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Biological role of major transplantation antigens in T cell self-recognition[1]

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Summary. The proposal is made, illustrated and supported by experimental evidence that T cell-mediated immunopathology triggered initially by low- or non-cytopathic infectious agents may cause diseases, susceptibility to which is linked to the major histocompatibility gene complex.
Key words. T cell-recognition; major histocompatibility gene complex; HLA-disease association; virus; immunopathology.

Introduction

Major transplantation antigens play a crucial role in lymphocyte interactions amongst themselves as well as with other somatic cells[2-4]. That this is their real biological function and not to make transplantation surgery or tumor research more difficult was first signaled by the finding that susceptibility to certain diseases is linked, albeit weakly, to the major transplantation antigens coded by the major histocompatibility gene complex (MHC, HLA in humans, H-2 in mice)[5-8]. Any list of the more clear cut HLA-disease association immediately suggests that they are all caused by immune mediated pathogenesis. How can these two phenomena, HLA-disease associations and their immune pathogenesis be explained? and can we understand why HLA-diseases associations are often rather weak?

The function of the immune system is to maintain homeostasis in higher vertebrates; its two main arms, cellular and humoral immunity very efficiently defend the host against acute cytopathic infectious agents. The main targets of T cells are intracellular agents, while those of antibodies are primarily extracellular ones. However this immune defence does not cover all viruses and bacteria with the same efficiency and many other causes of disease such as protozoan or metazoan infections, tumors etc. are more or less out of the reach of efficient immune surveillance.

T cell immunity is at its best when dealing with acute intracellular agents, such as cytopathic viruses. This T cell activity is easily measured in a classical ^{51}Cr-release cytotoxicity assay in vitro[4,9]. T cell-mediated lysis of virus-infected target cells is virus specific, since only target cells infected with the proper virus are lyzed. But in addition, target cell lysis of virus-infected cells depends upon T cells and target cells sharing classical transplantation antigens. Many experiments over the past 12 years have clearly documented that the following general rules govern lymphocyte-lymphocyte and lymphocyte-somatic cell interactions[2,4]:

- T cells recognize self-transplantation antigens together with foreign antigenic determinants exclusively on cell surfaces;
- T cell specificity for self-transplantation antigens a) is specific for polymorphic determinants; b) is selected for during differentiation in the thymus; c) determines the effector function of T cells: cytotoxic T cells recognize class I, i.e. the classical transplantation antigens HLA-A, B, C or H-2K, D, L whereas differentiation promoting T cells (helper or DTH T cells) are specific for class II, HLA-D or H-2I; d) regulates T cell responsiveness, i.e. the quality and quantity of cytotoxic T cell response is regulated by HLA-A, B, C or H-2K, D, L, that of differentiation-promoting T cells by HLA-D or H-2I gene products.

Role of cytotoxic T cells

One may question the physiological role of cytolytic T cells: why should T cells mediate cell and tissue destruction to combat intracellular infectious agents[4,10-14]? There is good evidence that cytotoxic T cells destroy virus-infected cells before viral progeny is assembled, thus eliminating virus during the eclipse phase of virus replication. Virus elimination via immunological host cell destruction is, in the case of cytopathic viruses, an efficient way to prevent virus spread and the resulting more extensive virus-mediated cell and tissue damage[4]. In the case of non-cytopathic viruses, this immunological defense mechanism becomes less attractive, because host cells are not destroyed by virus but only by the T cell immune response[4,6,11-13]. Because T cells can apparently not distinguish cytopathic from non-cytopathic viruses, im-

mune mediated cell and tissue damage results, in the latter infections, in immunopathology.

