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Therapeutic gene modified cell based cancer vaccines

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ABSTRACT

History of cancer immunotherapy lasts for more than 120 years. In 1891 William B. Coley injected bacteria into inoperable cancer (bone sarcoma) and observed tumor shrinkage. He is recognized as the """Father of Immunotherapy""". Cancer immunotherapy is based on the ability of the immune system to recognize cancer cells and to affect their growth and expansion. Beside the fact that, tumor cells are genetically distinct from their normal counterparts, and should be recognized and eliminated by immune system, the tumor associated antigens (TAAs) are often poorly immunogenic due to immunoediting. This process allows tumor to evolve during continuous interactions with the host immune system, and eventually escape from immune surveillance. Furthermore, tumor microenvironment consists of immunosuppressive cells that release immunosuppressive factors including IL-6, IL-10, IDO, TGFβ or VEGF. Interactions between cancer and stroma cells create network of immunosuppressive pathways, while activation of immune defense is inhibited. A key to successful immunotherapy is to overcome the local immunosuppression within tumor microenvironment and activate mechanisms that lead to tumor eradication. There are two clinical approaches of immunotherapy: active and passive. Active immunotherapy involves stimulation of immune response to tumor associated antigens (TAAs), either non-specifically via immunomodulating agents or specifically employing cancer vaccines. This review presents the progress and breakthroughs in design, development and clinical application of selected cell-based tumor vaccines achieved due to the generation and development of gene transfer technologies.

1. Introduction

History of cancer immunotherapy lasts for more than 120 years. In 1891 William B. Coley injected bacteria into inoperable cancer (bone sarcoma) and observed tumor shrinkage. Over the next 40 years he injected more than 1000 cancer patients with bacteria and bacterial products, later referred to as Coley's toxins or Coley's vaccines (Coley, 1893). He administered his vaccine intravenously, subcutaneously or directly into tumors. Detailed clinical assessment of treated over 1000 patients revealed that 500 of these demonstrated nearly complete regression (Nauts and McLaren, 1990). He is recognized as the """Father of Immunotherapy""".

The concept of cancer immunotherapy is based on the ability of the immune system to recognize cancer cells and to affect their growth and expansion. Beside the fact that, tumor cells are genetically distinct from their normal counterparts, and should be recognized and eliminated by immune system, the tumor associated antigens (TAAs) are often poorly immunogenic due to immunoediting (Schreiber et al., 2011). This process allows tumor to evolve during continuous interactions with the host immune system, and eventually escape from immune surveillance

Abbreviations: AAV, adeno-associated viruses; Ad6, adenovirus serotype 6; ABCB5+, ATP-binding cassette sub-family B member 5; ALDH, aldehyde dehydrogenase; AML, acute myeloid leukemia; APCs, antigen presenting cells; B7.1, (CD80) cluster of differentiation 80; BCG, Bacillus Calmette-Guérin vaccine; cDNA, complementary DNA; CMV, cytomegalovirus; CSCs, cancer stem cells; CTLA-4, cytotoxic T-lymphocyte antigen 4; DCs, dendritic cells; DNA, deoxyribonucleic acid; EGT, electro-gen-transfer; GM-CSF, granulocyte-macrophage colony-stimulating factor; GMTV, genetically modified tumor vaccine; gp100, glycoprotein 100; gp130, glycoprotein 130; H6, hyper interleukin 6; HER2/neu, human epidermal growth factor receptor 2; HIV-1, human immunodeficiency virus 1; HLA, human leukocyte antigen; HPV, human papillomavirus; hTERT, human telomerase; ICAM-1, intercellular adhesion molecule 1; IDO, indoleamine-pyrrole 2,3-dioxygenase; IFNα, interferon alpha; IFNγ, interferon gamma; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; IL-7, interleukin 7; IL-10, interleukin 10; IL-12, interleukin 12; IL-15, interleukin 15; JAK, Janus kinase; LFA-3, lymphocyte function-associated antigen 3; MAGE, melanoma-associated antigen; MAPK, mitogen-activated protein kinase; MART-1, melanoma antigen recognized by T-cells 1; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; MoMLV, Moloney murine leukemia virus; MSCs, melanoma stem cells; NK cells, natural killer cells; OS, overall survival; PD-1, programmed cell death protein 1; PI3K, phosphatidylinositide 3-kinase; RNA, ribonucleic acid; siRNA, short interfering RNA; SIV, human simian immunodeficiency virus; STAT, signal transducer and activator of transcription; SSEA-1, stage-specific embryonic antigen 1; TAAs, tumor associated antigens; TAMs, tumor-associated macrophages; TGFβ, transforming growth factor beta; TIM-3, T-cell immunoglobulin domain and mucin domain 3; TIM-4, T-cell immunoglobulin domain and mucin domain 4; T-regs, T regulatory cells; VEGF, vascular endothelial growth factor; RECIST, Response Evaluation Criteria in Solid Tumors.

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Table 1
Selected clinical non-cell based vaccines.

