

INTERVIEW about

Vaccination with peptide mimotopes

with

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What are immunogenic peptide mimotopes?

Erika Jensen-Jarolim and Angelika Riemer: Active induction of immune responses against malignancies by vaccination is the most attractive option for targeted therapy today. A number of tumor-associated antigens are overexpressed on malignant cells and represent targets for immunotherapy. However, there are two major drawbacks for vaccination strategies: 1.) Tumor-associated antigens are often large molecules and therefore difficult to express in recombinant form, and 2.) post-translational modifications, like the addition of sugar side chains, can significantly contribute to their conformation and, moreover, make them weakly immunogenic. Peptide mimotopes (antigen surrogate vaccines against tumors) are a means to overcome these limitations. They are three-dimensional mimics of certain parts of tumor-associated antigens, i.e. areas recognized by an antibody. Mimotopes are selected out of a huge variety of random peptides from phage libraries by this antibody of interest. This also works when the antibody is directed against a non-protein antigen, e.g. a sugar moiety. The selected peptide mimotope functions as a surrogate for the original target structure, and can be of higher immunogenicity than the original antigen.

Why is disialoganglioside GD2 an attractive target for immunotherapies?

Erika Jensen-Jarolim and Angelika Riemer: GD2 is a ganglioside, i.e. a sugar structure, which is specifically overexpressed on different kinds of tumors of neuroectodermal origin, like neuroblastoma and melanoma. Therefore, GD2 is an attractive target for immunotherapy. Monoclonal antibody therapies to GD2 exist and are already applied in passive immunotherapy phase III studies. One example is the chimeric IgG1 antibody 14.18, which has been tested on its own (1), or as fusion protein with IL-2 to enhance consecutive immune responses (2, 3). Passive immunotherapy with antibodies in general relies on the mediated effects. These may be direct, apoptotic or anti-metastatic, or indirect via antibody-(ADCC) and complement-dependent cellular cytotoxicity (CDC). 14.18 acts most likely through the latter cytotoxic mechanisms (4).

What is the difference between passive and active antibody immunotherapy?

Erika Jensen-Jarolim and Angelika Riemer: There are two options for the occurrence of anti-tumor antibodies: They may be passively given by infusions or actively

built up by the patient's own immune system. With respect to passive immunotherapy, a therapeutic anti-tumor antibody has to be applied to the patient in vast excess to achieve the necessary level at the tumor site. These high antibody levels are also one reason for side effects like chills, dyspnoe, muscle aches or fever. Moreover, hypersensitivity reactions towards the murine parts of a chimeric

antibody may occur, leading to immune complex disease or, in the worst case, anaphylaxis.

The situation is completely different for antibodies generated through vaccination. First, they are complete self antibodies and second, the antibody load, and thus the risk of side effects, is lower. Natural anti-tumor antibodies are produced by plasma cells, which can be detected at high density in tumor tissues, indicating on-site production. In concert with effector cells like e.g. neutrophils, eosinophils and NK cells this is an optimal system with high cytotoxic and equally specific potential. Antibodies against GD2 may thus be very useful for anti-tumor immunotherapy when induced actively by a vaccine.

Why don't you use the antigen GD2 itself for vaccination?

Erika Jensen-Jarolim and Angelika Riemer: There are at least two good reasons why GD2 itself is suited badly for the production of a vaccine. 1.) GD2 contains no protein, therefore it cannot be produced synthetically, but has to be purified from natural sources which limits its availability. 2.) Sufficient immunogenicity of the purified ganglioside GD2 can only be achieved when it is applied in conjugation with an immunogenic carrier or an adjuvant.

Therefore, other groups have already tried to replace GD2 by anti-idiotypic antibodies with higher immunization capacity than the original antigen (5). Anti-idiotypic antibodies are, however, sometimes difficult to express recombinantly in large scale or are complicated to be harvested from bacterial supernatants without aggregation. Mimotopes in contrast can be selected relatively easy from peptide libraries, can be pro-

duced synthetically and, coupled to a carrier, be used without the risk of endotoxin contaminations. Therefore, disialoganglioside (GD2) is a good example for a setting where mimotopes are practical tools for the realization of a vaccine (6,7). Going even one step further, minigenes can be directly deduced from the peptide mimotope sequence and have equally high potency of inducing anti-tumor immune responses (8).

Thus, these data are waiting for a translation into a human clinical trial. Unfortunately, tumors like neuroblastoma are orphan diseases and, therefore, not in the major focus of marketing strategies.

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