Lymphocytic choriomeningitis (LCM): a T cell-mediated immunopathology

Examples of infections with non-cytopathic viruses are lymphocytic choriomeningitis (LCM) in mice[4,6,10,15-17] and hepatitis B in humans[18,19]. Lymphocytic choriomeningitis disease in mice develops after intracerebral injection of LCMV only in immunocompetent mice. Mice lacking T cells or those immunosuppressed by irradiation or cytostatic drugs do not develop inflammatory reactions and thus no LCM disease; but they fail to eliminate virus and as a result become LCMV-carriers[7,13]. LCM-disease has been carefully analyzed and has been clearly shown to be T cell-mediated[6,17]. Lethal LCM disease apparently depends upon effector T cells being preferentially recruited to the acutely infected leptomeninges. This notion is supported by the finding that high doses of LCMV simultaneously injected i.c. and i.v. often do not cause fatal LCM disease, because effector T cells are recruited to infected cells all over the organism and therefore are diluted out.

Disease depends in both LCM and hepatitis B upon the balance between virus spread and immune response. Efficient T cell mediated immune response leads to rapid elimination of the virus, limited cell and tissue damage and therefore limited disease. Absence of an immune response results in unchecked growth of virus and in a virus-carrier state. Slow and low immune responsiveness allows extended spread of virus with chronic T cell-mediated tissue destruction; a classical immunopathological conflict situation.

Since major transplantation antigens are recognized as self by T cells and define their function and regulate their responsiveness, they may drastically influence the balance between virus and immune mediated tissue damage. Amongst many other variables characteristic for the virus or the host[13,14,20,21], severity of disease has in fact been shown to be determined also by major transplantation antigens, in both hepatitis B virus[18,19] infections in humans and in LCM-virus infections in mice[10,22].

Factors influencing susceptibility to LCM disease

Various LCMV isolates[10,14-16,23] that by conventional serology are indistinguishable have been tested recently and were found to vary greatly with respect to the disease they induce. It is unclear how these differences come about, but it seems that included among various other possibilities such as susceptibility to interferons, macrophage activation, natural killer cells etc., it is their antigenic quality that appears to vary. There are at least two types of host factors that regulate disease susceptibility to LCM in mice. First there is a very important general genetic influence that is independent of the MHC (H-2)[10]. Dependent upon this genetic background, the two LCMV strains used induce all possible 4 disease susceptibility patterns, i.e., susceptibility to both, to none or to one or the other of the LCMV strains. Second, in one inbred mouse strain tested in detail (B10) the major transplantation antigens coded by the H-2D region determine whether B10 mice are susceptible or not to one of the LCMV isolates[10]. Since the H-2D class I transplantation antigens mediate cytotoxic T cell function and regulate antiviral cytotoxic T cells, it was obviously important to evaluate whether these H-2D regulated differences in susceptibility to LCM correlated with T cell-mediated immunopathology caused by LCMV-specific cytotoxic T cells: the result was that high and early cytotoxic LCMV-specific and H-2D restricted T cell activity correlated positively with susceptibility to LCM diseases[10].

Conclusion

In a model infection with a noncytopathic virus (LCMV) in mice a clear cut influence of the MHC in disease susceptibility could be shown[10,22]. This influence was only seen if the right cloned virus isolate was used to infect the correct mouse strain. Susceptibility to LCMV correlated well with the capacity of mice to generate LCMV specific cytotoxic T cells; MHC genes regulating both susceptibility to disease and cytotoxic T cell activity mapped to the same H-2D MHC locus; the q allele conferred susceptibility and early and high cytotoxic T cell activity, the k (or b, d not shown) allele(s) conferred resistance and slow and low cytotoxic T cell activity.

