets						
GRP	Recombinant chimeric HSP-65 -GRP6 fusion protein	Murine breast carcinomas	SC	Ab, CTL	6 tandem repeats of GRP(18-27 aa) fused to HSP-65 P, T	Guojun W et a 2008 [115]
	Chimeric-HSP65-GRP6 DNA Vaccine	Murine melanoma	"Naked" DNA, IM	Ab	chimera also includes tetanus toxoid and HSP70 fragments; P	Fang J et al., 2009 [116]
LEGUMAIN	Allogeneic DNA vaccine	Murine non-small lung, colon and breast cancers	*S. typhimurium* , oral	CTL	Mutant polyubiquitin incorporated P, T	Luo Y et al., 2006 [119]
	Autologous DNA minigene	Murine breast carcinoma	*S. typhimurium* , oral	CTL	Angiogenesis inhibited more 90%; H-2K vaccine more potent than H-2D P	Lewen S et al 2008 [120]
MMP-2	Xenogeneic full-length MMP-2 DNA vaccine	Murine fibrosarcoma, hepatoma, lung carcinoma	"Naked" DNA, IM	Ab	Chicken MMP-2 P, T	Su JM et al., 2003 [123]
β3 Integrin	Xenogeneic β3 DNA vaccine	Murine fibrosarcoma, mammary carcinoma	"Naked" DNA, IM	Ab	Chicken β3 ligand binding domain P, T	Lou YY et al. 2002 [129]

Abbreviations in table; Ab, antibody response; AP-alkaline phosphatase; CTL, cytotoxic T-lymphocyte response; m, mouse; h, Human; LLO, listerolysin; P, protective vaccine approach in which pre-immunized mice show anti-tumor activity; T, therapeutic vaccine approach in which vaccine, administered after tumor inoculation, has anti-tumor efficacy; keyhole limpet hemocyanin; SC, subcutaneous, ID, intradermal, IM, intramuscular, TC, transcutaneous

Besides tumor cells [41], dendritic cells (DC) pulsed with peptide/protein epitopes (or DNA encoding these epitopes) have also been employed successfully to vaccinate animals against tumor endothelial antigens [42, 43]. DC process and present antigens to T and B cells and produce cytokines and chemokines which in turn activate NK cells [44]. DC-based therapies involve modification with pulsed (loaded) defined peptides, whole protein lysate, and/or transfected DNA or RNA [42, 43]. An interesting anti-cancer and anti-angiogenic approach was the use of a VEGFR2-loaded DCs that led to greater than 80% reduction in lung metastases of two different tumor models [45]. Different forms of nucleic acids have also been used for angiogenic peptides and proteins. In addition to peptides, proteins, and recombinant DNA, mRNA is another promising strategy to enhance cellular immunity [46]. For example, antitumor synergy was observed when dendritic cells were transfected with mRNA from two receptors (VEGFR-2 and Tie2) that are highly expressed on tumor endothelial cells [47]. Varying the routes of pulsed DC administration may also affect the efficacy of tumor vaccines. Pellegatta and colleagues determined that glioblastomas regressed significantly more when mice received both intratumoral and subcutaneous pulsed DC injections compared to those which received subcutaneous injections [48].

Although most authors have not compared different carrier systems with one another, it is evident that the carrier system and route of administration are critical for the success of the vaccine in animal models and in human clinical trials [49]. We have already discussed differences in the immune response to survivin based on whether electroporation or direct injection of DNA was used. In addition, when Lai et al. compared three different delivery approaches (gene gun with non-coated particles, gene gun with coated gold particles, and intramuscular injection) for the EGFR plasmid vaccine, the gene-gun with non-coated particle vaccine had the greatest cytotoxic T-lymphocyte (CTL) response and anti-tumor response [49]. Interestingly, the CD4+ response and the levels of EGFR-specific antibodies were much greater with the coated gold particle method. The required robust immune response to overcome self-tolerance will no doubt eliminate several carriers, and perhaps autoimmunity will eliminate other carriers. Which of the carriers can be translated successfully from the animal models to humans remains to be determined. The delivery vehicle and the immune-adjuvant will likely be as important as the selected angiogenic antigen to obtain a successful tumor response in humans.

