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Mimotope vaccines: Epitope mimics induce anti-cancer antibodies

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Abstract

Mimotopes are epitope-mimicking structures. When applied for immunizations they induce desired antibody specificities exclusively based on the principle of molecular mimicry. This is important as antibodies directed against tumor-associated antigens may harbor diverse biological effects depending on their epitope specificity. Thus they may inhibit or promote tumor growth. This review gives an update on different vaccination strategies based on the mimotope concept.

Keywords

Cancer; Immunotherapy; Mimotope; B-cell epitope; Her-2; EGFR

1. Introduction

Curing cancer requires removing or destroying all malignant cells. Ideally, an anti-cancer therapy discriminates between the tumor cells and their healthy counterparts, and affects only malignant cells. The high specificity of immune recognition renders immunotherapies likely to achieve this goal. Therefore, passive and active immunotherapies have been intensely studied for the last decades.

1.1. Anti-cancer antibodies

In 1975 the invention of monoclonal antibodies [1] ushered in a new era of cancer therapy, based on antibody-mediated immunotherapeutics. However, it became evident that the monoclonal antibody approach had serious practical limitations, like poor efficacy and limiting side effects due to passive application of – then murine – monoclonal antibodies. When the role of cytotoxic T cells for the destruction of cancer cells was recognized, another major trend began in the late 1980s: after humoral antitumor immunity, T cell-dependent immunity came into focus. For several years, efforts in tumor antigen identification were directed predominantly to those recognized by T cells, and immunotherapy trials sought to induce antigen-specific T cells rather than antibodies [2]. When these trials were not as successful as expected, it was understood that tumor cells use multiple mechanisms to escape especially from T cell-mediated immune recognition and

destruction [3]. With the development of chimeric and humanized monoclonal antibodies, and the successes seen with, e.g. rituximab or trastuzumab therapies, anti-cancer antibodies again took center stage and nowadays are recognized tools in cancer therapy.

However, one limitation of this therapeutic approach of passive immunotherapy is the need to repeatedly administer the antibodies to achieve effective titers and elicit antitumor activity. Unfortunately, the required amounts of monoclonal antibodies are very expensive. Active immunizations that elicit antibodies of the desired type would be an attractive alternative, both circumventing multiple infusions, as well as the danger of inducing an immune response against the non-human parts of the artificial antibodies.

1.2. The importance of epitope specificity

As more and more monoclonal antibodies against tumor antigens were developed, it soon became evident that biological effects were due to epitope specificity. When generating a battery of e.g. anti-EGFR and anti-HER-2 antibodies, depending on where on the receptor molecules certain antibodies bound, cell growth was inhibited—or even enhanced. This was attributed to stimulating or ligand replacing effects, i.e. the antibodies being classic agonists or antagonists [4–8]. Other researchers found opposing effects to be due to differences in internalization and degradation capacity [9,10]. Antibodies like cetuximab or trastuzumab were chosen for their inhibitory potential in various cell proliferation assays among dozens of others [11,12].

For designing a vaccine preparation aimed to induce a humoral immune response, epitope specificity has to be considered. To ensure the induction of beneficial, tumor growth-inhibitory antibodies, a rational selection of target epitopes needs to be performed.

2. Epitope-specific vaccination

Immunizations with whole antigens can induce antibodies with opposing biological affects. However, as most B cell epitopes are conformational in nature, simply taking small parts of the whole antigen does not work, as the conformational epitopes will be destroyed. Therefore, two strategies have been developed that lead to definition of structural mimics of antibody-binding sites.

2.1. Anti-idiotypic antibodies

According to the network theory of Jerne [13], every antibody has an anti-idiotypic antibody, i.e. an antibody directed to its specific paratope. This concept was first utilized in cancer therapy by Ron Levy and co-workers in the therapy of B cell lymphoma, where the tumor antigen already is an antibody, although membrane-bound. First, they generated anti-idiotypic antibodies against the patient's specific idiootype (expressed by the clonal malignant cells) and applied them as passive immunotherapy [14]. Second, they developed customized idiootype vaccines, which were indeed capable of inducing anti-Id antibodies [15].