Therefore, in this model LCMV-triggered cytotoxic T cell-mediated immunopathology that is regulated by H-2D is responsible for the linkage of LCM disease susceptibility to the MHC. These findings support the notion that many diseases, susceptibility to which is linked to the MHC, may be caused by T cell-mediated immunopathological mechanisms triggered by non-cytopathic infectious agents. Admittedly, in very few HLA-linked diseases do we know a causative infectious agent and one may therefore prefer to use other explanations for MHC-disease associations (reviewed in ref. 5). However our findings suggest that variants of rather common infectious agents may cause some of the HLA linked diseases, whereas yet unknown agents that do not usually cause acute infections may be the cause for others. These explanations are supported by the evidence[12,23] that LCMV isolates that are indistinguishable by classical serology differ greatly with respect to their recognition by T cells (and possibly by other factors) and therefore may cause differing diseases. Under the well-defined condition used here with inbred mice and cloned virus isolates, MHC disease association could be shown to be absolute. This is quite in contrast to all of the HLA disease associations found in humans, which as stated earlier, are usually weak[5]. Several explanations for this finding can now be offered. First, as already discussed, various isolates of infectious agents may differ despite the fact that they are serologically indistinguishable[24]; the cloned virus used in our experiments obviously renders this parameter constant. Second, HLA typing based on serology has similar limitations. Recent experiments using T cells or genetic probes for typing clearly show that serologically defined HLA-A or HLA-D antigens comprise a variety of subtypes[25,26]; in our experiments this variability is excluded by using inbred strains of mice. Third, the general genetic background of humans differs amongst individuals, families and races as much as it clearly differs between inbred strains of mice. HLA disease associations therefore only

can become visible if, as in mice, the right virus isolate infects humans of the correct general genetic background so that HLA-regulation of the T cell response becomes recognizable.

The presented results and interpretations lead to another important consequence, with respect to application of immune modulating therapeutic protocols used during immunopathologically mediated disease. Unless one knows the balance, kinetics and actual relationship between parasite and host response very precisely, it is equally likely that one will influence the host/parasite balance in a beneficial or a determinal direction. In conclusion, the proposal is made, illustrated and supported by experimental evidence that T cell-mediated immunopathology triggered initially by low- or non-cytopathic infectious agents may cause diseases, susceptibility to which is linked to the MHC. It is obvious that not all MHC-disease associations are explained by this pathophysiological mechanism, but a reasonable guess would be that many of such linkages may follow the outlined rules. Conversely, the proposal implies that MHC-disease associations quite generally signal T cell-mediated pathophysiology of the disease.

1 This summary is an updated version of the paper given on the occasion of the Paul Ehrlich Prize ceremonies in 1983; it was also presented at the meeting 'New Trends in Allergy II' in München 1985, and is reproduced here with the permission of Springer Verlag, Heidelberg.

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Virus-immune T cells and the major histocompatibility complex: Evolution of some basic concepts over the past two years

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Key words. T cells; major histocompatibility complex; cell-mediated immunity; immune response genes; influenza.

The lecture that I gave at the University of Frankfurt as part of the proceedings associated with the award of the Paul Ehrlich-Ludwig Darmstaeder Prize in March 1983 was not prepared in a format that was suitable for publication. My understanding of the subject has been summarized in two recent reviews that are readily accessible[1,2]. There would be little point in repeating the exercise here. However, on re-reading the outline of the 1983 lecture, it was obvious that a number of the ideas current then must now be considered to be rather dated. The present, short account, thus concentrates on the way that our understanding of major histocompatibility complex (MHC)-restricted T cell recognition of virus-infected cells has been modified over the past two years. Much of this change reflects the development of T cell clones and the application of molecular biology. Many of the speculations about the nature of molecular interactions that were raised by cell-biology experiments have been, or are in the process of being, resolved. Other problems appear to be more intractable.

The T cell receptor

The debate about whether or not the T cell had two polymorphic receptors[3] for virus and MHC glycoprotein, or one receptor which recognizes some complex (or interaction product) of virus and MHC[4], was very much alive in 1983 and is still not buried. Some of us have long been of the opinion that only the one-receptor model can explain the results of various biological experiments[5-7], though we have tried to explore conceptually the ways in which a two receptor model might operate[8,9].

Much of the current evidence[10] seems to indicate that a single, clonotypic T cell receptor is central to MHC-restricted T cell recognition. This receptor consists of covalently-linked α and β chains, which are immunoglobulin