4. Anti-idiotype antibody vaccine therapies of cancer

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1. Introduction

Immunotherapy of cancer is divided into two overlapping categories: active and passive. The goal of active immunotherapy is the stimulation of host antitumor immunity, either cellular or humoral. This can be accomplished in a direct or specific fashion by using tumor vaccines to generate an immune response to tumor-associated antigens (TAAs). Nonspecific antitumor immunity can be propagated by compounds such as bacillus Calmette–Guerin (BCG). Passive immunotherapy relies on the administration of biologically active agents with innate antitumor properties, such as antibodies reactive with growth factor receptors. In most instances, host immunity is an important cofactor in active immunotherapy. In addition, some agents, such as antibodies, can exert anti-immune circuits that are set into motion by these therapies and account for the imperfect but nonetheless useful division into active and passive types.

Immunotherapy is very effective in certain animal model systems, and it has been used to treat human cancers for several decades [1]. The active immunotherapy of cancer patients with tumor-derived material has been studied by numerous investigators, with positive clinical responses reported. A number of problems exist with using tumor material for immunization, and TAAs are often found to be poorly immunogenic. A common explanation for the absence of antitumor immunity is that the immune system has been tolerized by the tumor antigen. If this is true, steps could be taken to break the existing antitumor tolerance. An effective method of breaking tolerance is to present the critical epitope in a different molecular environment to the tolerized host [2]. While this can be done easily with haptens and other small, well-defined antigens, it is impossible with most tumor antigens because they are chemically ill defined and difficult to purify — especially carbohydrate antigens, vaccines for which cannot be produced by recombinant techniques.

The immune network hypothesis offers a unique approach to transform epitope structures into idiotypic Id determinants expressed on the surface of antibodies. Immunoglobulin (Ig) molecules possess variable regions specific for antigen recognition. The variable region is encoded by $V_H$, $D$, and $J_H$ genes.
for the heavy chains and \( V_L \) and \( J_L \) chains for the light chain [3]. The variable region contains determinants known as idiotypes (Ids), which are themselves immunogenic. Antibodies can be made to many structures in the variable region that are associated with the light chain, heavy chain, or a combination of both chains [4,5]. Early studies indicated that an Id was unique to a small set of antibody molecules [4,5]. However, the Id determinants may show a continuum of specificity from more or less private to semipublic [6,7]. For example, if different antibodies are coded by the same \( V_H \) gene segment, a shared or semipublic Id may be found. The Id is often defined by the antibody made against it, which is known as anti-Id antibody.

Jan Lindemann in 1973 [8] and Niels Jerne in 1974 [9] proposed theories that describe the immune system as a network of interacting antibodies and lymphocytes. According to this original network hypothesis, the Id–anti-Id interactions regulate the immune response of a host to a given antigen. Both Ids and anti-Ids have been used to manipulate cellular and humoral immunity.

The network hypothesis predicts that within the immune network the universe of external antigens is mimicked by Id expressed by antibodies and T-cell receptors. According to the network concept, immunization with a given antigen will generate the production of antibodies against this antigen, termed \( Ab_1 \). This \( Ab_1 \) can generate a series of anti-Id antibodies against \( Ab_1 \), termed \( Ab_2 \). Some of these \( Ab_2 \) molecules can effectively mimic the three-dimensional structures of external antigens. These particular anti-Ids, called \( Ab_2\beta \), which fit into the paratopes of \( Ab_1 \), can induce specific immune responses similar to responses induced by nominal antigen. Anti-Id antibodies of the \( \beta \) type express the internal image of the antigen recognized by the \( Ab_1 \) antibody and can be used as surrogate antigens. Immunization with \( Ab_2\beta \) can lead to the generation of anti-anti-Id antibodies (\( Ab_3 \)) that recognize the corresponding original antigen identified by the \( Ab_1 \). Because of this \( Ab_1 \)-like reactivity, the \( Ab_3 \) is also called \( Ab_1' \) to indicate that it might differ in its other idiotypes from \( Ab_1 \). This cyclic nature of complementary binding sites and idiotopes is the basis for the approach to Id vaccines. In figure 1, the relationships of antigen, idiotype (\( Ab_1 \)), anti-idiotype (\( Ab_2 \)), and anti-anti-idiotype (\( Ab_3 \)) are shown schematically.

The utilization of the Id network in tumor immunotherapy opens new perspectives and may enrich the therapeutic armamentarium. There are two basic approaches that utilize the Id network for tumor immunotherapy. The first takes advantage of the existence of internal antigen images in the Id repertoire. This approach has already been used successfully by several investigators and has the advantage of not being genetically restricted. Internal-image Ids mimic the three-dimensional shapes of antigens and thus are effective across the species barrier. At the same time, antigens can be presented in a different molecular environment.

The other method of using the Id network rests on the existence of so-called regulatory Ids [10–12], which may also be linked to the regulatory network of