Biomedicine & Pharmacotherapy 76 (2015) 24–29

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Review

Multiple-purpose immunotherapy for cancer

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ARTICLE INFO

Article history:
Received 25 July 2015
Accepted 16 October 2015

Keywords:
Antitumor immunoprotection
Immunosuppression
Cancer cell-based vaccines
Combined immunotherapy

ABSTRACT

Anti-cancer vaccination is a useful strategy to elicit antitumor immune responses, while overcoming immunosuppressive mechanisms. Whole tumor cells or lysates derived thereof hold more promise as cancer vaccines than individual tumor-associated antigens (TAAs), because vaccinal cells can elicit immune responses to multiple TAAs. Cancer cell-based vaccines can be autologous, allogeneic or xenogeneic. Clinical use of xenogeneic vaccines is advantageous in that they can be most effective in breaking the preexisting immune tolerance to TAAs. An attractive protocol would be to combine vaccinations with immunostimulating and/or immunosuppression-blocking modalities. It is reasonable to anticipate that combined immunotherapeutic strategies will allow for substantial improvements in clinical outcomes in the near future.

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1. Introduction

The first line systemic anti-cancer treatment is based mainly on chemotherapy, which does not deliver an effective systemic treatment in many cases. Somatic cell genetic differences in tumor cells result in high proportion of drug-resistant cells. Furthermore, the proportion of resistant cells progressively increases during the course of treatment because of the selective growth advantages of drug-resistant cells, as compared with drug-susceptible cells. Another problem is that the cytotoxic activity of anticancer drugs is not selective, with drugs exerting their effects not only on tumors but also on normal cells. Therefore, chemotherapy may lead to serious potentially life-threatening side effects, which frequently require additional medical intervention. The development of drugs with targeted cytotoxic activity is unlikely in the foreseeable future because the key biochemical pathways are similar in tumor and normal cells. Nevertheless, tumor cells can be identified by quantitative and qualitative differences in potentially immunogenic markers (antigens) expressed on the cell surface. The current paradigm holds that tumor antigen-specific immune responses are capable of destructing tumor cells, and that the immune system functional status is related to cancer prognosis and clinical outcome [1].

2. Tumor-associated antigens

Tumor-associated antigens (TAAs) can be divided into two groups: (i) those consisting of the unique products encoded by

Abbreviations: Ab, antibody; ADCC, antibody-dependent cell cytotoxicity; APC, antigen-presenting cell; CTA, cancer/testis antigen; CTL, cytotoxic T lymphocyte; DC, dendritic cell; GITR, glucocorticoid-induced tumor necrosis factor receptor; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; LAK, lymphokine-activated killer; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; NK, natural killer (cell); TAA, tumor-associated antigen; Th, T-helper cell; TLR, toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cell.

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http://dx.doi.org/10.1016/j.biopha.2015.10.020
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mutated or viral genes, which are expressed exclusively in cancerous cells, and (ii) those containing shared antigens that can be expressed both by tumor and normal cells in a constitutive or a developmental stage-dependent pattern (e.g., during the perinatal period) [2]. Some unique TAAs are directly linked to the development of cancer (e.g., products of DNA repair or apoptosis-related genes, products of tumor suppressor genes, altered proteins encoded by mutated proto-oncogenes), and in addition they could be relatively resistant to immunoselection due to their essential role in maintaining the neoplastic state. Other unique TAAs may have no direct or indirect association with malignant transformation, resulting fromthe general genetic instability of cancer cells. Unique TAAs can be considered as tumor-specific antigens. However, TAA-mediated specificity is imperfect, as these mutated antigens arise from normal proteins and can be also expressed in altered but non-malignant cells [2].