To elicit anti-idiotypic antibodies for solid tumor therapy (where the tumor antigen is not an antibody), mice were immunized with monoclonal antibodies against the desired tumor antigen, and monoclonal anti-idiotypic antibodies derived. Vaccination with these anti-idiotypic antibodies yields anti-anti-idiotypic antibodies, again recognizing the original antigen. Especially in melanoma, promising clinical results have been obtained [16–18], but this technique of antigen mimicry has also been applied in colorectal cancer, ovarian cancer, and lately in breast cancer (reviewed in [19]).

2.2. Mimotopes

As generating anti-idiotypic antibodies is difficult and time-consuming, and they are big and mostly foreign proteins, other ways of mimicking epitopes were investigated. The minimal structural elements which are required to elicit a specific humoral and cellular immune response were found to be peptides from 6 to 20 amino acids length. Definition of peptide mimics of epitopes, so-called mimotopes, was made feasible by the application of a novel technique: screenings of random peptide phage display libraries [20].

2.2.1. The phage display technique— 10^9 or more different peptides can be introduced into such libraries, rendering a diversity very similar in size to the human antibody repertoire. By *biopanning* the libraries with an antibody of interest, those phages bearing respective epitope-mimicking peptides are selected and can further be enriched [21]. The amino acid sequence of the peptides can be easily obtained. Often, the sequence found is different from that of the natural antigen, suggesting a structural mimicry of the epitope at peptide level.

2.2.2. Ligand mimicry—In 1993, it was demonstrated that mimicry of discontinuous epitopes is feasible with peptide mimotopes [22,23]. This was crucial for the technique, as the majority of antibodies recognizes and binds discontinuous, i.e. conformational epitopes. It was also shown that peptide mimics of nonproteinaceous ligands could be found [24]. Furthermore, mimotopes can be identified with no prior information concerning antibody specificity [25].

The issue of correct conformation of the peptides was further addressed by the development of constrained peptide libraries. Constant residues were included into the random peptide libraries, which often are cysteine residues, causing the random-sequence peptide to form a constrained loop. Constrained peptides possess a more defined structure and are, therefore, more likely to interact with a target molecule. Even structurally sensitive protein regions, that exist only in the native form of the protein, may be mimicked by cyclic amino acid sequences of constrained peptides [26].

2.2.3. Advantages of peptide mimics—There are several advantages that make synthetic peptide mimotopes an attractive option for vaccination [27]:

- they are chemically defined and easy to manufacture on a large scale;
- they are stable and can be stored as a freeze-dried powder for prolonged periods;
- there is no infectious material involved in their manufacture and they are therefore safe;
- they elicit a predetermined type of immune response and undesired epitopes are avoided; and
- they can be coupled to immunogenic carrier molecules to enhance immunogenicity.

Antibodies have been found after mimotope vaccination in various studies, e.g. in experimental hepatitis B and C immunizations [28,29], as well as in allergy immunotherapy [30,31].

3. Anti-cancer mimotope vaccinations

In the cancer immunology field, mimotopes were first used to study an anti-MUC1 antibody's specificity more in detail, but the notion of using the obtained epitope mimics as vaccines was immediately raised [32] (Fig. 1). It was subsequently shown that the basic principle of mimotope vaccination resulting in antibodies recognizing the original antigen

was also true for tumor antigens, in this case in prostate-specific membrane antigen (PSMA) [33]. Further research made use of different aspects of epitope mimicry.

3.1. Unknown target antigen

Popkov et al. exploited the fact that with the phage display technology, the target antigen need not even be known. They used a monoclonal antibody recognizing fibrosarcoma cells, generated mimotopes, and immunized with them. They were able to show that the resulting antibodies competed with the original antibody in target cell binding, and prolonged survival in a nude mouse fibrosarcoma lung metastases model [34].

