HUMAN IMMUNITY TO VIRUSES

Edited by

FRANCIS A. ENNIS

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PREFACE

Effective control of many infectious diseases is now possible through the use of vaccines. Pioneering work by Pasteur and Jenner led to early prevention of, respectively, rabies and smallpox. In more modern times the breakthrough in tissue culture growth of human viruses by Enders led to the successful developments of effective viral vaccines against poliomyelitis, measles, mumps, and rubella.

These successes were accomplished with little appreciation of the immune responses of the host to the pathogen or to the vaccine. Gradually, evidence was developed that antibodies capable of blocking infection by the virus *in vitro* were associated with resistance against certain viral infections. Little information, however, was available on the contribution of cell-mediated mechanisms to the pathology of, recovery from, or protection against viral infections.

This situation is now changing dramatically because of several major developments. The observation that virus-specified killer T lymphocytes need to recognize both self and viral antigens on virus-infected cells in order to kill them was made by Zinkernagel and Doherty in 1974. Subsequently, another set of lymphocytes, called natural killer lymphocytes, which killed virus-infected cells, was described by Welsh and Zinkernagel. These results provided *in vitro* markers for detecting the presence and activity of these lymphocytes in virus infections.

With the simultaneous development of hybridomas and the production of monoclonal antibodies by Kohler and Milstein, it has become possible to separate these killer lymphocytes from lymphocytes with other functions, such as helping or suppressing antibody formation. It has also become possible to assess the effects of treatment with specifically separated lymphocytes in animal experiments, some of which have demonstrated key roles for killer T lymphocytes in recovery from influenza.

At the same time, less detailed but promising data are being developed in human studies. McMichael *et al.* reported that influenza-specific cytotoxic T lymphocytes were also restricted by viral and HLA antigens. Recently, induction of these cells by vaccines has been reported by Ennis *et al.*, and Quinnan has demonstrated that these cells are important in recovery from serious cytomegalovirus infections observed after bone marrow transplantation.

The purpose of this book is to help provide a bridge between these exciting basic laboratory observations and their contributions to a variety of serious viral diseases of humans. Our selection of viral infections to include in this book relied in large part on diseases currently under investigation with varying degrees of progress.

The authors were asked to use their expertise to help the reader become aware of research progress and opportunities in their specialized field of interest. The first portion of the book describes developments in measuring immune responses to viruses, emphasizing areas of recent progress. These general reviews are followed by detailed papers on the application of these techniques to a number of human viral diseases. The pathogenesis and natural biology of the infection is described initially, followed by a review of the immune response to the infection.

We have included a number of serious viral infections being investigated: influenza, herpes simplex, cytomegalovirus, Epstein–Barr virus, measles, dengue, and polio are included. We did not include other suggested viruses, e.g., rubella, hepatitis, because there was little new information available regarding cellular immune responses.

Ultimately, the reason for understanding the immune responses to viral infections is to be able to prevent illness and death. It is essential to apply these new techniques as much as possible to improving our understanding of human immune responses, whether antibody, lymphocyte, or lymphokine-mediated, to viruses and to viral vaccines. It is obvious that much more basic laboratory work needs to be performed in this research area, but the time has come to apply these techniques to clinical investigations of viral infections and vaccines.

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I

IMMUNE RESPONSES TO VIRUSES — OVERVIEWS

CHAPTER 1

VIRUS SPECIFIC CYTOTOXIC T CELLS

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INTRODUCTION

Cytotoxic T lymphocytes were first recognised as cells which kill foreign cells in vitro. They were thought to mediate graft rejection in vivo, but this function is now not certain (1) and cannot be their normal biological role. Their ability to kill virus infected cells was first demonstrated about ten years ago (2). These findings indicated that cytotoxic T cells could have a role in real life. Since these first experiments a wealth of information has accumulated on the function of cytotoxic T cells, particularly with regard to their recognition of infected cells and the involvement of histocompatability antigens (reviewed in 3). In this short review we shall concentrate on work with human cells which has proceeded in parallel with the more well known work on the mouse.