Vaccine type	Vaccine	Indication	Status
Peptides/proteins	MART-1	Adjuvant in resected melanoma	I
	MAGE-A3	Metastatic melanoma	I/II
	gp100, tyrosinase	Metastatic melanoma	II
	gp100 + IL-2	Metastatic melanoma	III
	Multipeptide	Adjuvant in resected melanoma	II
	Multipeptide + GM-CSF	Adjuvant in resected melanoma	II
	Multipeptide + GM-CSF or IFNa		II
	HER2/neu	Breast cancer	I/II
Viral	Fowlpox virus (gp100)	Metastatic melanoma	II
	OncoVEX — Herpes simplex virus I (GM-CSF)	Metastatic melanoma, head and neck	III
	Vaccinia virus (B7.1, ICAM-1, LFA-3)	Metastatic melanoma	II
DNA	MELAN-A/MART-1	Metastatic melanoma	I
	Allovectin-7 (HLA-B7, beta-2-microglobulin)	Metastatic melanoma	III
Heat shock protein	Oncophage Autologic HSP + GM-CSF + IFNa	Metastatic melanoma	II

(control). Furthermore, tumor microenvironment consists of immunosuppressive cells, such as T regulatory cells (T-regs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and fibroblasts that release immunosuppressive factors including IL-6, IL-10, IDO, TGFβ or VEGF (Kortylewski and Yu, 2008; Vesely et al., 2011). Interactions between cancer and stroma cells create a network of immunosuppressive pathways, while activation of immune defense is inhibited, e.g. by down-regulation of major histocompatibility complexes and lack of costimulatory molecules. Phenotypic analyses show that tumor contains heterogeneous cell populations displaying different karyotype, growth rate, antigenic profiles, gene expression and immunogenicity. Most solid tumors contain a population of slowly dividing cells expressing stem cell markers, which is reported to be resistant to conventional treatment regimens and gives rise to metastatic tumors (Visvader and Lindeman, 2012).

A key to successful immunotherapy is to overcome the local immunosuppression within tumor microenvironment, and activate mechanisms that lead to tumor eradication. There are two clinical approaches of immunotherapy: active and passive. Passive approach encompasses administration of cytokines, activated effector cells or specific monoclonal antibodies targeting tumor cells. Active immunotherapy involves stimulation of immune response to tumor associated antigens (TAAs), either non-specifically via immunomodulating agents such as anti-CTLA-4 antibodies or specifically employing cancer vaccines.

The term 'cancer vaccine' comprises both non-cell and cell based products. Non-cell based approaches include DNA, peptide, protein vaccines, viral or vector based vaccines, anti-idiotypic antibody vaccines or particle based vaccines (Table 1). Cell based vaccines include: whole cell vaccines with adjuvants, whole cell genetically modified tumor vaccines (GMTVs), dendritic cell (DC) vaccines pulsed with nucleic acids, peptides, proteins or cell lysates, cancer cell lysates, pulsed DCs with immune stimulators, immune stimulators fused with TAA, cancer cells fused with DCs or lymphocytes B (Table 2.).

This review presents the progress and breakthroughs in design, development and clinical application of selected cell-based tumor vaccines achieved due to the generation and development of gene transfer technologies. Original work of Dr. Waclaw Szybalski (Szybalska and Szybalski, 1962; Szybalski, 1992) pawed the way into current state of the genetic cancer vaccinology.

Table 2
Selected clinical whole cell vaccines.

Vaccine type	Cell type	Vaccine	Indication	Status
Non-modified	Autologous	+BCG	Metastatic melanoma	I
		VMO — Vaccinia melanoma oncolysate	Adjuvant in resected melanoma	III
	Allogeneic	CanVaxin + BCG	Metastatic melanoma	III
	Allogeneic	Melacine	Adjuvant in resected melanoma	III (approved in Canada)
	Autologous	OncoVAX	Nonmetastatic colon cancer	III
	Autologous	Reniale	Nonmetastatic renal cancer	III
GMTV	Autologous	HLA-B7	Metastatic melanoma	I
	Autologous	IL-2	Metastatic melanoma	II
	Autologous	IL-7	Metastatic melanoma	I
	Autologous	IL-12	Metastatic melanoma	I
	Autologous	GM-CSF	Metastatic melanoma	I
	Autologous	MVAX-dinitrophenyl	Metastatic melanoma	III
	Allogeneic	IL-2	Metastatic melanoma	I, I/II
	Allogeneic	IL-4	Metastatic melanoma	I
	Allogeneic	AGI-101H-secreting designer cytokine hyper IL-6	Metastatic melanoma, adjuvant in resected melanoma	Completed II
	Allogeneic	GVAX — Two allogeneic cultured cancer lines, irradiated and bioengineered to secrete GM-CSF.	Hormone refractory prostate cancer, leukemia	III
	Autologous	Sipuleucel-T (Provenge). DCs pulsed with fusion protein PAP-GM-CSF.	Hormone refractory prostate cancer gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma.	Approved in 2010
	Allogeneic	Onyvax-P — Three human cell lines representing different stages of prostate cancer	Hormone-resistant prostate cancer	II
	Allogeneic	Lucanix — Four non-small cell lung cancer cell lines carrying antisense oligonucleotides against transforming growth factor β	Advanced non-small cell lung cancer	III
	Autologous	Ad/HER2/Neu DC	Breast neoplasms breast cancer, adenocarcinomas	I

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