3.2. Non-immunogenic target antigens

This problem is mostly encountered with tumor-associated carbohydrate antigens (TACAs). Not only are sugar moieties weakly immunogenic, but it is also very difficult to produce them as standardized vaccines. In this situation, peptide epitope mimics come in as ideal tools. It is therefore not surprising that mimotopes were generated for a panel of TACAs, i.e. sialylated Lewis a/x [35], LeY [36,37], GD3 [38], and GD2 [36,39,40]. Mimotopes were used for immunizations in peptide form [41], but also as DNA minigene vaccines [40,42]. Importantly, in preclinical prophylactic and therapeutic vaccination studies, mimotopes were efficacious in eliciting immune responses that reduced tumor burden and inhibited metastatic outgrowth (reviewed in [43]).

3.3. Huge and post-translationally modified antigens

The paradigm antigen for this category is the high-molecular weight melanoma-associated antigen (HMW-MAA). It has over 400 kDa, and is heavily glycosylated. Therefore, it is not feasible to procure sufficient amounts for direct immunizations. HMW-MAA was one of the first solid tumor antigens targeted by the anti-idiotypic strategy (see above), and was again of interest when the mimotope technology emerged. Immunizations with HMW-MAA mimotopes induced antibodies eliciting ADCC (antibody-dependent cellular cytotoxicity) against melanoma cells [44,45], as well as causing direct growth inhibition [45,46].

3.4. Growth factor receptors

As mentioned above, especially when targeting growth factor receptors immunologically, epitope specificity is of vital importance. The induction of tumor growth stimulating antibodies has to be ruled out. Our group therefore has chosen to work with well-defined growth-inhibitory antibodies in this setting, namely the FDA-approved antibodies cetuximab, recognizing EGFR, and trastuzumab, recognizing HER-2.

Two mimotopes for the cetuximab epitope on EGFR were defined. Interestingly, the mimotope that bound to the selecting antibody with higher specificity was also found to induce antibodies with a higher growth-inhibitory potential on EGFR-overexpressing cancer cells. In eliciting immunologically mediated cytolytic mechanisms, antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), antibodies induced by both mimotopes were shown to be equal [47]. This argues for the definition of highly specific mimotopes in cases of antibodies with direct growth inhibitory effects.

Immunizations with the trastuzumab-HER-2 mimotope resulted in antibodies reactive with HER-2. Like the original antibody, they led to internalization of the receptor molecule from the cell surface into endosomal vesicles, thus reducing receptor density and therefore signaling intensity [48]. In this antigen system we could also show that mimotopes can be utilized to define previously unknown epitopes. A computer algorithm was devised that matches mimotope surface information onto the surface of the original antigen, thus indicating where the selecting monoclonal antibody binds [49]. Currently we are

investigating the effects of trastuzumab mimotope immunizations in a HER-2 transgenic mouse model, to address the issues of immunological tolerance that will also arise in patients with HER-2 positive cancers.

4. Conclusions

In conclusion, mimotope immunization is a powerful tool in inducing epitope-specific anti-cancer antibodies. It is capable of eliciting antibodies with comparable biologic properties as the original monoclonal antibodies, with the advantages of production by the patient him- or herself. Additionally, the resulting antibodies are not restricted to one given isotype, but are of various antibody classes, thus able to mediate the full range of immune effector mechanisms. Moreover, the induction of immunological memory could prove beneficial in the event of disease recurrence. Of course, so far only animal studies are available, but these are very promising for a variety of antigens, and warrant translation of this approach into humans.

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Fig. 1.

The principle of a tumor mimotope vaccine. Mimotopes are epitope-mimicking structures suitable for vaccination. They may be linear or circular peptides (as depicted), or anti-idiotypic antibodies. By virtue of molecular mimicry these mimotopes can induce antibodies not only directed against the immunogen, but also towards the natural epitope expressed or overexpressed on a cancer cell. The antibody response is polyclonal and acts cytotoxic against tumor cells by exploiting several effector functions.