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HLA-LINKED *IMMUNE SUPPRESSION GENES*

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Summary Genetic control of immune response was investigated by family and population analyses in humans. It was first recognized that there are high responders and low or non responders to natural antigens in human population. Family analysis revealed that low responsiveness to streptococcal cell wall antigen (SCW) was inherited as an *HLA*-linked dominant trait. $CD8^+$ suppressor T cells existed in low responders and depletion of the $CD8^+$ T cells from low responders could restore the strong immune response to SCW. Therefore the gene controlling the low response to SCW was designated as an *immune suppression gene* for SCW. *Immune suppression gene* for SCW was in strong linkage disequilibrium with particular alleles of *HLA-DQ locus*. The association between *HLA-DQ alleles* and low responsiveness mediated by $CD8^+$ suppressor T cell was also observed for schistosomal antigen, *Mycobacterium leprae* antigen, tetanus toxoid, cryptomeria pollen antigen and hepatitis B virus surface antigen suggesting that low responsiveness to those antigens was also controlled by *immune suppression genes*. Anti-HLA-DR monoclonal antibodies inhibited the immune response to those antigens of high responders *in vitro*, but anti-HLA-DQ monoclonal antibodies did not. On the other hand, anti-HLA-DQ monoclonal antibodies restored the immune response in low responders. Therefore, it is suggested that *HLA-DR* upregulates immune response and that *HLA-DQ* downregulates it and that *HLA-DQ* is epistatic to *HLA-DR* in the regulation of immune response in humans. Furthermore, direct evidence for the differential in immune regulation between *HLA-DR* and *DQ* was obtained by analyzing the SCW specific T cell lines from low responders. SCW specific and HLA-DQ restricted $CD4^+$ T cell lines could activate $CD8^+$ suppressor T cells which in turn downregulate SCW specific $CD4^+$ T cells whereas SCW specific and HLA-DR restricted $CD4^+$ T cell lines could not activate $CD8^+$ suppressor T cells. All these observation clearly demonstrated that the *HLA*-linked

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immune suppression genes exist in humans to control low response to natural antigens.

Key Words immunogenetics, *HLA*, *immune response gene*, *immune suppression gene*, suppressor T cell

Introduction

Since the *H-2* linked *immune response genes (Ir-genes)* were described in mice by McDevitt *et al.* (1972), and Benacerraf and McDevitt (1972), it has been long assumed that *HLA*-linked *Ir-genes* exist in humans. Actually there is no doubt that HLA-DR molecules are acting as the products of *HLA*-linked *Ir-genes*, because (1) HLA-DR molecules are the restriction elements in the interaction between $CD4^+$ helper T cells and antigen presenting cells in the response to many antigens such as streptococcal cell wall antigen (SCW) (Nishimura and Sasazuki, 1983; Sone *et al.*, 1985; Hirayama *et al.*, 1986), schistosomal antigen (Sj) (Hirayama *et al.*, 1987), *Mycobacterium leprae* antigen (ML) (Kikuchi *et al.*, 1986) and so on, and (2) anti-HLA-DR monoclonal antibodies completely abolish the immune response to those antigens (Nishimura and Sasazuki, 1983; Sone *et al.*, 1985; Hirayama *et al.*, 1986; Kikuchi *et al.*, 1986; Hirayama *et al.*, 1987). However, genetic analysis of the immune response to those antigens in families or populations revealed that responsiveness is recessive and nonresponsiveness to those antigens is a dominant genetic trait which is tightly linked to *HLA* (Sasazuki *et al.*, 1980a; Sasazuki *et al.*, 1983; Watanabe *et al.*, 1988). This is completely opposite to the situation under the *H-2* linked *Ir-gene* control where responsiveness is dominant and nonresponsiveness is recessive. In this paper, I would like to summarize the evidence for the *HLA*-linked *immune suppression genes (Is-genes)*, and show the evidence for the epistatic interaction between *HLA-DR* and *DQ* to determine the immune response to several antigens in humans. Furthermore the differential roles of the *HLA-DR* and *DQ* in the immune regulation are demonstrated.

Evidence for the presence of nonresponders to several antigens in human population

Figure 1 summarizes the immune response to natural antigens in human population. There is a small area in Japan where schistosomiasis was endemic. Individuals infected with *Schistosoma japonicum* were divided by their response to Sj into two groups, high and low responders (Fig. 1a) (Sasazuki *et al.*, 1980b). A small proportion of the high responders developed postschistosomal liver cirrhosis whereas low responders did not (Ohta *et al.*, 1982). Healthy individuals showed either high or low T cell response *in vitro* to SCW (Fig. 1b) (Sasazuki *et al.*, 1980a).