The vast majority of TAAs are shared with normal somatic cells. The shared TAAs are divided into four subgroups including cancer/testis, oncofetal, differentiation, and overexpressed antigens. Cancer/testis antigens (CTAs) [3] and oncofetal antigens [4] are two closely related categories of TAAs encoded by awakened 'silent' genes. In adult organisms, CTAs are normally expressed exclusively in immune privileged organs including the testis and placenta, and they can also be aberrantly expressed in tumor cells. The reasons underlying the expression of these genes in tumors have been examined for the MAGE genes, suggesting that the expression is triggered by promoter demethylation, which has a high CpG content [4]. CTAs are highly immunogenic because they are 'unknown' to the immune system and thus are not tolerated [5]. Very low expression levels of oncofetal antigens have been shown in normal tissues (e.g., fetoprotein is expressed in the liver), in contrast with high expression levels in some cancers or during various non-malignant pathologies [4,5]. Overexpressed oncofetal antigens are less immunogenic than CTAs because they are presented to the immune system in the neonatal period during the establishment of immune tolerance. Differentiation TAAs exhibit tissue-specific and in some cases differentiation stage-dependent expression patterns. The expression of these proteins is generally increased in malignant cells, originating from a particular tissue. For example, gp100, and tyrosinase, Melan-A/MART-1 are expressed in normal melanocytes and overexpressed in melanoma cells [6]. Overexpressed antigens are widely distributed in many normal tissues at very low to moderate levels, while these antigens are overexpressed in a variety of histologically different tumor types. Approximately 20% of all TAAs identified so far belong to this antigenic subgroup, and such proteins, as Wilm's tumor-1, telomerase, Her2/neu, and survivin fall into this category [2,5]. TAAs (mainly shared) can also be of non-protein in origin, with some tumor-associated carbohydrates [7] and (glyco) lipids [8] implicated in antitumor immune protection. Although these non-protein TAAs are not recognized in the context of conventional Major Histocompatibility Complex (MHC)-restricted T cells, they constitute targets for other components of antitumor immune responses, including natural killer (NK) cells, NK T cells, and γδ T cells [1].

3. Cancer cell-based vaccines

There is considerable interest in developing therapeutic vaccines for cancer, as they hold promise of delaying or preventing cancer recurrence, particularly in early-stage disease patients. However, clinical application of cancer vaccines is complicated by the fact that most TAAs are non-mutated proteins, which are poorly immunogenic [2]. Moreover, immunizations with only one or several tumor-associated antigenic peptides frequently fail to control overall tumor development, creating favorable conditions for the growth of the tumor cell clones that lack the antigens present in the vaccine. The use of whole tumor cells or lysates derived thereof as vaccines offers several advantages compared to individual TAAs. First, whole tumor cells elicit broad spectrum immune responses to different TAAs. In fact, a single histologically identical tumor consists of antigenically diverse cells [9]. Second, after internalization by antigen-presenting cells (APCs), tumor cell debris facilitate cross-presentation of antigens to CD4+ and CD8+ T cells, thus generating long-term CD8+ T cell memory with CD4+ T cell help [10]. Antigenic peptides expressed inside cells and/or on the cell surface are generally more immunogenic than the same peptides in a soluble unbound form. In fact, the immune system is better adapted to combat cells bearing an infectious or cancerous danger signals, compared with the relatively safe soluble products. Published data indicate that necrotic tumor cells can promote dendritic cell (DC) maturation [11], possibly because dead cells release heat shock proteins (HSP), such as HSP 70 and 90, the pro-inflammatory factor high mobility group box 1 (HMGB1), and pro-inflammatory cytokines [10]. Furthermore, RNA and DNA of injured cells are rapidly degraded to purine bases, with subsequent convertion into uric acid (an end product of the purine metabolic pathway), which can serve as a critical endogenous danger signal driving DC maturation [10,12]. Table 1 presents the characteristics of various types of cell-based vaccines.

Autologous tumor cell vaccines are prepared from patient-derived tumor cells. These tumor cells are typically lysed or irradiated, combined with an immunostimulatory adjuvant (e.g., Bacillus Calmette-Guérin, BCG), and then administered to the individual from whom the tumor cells were isolated. The major advantage of this type of vaccine is that all vaccine antigens are homologous to those of the patient's tumor. However, a sufficiently large tumor specimen is required to prepare autologous tumor cell vaccines, thus limiting this approach to certain tumor types or stages [13].

Allogeneic tumor cell vaccines typically contain two or three established human tumor cell lines potentially overcoming many of the limitations of autologous tumor cell vaccines. Potential advantages of this approach consist in a limitless source of tumor

Table 1
Characteristics of different types of cell-based vaccines [1].

Types of tumor cell vaccines	Characteristics
Autologous vaccines	Full overlapping of vaccine antigens with the antigens of the patient's tumor; no considerable immunogenic activity without adjuvants; limited source of tumor material; no opportunities for standardization or large-scale production.
Allogeneic vaccines	Partial overlapping of vaccine antigens with the antigens of the patient's tumor; no considerable immunogenic activity without adjuvants; limitless source of tumor material; opportunities for standardization and large-scale production.
Xenogeneic vaccines	Partial overlapping of vaccine antigens with the antigens of the patient's tumor; considerable immunogenic activity in the absence of any adjuvant; involvement of natural Abs in cross-presentation by APCs of vaccine antigens; limitless source of tumor material; opportunities for standardization and large-scale production.

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