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Autoimmunity Reviews 4 (2005) 403–409

AUTOIMMUNITY REVIEWS

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Autoimmunity, alloimmunization and immunotherapy of AIDS

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Received 12 December 2004; accepted 10 January 2005
Available online 10 February 2005

Abstract

The nature of clinical and physiological manifestations associated with HIV infection suggests that AIDS is an autoimmune disease. The conventional immunotherapeutic approaches aimed at enhancing the immune response against HIV have repeatedly failed when applied in the clinical practice. The results of several dozen therapeutic AIDS vaccine trials have consistently shown that while in vitro measured HIV-specific immune responses were evident as a result of vaccination the clinical improvement has been seldom observed. The clinical benefit, however, was invariably associated with the usage of vaccines that acted in accord with the principles of alloimmunization. The majority of these vaccines were derived from the blood of HIV carriers or a cell culture and thus they inherently contained alloantigens unrelated to HIV. The clinical experience with alloimmunization in a range of autoimmune diseases indicates that immune tolerization is an active immune process with benefits the vaccinees. The alloimmunization, which primarily induces tolerance rather than immune activation, might be a better strategy for the immunotherapy of AIDS.

Keywords: AIDS; Autoimmunity; Alloimmunization; Vaccine; Immune tolerance; Immunitor

Contents

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doi:10.1016/j.autrev.2005.01.004

1. Introduction

Autoimmunity occurs when the immune system begins attacking "self" components of the body. The clinical and immunological manifestations associated with HIV infection suggest that AIDS is an autoimmune disease—a view that was first opined even before HIV was discovered. AIDS patients often present a wide range of autoimmune symptoms including systemic lupus erythematosus, anti-phospholipid syndrome, vasculitis, primary biliary cirrhosis, polymyosits, Graves' disease, and idiopathic thrombocytopenic purpura [1]. Reactive arthritis, psoriatic arthritis, acute nonspecific arthritis, Sjogren syndrome, and inflammatory myositis have also been often reported [2]. The autoimmune manifestations are not specific to HIV alone. They are commonly associated with other human retroviruses such as HTLV-I and are also frequently found in primates infected with lentiviruses [3]. There are many hypotheses as to why autoimmunity occurs in AIDS but no definitive answers are available until today [1–3]. Nevertheless, if we argue that AIDS is an autoimmune disease then enhancing the immune response in a situation where the body turns on itself would be illogical and against the basic principles of immunology.

Following the introduction of highly active antiretroviral therapy (HAART) in mid-1990s the number of HIV-related deaths has declined dramatically. However it is clear by now that HAART does not eradicate the virus and cessation of the therapy results invariably in rebound of viremia. Drug-related toxicities, viral resistance, and compliance issues complicate further the use of HAART. These drawbacks have prompted the renewed interest in therapeutic vaccination as an alternative to HAART [4]. Even for HIV-infected patients with access to HAART the therapeutic immunization may represent an important treatment option. As an adjunct to HAART the immunotherapy may reduce adverse side effects, may allow "structured treatment interruptions", and may limit the emergence of viral mutations.

These factors argue that therapeutic vaccines may represent a valuable addition to current treatment options. If a therapeutic vaccine were safe, inexpensive and easy to administer this would be an ideal treatment strategy for people with HIV worldwide. Daniel Zagury was perhaps the first to introduce intentionally this approach into clinical practice in 1986 [5]. Since then over 60 therapeutic AIDS vaccine trials have been carried out [4]. Many animal studies of therapeutic HIV or SIV vaccines have been published in the past. However for the sake of relevance the clinical experience in humans will be mainly described to show which vaccines have failed or succeeded.

So far every tested therapeutic AIDS vaccine did produce an indication of the immune response but it was often argued that such a response was not sufficiently broad or potent to produce meaningful clinical benefit [4]. However, it would be logical to expect that after several dozen therapeutic vaccine trials there should have been at least a partial evidence of the efficacy. This did not happen. Thus we still do not know what are the immune correlates associated with the clinical response. However if we accept the premise that AIDS is an autoimmune disease then we may need to consider an option that would be opposite to the current thinking, an option that calls for the induction of the tolerance instead of immune activation. The opinion that AIDS is an autoimmune disease and alloimmunization is perhaps the answer to the problem has been expressed by many researchers over the last two decades [1–3,6–11].

2. Alloimmunization

The corollary to the autoimmune theory is an observation that was first made by Stott [12]. In 1991 he reported that macaques vaccinated with a preparation made of whole killed human cells infected with SIV were fully protected against subsequent challenge. Paradoxically, animals immunized with a control preparation consisting of killed human cells without SIV were also protected. This observation was attributed to the phenomenon that during the budding process through the cell membrane, virus acquires host cell proteins and thus the immunization against host antigens was as effective or even more effective than immunization with "pure" viral antigens. Furthermore, the intriguing findings recently reported by Maksyutov et al. indicate that most epitopes on every HIV protein appear to display a high degree of similarity with human proteins [13]. In fact there are very few regions within HIV that are