In leprosy there are at least two well defined clinical types, tuberculoid leprosy and lepromatous leprosy. Peripheral blood lymphocytes (PBL) from patients with tuberculoid leprosy showed vigorous T cell response to ML *in vitro*, whereas T cell response was not observed at all in patients with lepromatous leprosy (Fig. 1c) (Kikuchi *et al.*, 1986). This nonresponse of patients with lepromatous leprosy to ML was antigen specific, because the patients would show strong T cell response

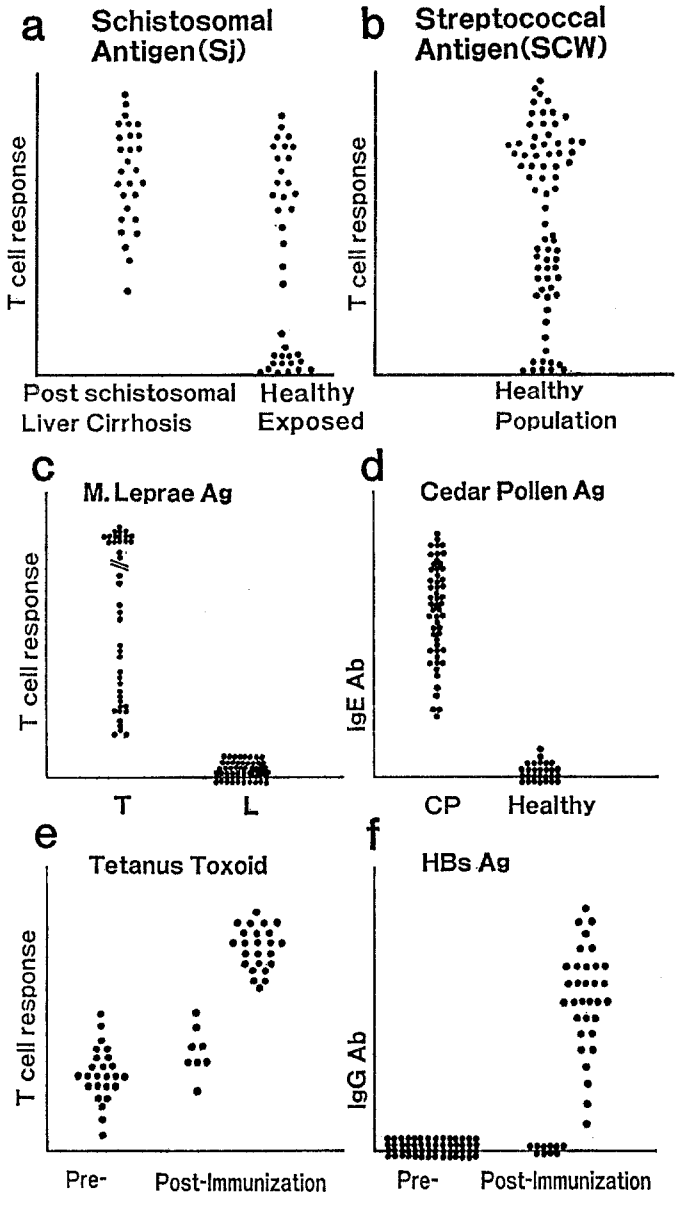

Fig. 1. Polymorphism of immune responsiveness to natural antigens or vaccines in humans. Proliferative response of peripheral T cells specific to *Schistosome japonicum* antigen (a), streptococcal cell wall antigen (b), *Mycobacterium leprae* antigen in patients with lepromatous leprosy (L) or tubercloid leprosy (T) (c) or tetanus toxoid in healthy individuals pre and post immunization (e). IgE levels specific to cedar pollen antigen among patients with cedar pollinosis, or healthy controls (d). IgG levels specific to hepatitis B virus surface antigen in healthy vaccinese, pre and post immunization (f).

to other antigens such as SCW and cedar pollen antigen (CP).

In early spring about 10 to 20% of Japanese suffer from type I allergy, cedar pollinosis, following the extensive exposure to pollen from *Cryptomeria japonicum*. Most unaffected individuals did not show any appreciable IgE response to purified antigen from the cedar pollen whereas affected individuals showed IgE antibody production to the antigen both *in vivo* and *in vitro* (Fig. 1d) (Matsushita *et al.*, 1987). All these observations clearly indicate that there are low or nonresponders in human populations to several antigens after natural exposure to these antigens.

