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Vaccination and Autoimmunity

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INTRODUCTION

Diseases encompassing manifestations caused by an autoimmune process are not infrequent and are known to appear in age groups that are often selected as targets for vaccination programs. Therefore, in the context of a rapidly increasing number of vaccination events, it may not be surprising that the question of a potential interaction between vaccines and autoimmune diseases is being raised with an increasing insistence. It is estimated that as much as 5% of the population in Western countries suffers from autoimmune diseases (1). These disorders represent a growing burden for health budgets as their incidence has significantly increased over the past years, as documented for type I diabetes (2) and multiple sclerosis (MS) (3). It is generally assumed that autoimmune disorders result from complex interactions between genetic traits and environmental factors. Indeed, although there is a frequent concordance of autoimmune diseases among monozygotic twins (4), the concordance rate is lower than expected. Similarly, changes in the incidence of type I diabetes and MS when children from a given population migrate from one region to another (5,6) strongly suggest a critical role for environmental causes in addition to genetic predisposition. In most autoimmune diseases, the trigger has not been formally identified, leaving room for hypotheses and allegations not always substantiated by facts.

Mechanisms leading to autoimmune responses and their occasional translation into autoimmune diseases are now better understood. Autoimmune responses result from the combined effects of antigen-specific stimulations of the immune system and an antigen nonspecific activation of antigen-presenting cells in the context of a genetically determined predisposition. Most often, such responses are not followed by any clinical manifestations unless additional events favor disease expression, for example, a localized inflammatory process at tissue level. Infections have occasionally been demonstrated either as etiologic factors or as triggering events in autoimmune diseases. Well-known examples are post-streptococcal (Group A *Streptococcus pyogenes*) heart disease or the Guillain-Barré syndrome (GBS) that follows *Campylobacter jejuni* infections. Such observations have emphasized the multifactorial immunological pathogenesis of secondary autoimmune pathology. First, there is a potential role of antigenic similarities between some microbial molecules and host antigens (antigenic mimicry). Second, infection-related signals that trigger innate immunity appear to play an essential role in enhancing the immunogenicity of host antigens or of host-mimicking epitopes, and in possibly overcoming regulatory mechanisms that limit autoimmune responses. It should be stressed that post-infectious autoimmune responses are not infrequent whereas associated autoimmune diseases remain rare events and often require additional infection-related inflammatory processes.

It is on the basis of such observations that questions are raised regarding the potential risk of autoimmune responses and of autoimmune diseases following vaccination. Is there a significant risk that some vaccines may induce autoimmune responses through the introduction of microbial epitopes that cross-react with host antigens? Can adjuvant-containing vaccines trigger the clinical expression of an underlying autoimmune process through a ''nonspecific'' activation of antigen-presenting cells and the release of inflammatory cytokines? Until now, answers to these questions have been largely based on epidemiological studies, with limitations due to the difficulty to assess the frequency of relatively rare events during clinical trials or post-marketing surveillance. When considered as a whole, autoimmune diseases affect up to 3% of the general population in industrialized countries, but many specific autoimmune diseases have a relatively low natural incidence. Whereas diseases such as rheumatoid arthritis may reach 1% prevalence, others such as MS or systemic lupus erythematosus (SLE) are less frequent (around 0.1%) and many others are relatively rare diseases. Therefore, for most of these clinical entities, only very large epidemiological studies or huge clinical trials may allow for a consistent assessment of the relative risk of vaccine-related effects.

Understanding the mechanisms by which autoimmune responses are generated and how they may or may not lead to autoimmune diseases is of paramount importance for defining the real risk of vaccine-associated autoimmune reaction. During the course of vaccine development, it is now becoming conceivable that a comprehensive and multidisciplinary approach would help to reduce to a minimum the risk that a new vaccine would induce autoimmune manifestations. Later, once the new vaccine is largely used in public health programs, systems should be in place to readily assess observations or allegations of unexpected autoimmune adverse effects. Although the past few years have seen a dramatic increase in the number of such allegations, it is somewhat reassuring that autoimmune adverse effects were demonstrated in only very few instances.