Virus specific cytotoxic T lymphocytes have been demonstrated for a number of viruses which infect humans. These include Influenza A and B, (4,5) Epstein-Barr (6), measles (7), mumps (8), cytomegalo (9) and herpes simplex (9) viruses. As cellular immunity to many of these viruses is discussed in this volume, we shall concentrate on cytotoxic T lymphocytes specific for influenza, which in many ways form the prototype for studies with other viruses.

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INDUCTION

Cytotoxic T lymphocytes can be induced in vitro from immune volunteers. As all adults have been infected with influenza virus, the reaction measured in vitro is normally a secondary immune response. Cytotoxic T cells specific for influenza have been demonstrated in vivo during the course of influenza and after vaccination with live virus (10); similar cells specific for measles and mumps viruses have been reported as being present during the course of these diseases (7,8). Studies have indicated that induction of cytotoxic T cells from peripheral blood lymphocytes of immune volunteers requires virus antigen (11). This is normally presented as virus infected cells or live virus, but UV inactivated virus (11) and membrane fragments (12) are sufficient. Viruses are normally presented on autologous infected cells but we have found that allogeneic cells or allogeneic membrane fragments from infected cells will stimulate induction of cytotoxic T cells provided that HLA Class I histocompatability antigens are shared (12). Thus, cytotoxic precursor cells see both HLA glycoproteins of self and virus antigens on the stimulating cell.

TABLE 1. HLA Restricted Induction of Influenza Virus Specific Cytotoxic T Cells

Effector	Stimulus"	HLA Match'	%Lysis MN-A**	WT-A*	JM-A*
MN	MN-A(c)	1,8,40	21	3	
	JR-A(c)	none	6	0	
	AR-A(c)	1,8	20	0	
	AR-A(mem)	1,8	27		
	JM-A(mem)	none	3		
JM	JM-A(c)	2,15,51	2		27
	JM-A(mem)	2,15,51	2		30
	AR-A(mem)	none	0		0

"Effector lymphocytes were induced by incubation with influenza A virus infected cells (c) or membranes (mem) prepared from influenza virus infected cells.

'HLA type of MN was A1,1,B8,40; JM was A2,2B15,51; AR shared A1 and B8 with MN and no antigen with JM.WT shared no HLA antigens with MN.

*Target cells were infected with influenza A virus.

The responding cells are T lymphocytes that bear glycoproteins shared by cytotoxic and suppressor cells. Induction requires both adherent cells and helper T lymphocytes (13). A period of culture is required which must exceed 3 days. Cytotoxic T cells can be grown in media containing interleukin 2 and we have maintained influenza specific cytotoxic T cell lines for up to two months. At the end of the induction period, cytotoxic effector cells which carry the cytotoxic/suppressor (T8) and T (T3) markers (14,15), are present in the culture. The normal targets used for assay are not sensitive to natural killer cells, but if NK sensitive cell lines, such as Daudi or K562, are tested, this kind of cytolytic activity can be demonstrated (11).

Cytolytic activity is demonstrated using a chromium release assay where freshly prepared lymphocyte target cells are labelled with ^{51}chromium, infected with influenza virus and then cultured for 4 hours to allow expression of influenza virus antigens. Killing is demonstrated in a five hour chromium release assay, where effectors and target cells are mixed at varying ratios. It should be noted that maximum killing is normally in the range of 30-40%. We have found this correlates with the number of cells expressing detectable amounts of haemagglutinin on the surface after infection, using a monoclonal antihaemagglutinin antibody in the cytofluorograph (unpublished results).

VIRUS SPECIFICITY

Cytotoxic T cells stimulated by influenza virus have been shown to be specific for the influenza virus type (4,5,11). T cells induced with influenza A fail to lyse target cells infected with influenza B and vice versa (Table 2). Occasionally, however, a low degree of cross reactivity is observed which remains unexplained. Provided natural killer cell activity is excluded, influenza specific cytotoxic T cells do not lyse EBV transformed cell lines (unpublished results).

A particularly interesting finding has been the observation that there is full cross rectivity between different influenza A viruses. This was first observed in the mouse and has been confirmed in several laboratories working with both mouse and man (17,18,5,11). In the secondary induction system described above, this cross reactivity is universal. In certain situations such as a primary immune response in vivo and secondary induction in mice, with purified haemagglutinin, a degree of influenza A