However, since we measured the immune response after natural exposure, we could not control the antigen dose and the period of the exposure, which may or may not affect the immune response in question. To overcome these problems we investigated the immune response after planned immunizations. Two weeks after the injection of tetanus toxoid (TT) 84.8% (78/92) of medical students showed strong T cell response to TT *in vitro* whereas 15.2% showed no response at all (Fig. 1e) (Sasazuki *et al.*, 1978). In the case of hepatitis B vaccine we measured IgG response to hepatitis B virus surface antigen (HBs) both *in vivo* and *in vitro*. Even after 3rd immunization 22.4% (19/85) of medical students did not show any antibody production (Fig. 1f) (Watanabe *et al.*, 1988). Thus we conclude that there are nonresponders to several antigens in human population even after planned immunization.

Evidence for the genetic control of nonresponsiveness

T cell response to SCW was measured *in vitro* and concordance in the immune response to SCW between monozygotic twins was 0.79 whereas that between dizygotic twins was less than 0.30 indicating that the immune response to SCW was

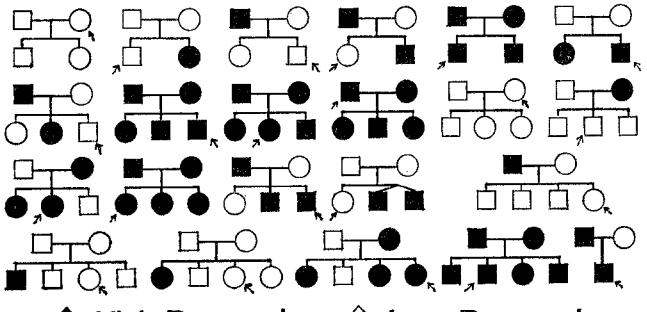

Fig. 2. Autosomal dominant inheritance of the low responsiveness to SCW in 22 families. Only high responders (black symbols) were segregated from the matings between high responders whereas high and low responders were segregated from the matings between low responders (open symbols). The mode of inheritance of the immune responsiveness to SCW was investigated by the maximum likelihood method and the observed segregation of low responsiveness fitted a dominant model very well.

Table 1. Genetic analysis of nonresponsiveness to HBs vaccine.[a]

	$\frac{DRw53(+)}{DRw53(+)}$	$\frac{DRw53(+)}{DRw53(-)}$	$\frac{DRw53(-)}{DRw53(-)}$	$\chi 2$
Observed (n=19)	6	12	1	
Expected				
Recessive	11.18	6.72	1.00	6.97[b]
Dominant	5.52	12.48	1.00	0.06[c]

[a] For the recessive case of nonresponders, expected antigen genotype frequencies of homozygote *DRw53*(+)/*DRw53*(+), heterozygote *DRw53*(+)/*DRw53*(−), and *DRw53*(−)/*DRw53*(−) are calculated as k^2, $2k(1-k)$, and $(1-k)^2$, respectively. k is the suspected ratio of some antigen present; for the recessive case, k is calculated as $1-\sqrt{1-Df}$, where Df is the antigen frequencies among nonresponders. For the dominant case, expected antigen genotype frequencies of *DRw53*(+)/*DRw53*(+), *DRw53*(+)/*DRw53*(−) and *DRw53*(−)/*DRw53*(−) are calculated as kF, $k(1-F)+(1-k)F$ and $(1-k)(1-F)$, respectively. k is calculated as $1-(1-Df)/(1-F)$, where F is the gene frequency in the normal population.

[b] $p<0.05$.

[c] $p>0.95$.

Table 2. *HLA*-linked *immune suppression genes.*

Antigen	Immune response observed as	Mode of inheritance of low responsiveness[a]	Marker of suppressor T cell	Linkage with[b]	Linkage disequilibrium with
SCW	T cell proliferation	Dominant	CD8	HLA	DR2, DR5, DQw1
Sj	T cell proliferation	(Dominant)	CD8	HLA	DR2-DQw6-Dw12
ML	T cell proliferation	Dominant	CD8	HLA	DR2-DQw6-Dw2
CP	IgE response	Dominant	CD8	HLA	DQw3 (negative)
HBs	IgG response	Dominant	CD8	HLA	DR4-DRw53-DQw4-Dw15

[a,b] The *HLA*-linked dominant inheritance of low responsiveness was elucidated by family study for SCW and CP and by population study for Sj, ML and HBs.

controlled genetically. Genetic analysis of the immune response to SCW using 23 families revealed that nonresponsiveness is a dominant genetic trait and is closely linked to *HLA* (lod sore=4.31 at $\theta=0.00$) (Sasazuki *et al.*, 1980a, 1983) (Fig. 2). Genetic analysis of response to HBs using the formula by Thomson and Bodmer (1977) also suggested that nonresponse to HBs was a dominant genetic trait which was closely linked to HLA (Watanabe *et al.*, 1988) (Table 1). As shown in Table 2, the statistical association or genetic linkage between nonresponsiveness to many antigens and *HLA-class II alleles* also confirmed the genetic control of immune response and suggested that genes controlling low responsiveness to those antigens

may be mapped within the *HLA class II region* (Sasazuki *et al.*, 1978; Sasazuki *et al.*, 1980b; Sasazuki *et al.*, 1983; Kikuchi *et al.*, 1986; Watanabe *et al.*, 1988).