Approaches for Anti-Angiogenic Vaccines

A goal of vaccination in anti-angiogenic therapies targeting tumors is to break immune tolerance to self-antigens and induce specific, strong, and persisting immune response leading to eradication of cancer. Complex networks created by

several immune-competent cells such as dendritic cells, B cells, cytotoxic CD8+ T, CD4+ T-helper, and NK cells in combination with cytokines, chemokines and other immune mediators are required for effective vaccines and immune reactions against cancer (Figure 1). Two anti-angiogenic vaccine approaches have shown promising results in reducing tumor growth and/or metastases: endothelial cell vaccines that demonstrate antitumor activity and vaccines targeting specific angiogenic targets. Figure 1

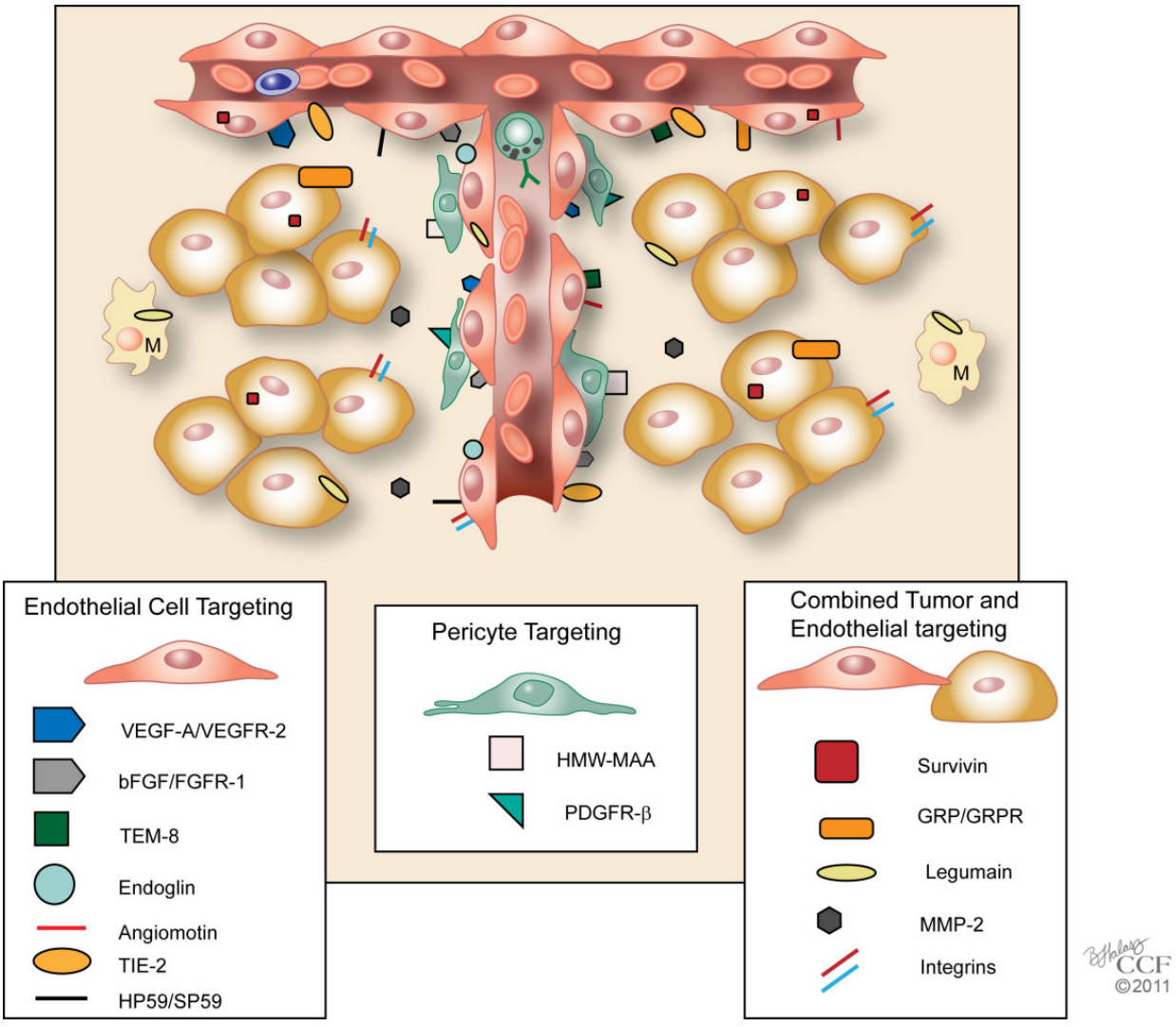
Major mechanistic immune pathways of anti-angiogenic vaccines and their targets. Vaccine antigens are processed by antigen processing cells such as dendritic cells and presented to T cells. Depending on the antigen, the route of administration, and the vector, peptide presentation to either major histocompatibility complex (MHC) class I or II occurs, with subsequent interaction with T-cell receptors on CD4+ or CD8+ cells. Cytotoxic CD8+ T cells recognize and lyse tumor endothelial cells directly by perforin-mediated and Fas-mediated cytotoxic mechanisms. CD4+ T-helper cells, through release of different cytokines, can induce Th1 or Th2 responses that stimulate B-cells to produce antibodies and/or activate NK cells and macrophages to inhibit tumor endothelium. Representative targets related to endothelial and cancer cells and their environment for anti-angiogenic vaccines are depicted. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2010. All Rights Reserved.

