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DO SUPPRESSOR T CELLS EXIST?

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INTRODUCTION

The concept of suppressor T cells have had an enormous impact in immunology and clinical medicine. A number of diseases, such as allergy and and autoimmunity, are considered to be caused by a relative lack of suppressor T cells, whereas too many suppressor cells can result in immunodeficiencies. Even fundamental immunological concepts, such as immunological tolerance and the distinction between self and non-self, are often thought to be regulated by a delicate balance between controlling suppressor cells and potentially autoreactive T and B cells.

In textbooks of immunology T lymphocytes are divided into three subsets: helper, cytotoxic and suppressor T cells. However, in reality it is only possible —by the use of monoclonal antibodies— to separate lymphocytes in two T cell subsets: helper and cytotoxic/suppressor T cells. Suppressor T cells cannot be separated from cytotoxic T cells by the use of any markers. Therefore, it is incorrect to use the term suppressor T cells. This subpopulation should be referred to as the cytotoxic/suppressor T cells.

The notion of suppressor T cells has profoundly affected the way immunologists interpret their findings. A depressed response is generally considered to be caused by suppression and implicity by suppressor T cells. It is quite interesting to observe the change that has occurred during

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There are at least three strong reasons to question the existence of suppressor T cells as a separate T cell subpopulation and I will briefly discuss them.

There are no unique markers for suppressor T cells

As already mentioned, there are no markers to distinguish cytotoxic from suppressor cells. This is quite remarkable, since much effort has been spent on finding specific markers for suppressor cells by the use of monoclonal antibodies. This lack of success should be compared with the ease by which markers for a variety of other cell types have been found and the number of markers that distinguish different T and B cell subpopulations. In addition, there are considerable economic interests in isolating a monoclonal antibody identifying suppressor T cells. But none has been found so far. It follows that no one has yet been able to separate suppressor cells from cytotoxic T cells.

The illusive suppressor T cell gene

A large number of papers has been published on the I-J gene that governs the function of suppressor T cells (7). The gene was localized to the MHC region. By the use of several methods, the I-J gene was exactly mapped within the I complex of the MHC region. The I-J region controlled the synthesis of I-J antigens that were expressed on soluble suppressor molecules secreted by suppressor T cells. There was no doubt about the I-J gene and its product; both had been studied carefully by a large number of immunologists using genetic as well as immunological methods.

Therefore, it came as something of a shock for many scientists when hybrid DNA technology failed to confirm the existence of the gene within the MHC complex (10).

In addition, it was found that mRNA from hybridomas producing suppressor factors containing I-J antigen failed to hybridize with DNA from the MHC region (6). Finally, it seems possible that the two mouse strains used to define the I-J antigen do not differ at all at the MHC region (4). If this is so, I-J does not exist.

The publication of these results had different effects on different scientists. Some conveniently ignored the findings and continued to work and publish on I-J positive suppressor factors as if nothing had happened. Others were more impressed by the molecular biologists, as evidenced by Jan Klein (4): "We see very little sense in continuing working as if nothing has happened. Molecular biologists have thrown down a gauntlet and we should accept the challenge. We shoul not go on using J as a marker for

Suppressor factor

Above, I have outlined three strong reasons to question suppressor T cells. But there are also other reasons. One concerns soluble suppressor molecules, which have attributes changing with time and fashion. They have contained Ia antigens, I-J antigens, they have been V_H restricted and I-J restricted and antigen-specific and non-specific, they have had one chain and A and B chains, they could be suppressor factors or helper factors depending on glycosylation and so on.

Another reasons to doubt suppressor T cells comes from the immense complexity of the field. Thus, at least three different suppressor T cells have been identified that secrete various suppressor factors. Contrasuppressor cells and veto cells with suppressor functions have been reported. Hypotheses have been published outlining complex interactions between inducer, transducer and effector suppressor cells involving cell contact or the release or synthesis of soluble factors suppressing at different levels (level 1 and level 2). It is unlikely, in my opinion, that these hypotheses can be based on solid facts. Is is simply not possible with the available technology to trace all these cells, their soluble products and their interactions in such detail.

Melvin Cohn summarized is view on suppressor cells and factors in the following way (8): "I cannot help having doubts about the existence of a normally functional suppressor circuit .... I wonder to what extent this suppressor pathway will turn out to be a laboratory construct of no physiological significance. I question the existence of I-J restricted suppressor factors or, for that matter, I-J restricted suppressor T cells". This was said before the finding that suppressor T cells lack functioning genes for the antigen-binding receptor.

My own experience

In connection with various studies on tolerance and genetically determined unresponsiveness in mice to different antigens, we have studied whether the phenomena were regulated by suppressor cells, but we were never able to detect any influence of suppressor cells of any type. However, in two cases we have deliberately studied suppressor T cells. One study (9) involved the generation of suppressor T cells *in vitro* by activation of T cells with Con A. These activated cells suppressed a mixed lymphocyte culture reaction *in vitro*, as found by many others. However, the mechanism of suppression was rather unexpected. Suppression disappeared when IL-2 was added to the reaction and, most revealing, when the activated suppressor cells were incubated for a short period *in vitro* with

Weaker arguments include the ever changing and fashionable attributes ascribed to suppressor T cell factors, the immense complexity of the cells, factors and interactions postulated, which cannot be based on facts in many cases, since the available technology does not have sufficiently high resolution and my own failure to ever come across a suppressor T cell.