I. Endothelial Cell Vaccines

II. Vaccines Expressing Defined Targets

Defined endothelial vaccines are based on specific targets and include peptides and nucleic acids (DNA or RNA) that encode these peptides (see Table 1, Figure 2). Suitable angiogenic targets in tumors may be receptors/markers on endothelial cells or alternatively, may be growth factors secreted by cells other than endothelial cells. To date, there has been no target or epitope that is completely specific for tumor endothelial cells. For example, TEM8, one of the more specific tumor endothelial cell markers identified thus far, was originally found in the tumor vasculature and the developing embryo, but it has since been found on cell surfaces of melanomas, breast cancers, and dendritic cells. Despite the overlap in this system, we think that classification of angiogenic vaccines based on preponderance of their targets within most tumors may be useful. As a result, we have divided tumor endothelial vaccines with defined targets into three classes: 1) growth factors/receptors or epitopes that are primarily associated with growth of tumor endothelial cells; 2) growth factors/receptors or epitopes that promote growth of pericytes; and 3) proteins/growth factors/receptors that enhance both tumor and endothelial cell growth or survival. The growth factors were classified, not on their cells of origin, but on the location of their receptors.

Figure 2



Tumor Endothelial Vaccines with Defined Targets. Schematic model of a tumor and its angiogenic vessels are shown with targets of tumor endothelial vaccines. These vaccines may be classified on their specific targets 1) that are primarily associated with tumor endothelial cells, 2) that promote growth of pericytes, or 3) that enhance both tumor and endothelial cell growth or survival. Growth factors were classified based on the location of their receptors. M, Macrophage.

Conclusion

Significant resources including numerous pre-clinical and clinical studies have been devoted to the development of tumor vaccines. Thus far, these results have progressed and culminated in the approval a vaccine targeting advanced prostate cancer (Provenge). Although the benefits with this FDA-approved vaccine are modest, further improved vaccine versions are no doubt on the horizon and will aid with other vaccines approaches, including those against the tumor endothelium. Compared to tumor vaccines, the number of varied approaches for tumor endothelial vaccines is relatively limited and is currently restricted to pre-clinical experiments and primarily phase I trials.

As discussed in this review, several studies with tumor endothelial vaccines show anti-tumor efficacy in both transplantable and transgenic tumor-bearing animal models. Of particular note were the bacteria-based vaccines that showed marked anti-tumor response with varied anti-angiogenic genes and few if any side effects. Nevertheless, major obstacles still remain, including identification and validation of specific targets on the tumor endothelium, inhibition of local suppression mechanisms, and boosting anti-tumor immunity through NK cells [132]. Thus far, there have been few data from the endothelial vaccine studies on the various T-cell subtypes, including regulatory T-cells or myeloid derived suppressor cells [25, 133, 134], and comparison of T-cell subtypes in the tumor and peripheral tissues may be useful in development of more effective vaccines. Other immune cells such as NK cells have not yet shown a direct role in augmenting the efficacy of tumor endothelial vaccines [64, 87, 94, 130], but more research examining interactions among NK cells, dendritic cells, and immunomodulatory agents is needed [132, 135, 136].

Since tumor angiogenesis is a complex process, targeting a single epitope is unlikely to be successful. In many cases, the treated tumor adapts and finds alternative mechanisms of tumorigenesis eventually leading to resistance to therapy. Thus, combinations of anti-angiogenic vaccines with existing chemotherapy or immunomodulatory therapies offer interesting and exciting possibilities. For example, as discussed previously in this review, combinatory treatments between vaccines and IL-12, GM-CSF, CCL21, or β-defensins markedly increased the immune response toward tumor endothelial cells [39, 41, 62, 64]. Nevertheless, these co-stimulatory therapies have been used sparingly and other commonly used cytokines such as IL-2, IFN α or β [137– 139] have not been co-administered or transfected into immune and/or endothelial cells to augment vaccine efficacy. Moreover, considerable more research is needed to determine the optimal co-stimulatory therapy to be administered with the vaccine for the different delivery methods.

Another consideration in developing anti-angiogenic vaccines is their potential for causing complications. Cross-reactivity between tumor and non-tumor disease tissues due to tumor endothelial vaccine may result in reduced compensatory biological processes. The classic tumor endothelial target is VEGFR2 up-regulated not only in the endothelial vessels of tumors but also in healing wounds and hypoxic cardiac tissues. Interestingly, at least with 4 vaccine studies (VEGFR2, VEGF-A, bFGF, survivin/CCL21) tumor angiogenesis was markedly inhibited, but these vaccines did not interfere with normal physiologic processes in several studies [32, 35, 47, 76, 77]. The mechanism whereby tolerance to self-angiogenic antigens in tumors but not in normal angiogenic processes is broken remains unknown. It has been suggested that differences in breaking self-angiogenic antigen tolerance between tumors and normal physiological processes may be based on the difference of their vascular organization [32, 140]; determining whether or not this is the mechanism for this difference will require further study.

To ensure effective tumor eradication and reduce autoimmune side effects, intensive efforts are still needed to identify additional targets specific to the tumor endothelium. One such study recently found highly specific and expressed markers of the tumor endothelium that were not expressed in quiescent blood vessels or physiologic angiogenesis [13]. Nevertheless, the efficacy of vaccines against these new markers has not yet been determined. Alternatively, finding tissue-specific vascular targets (e.g., prostate) may enable development of tumor endothelial vaccines with acceptable side effects [141, 142]. There is also the possibility that tailored endothelial vaccines may be developed based on specific endothelial epitopes associated with certain tumors [143]. As new anti-angiogenic targets are discovered, we anticipate that promising new therapeutic approaches are on the horizon.

Abbreviations

- **bFGF:**
  basic fibroblast growth factor
- **CTL:**
  cytotoxic T-lymphocyte
- **DC:**
  dendritic cells
- **FGFR-1:**
  fibroblast growth factor receptor-1

- **GRP:**
gastrin-releasing peptide
- **GM-CSF:**
granulocyte macrophage-colony stimulating factor
- **HMW-MAA:**
High Molecular Weight-Melanoma Associated Antigen
- **HUVECs:**
human umbilical vein endothelial cells
- **IFN:**
interferon
- **im:**
intramuscular
- **ip:**
intraperioneal
- **IL:**
interleukin
- **-LLO-HMW-MAA :**
that contains and secretes a fragment of HMW-MAA fused to the N-terminal listeriolysin O
- **MHC I:**
Major Histocompatibility Complex I
- **MMP-2:**
Matrix Metalloproteinase-2
- **NK:**
Natural Killer cells
- **PDGFR-β:**
platelet derived growth factor receptor beta
- **TEM:**
tumor endothelial marker
- **Th:**
T helper
- **VEGF:**
vascular endothelial growth factor.

Declarations

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Authors' original submitted files for images

Below are the links to the authors' original submitted files for images.

Authors' original file for figure 1

Authors' original file for figure 2

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AM, QL, S-TC, and AJM were involved in preparation of the manuscript. AM and AJM also revised the manuscript for final approval. All authors have read and approved the final manuscript.

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