Possible mechanisms of nonresponsiveness controlled by HLA-class II genes

The nonresponsiveness controlled by the *HLA-class II genes* is explained by at least four mechanisms as follows. (1) Lack of *Ir-genes:* HLA-class II molecules of nonresponders can not bind processed antigen (Buus *et al.*, 1986; Ceppellini *et al.*, 1989). (2) Cross tolerance: HLA class II molecules of nonresponders share epitopes with antigen in question. (3) Clonal deletion of T cell repertoire: HLA class II molecules of nonresponders eliminate auto-reactive T cell clones during intrathymic differentiation resulting in "hole" in T cell repertoire (Kisielow *et al.*, 1988; Marrack *et al.*, 1988). (4) Suppression: HLA class II molecules of nonresponders generate active suppression.

If nonresponsiveness was due to the lack of *HLA*-linked *Ir-genes*, nonresponsiveness should be recessive and responsiveness should be dominant. As was discussed previously, the genetic analysis revealed that nonresponsiveness is dominant, therefore, the first possible mechanism was ruled out. If nonresponsiveness is due to the cross tolerance or clonal deletion, restoration of immune response in nonresponders can not be expected by any means. Only in the case that nonresponsiveness is due to the active suppression, restoration of the immune response might be expected by blockage of active suppression. Therefore, we focused our effort on the investigation of restoration of immune response in nonresponders to understand the possible mechanisms of nonresponsiveness controlled by *HLA-class II genes.*

Evidence for the active suppression and epistatic interaction between HLA-DR and DQ to control the immune response

After removal of $CD8^+$ T cells from PBL, even nonresponders showed strong immune response and this implied that even nonresponders have $CD4^+$ T cell clones responding to the antigens such as SCW, Sj, ML, CP and HBs (Nishimura and Sasazuki, 1983; Ohta *et al.*, 1983; Kikuchi *et al.*, 1986; Matsushita *et al.*, 1987; Watanabe *et al.*, 1988) (Fig. 3). Furthermore if we add back the CDB^+ T cells to the culture system, the response was completely abolished, thereby suggesting that the non responsiveness to these antigens were determined by the presence of the $CD8^+$ suppressor T cells.

It is interesting to note that monoclonal antibody directed against HLA-DQ also restored the immune response to Sj *in vitro* in nonresponders with *HLA-DR2-DQw6-Dw12 haplotype* (Hirayama *et al.*, 1987) (Fig. 4). This observation provides fine contrast to the fact that monoclonal antibodies to HLA-DR completely block the immune response. Furthermore, the restored immune response of the nonresponders after depletion of $CD8^+$ T cells was also blocked by anti-HLA-DR monoclonal antibody. For instance, *HLA-DR2-DQw6 (Dw12 heplotype)* controls nonresponse to Sj, but even the nonresponders homozygous for *HLA-DR2-*

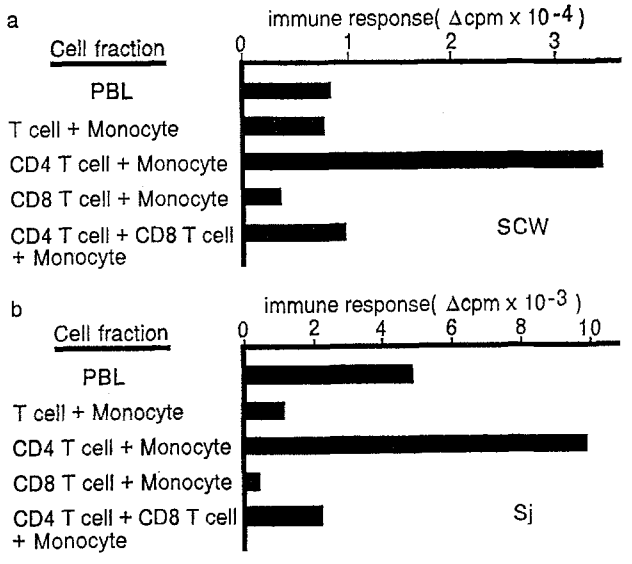

Fig. 3. Evidence for the presence of active CD8+ suppressor T cells in low responders. Proliferative response of T cells to SCW (a) or Sj (b) was investigated in low responders to each antigen.

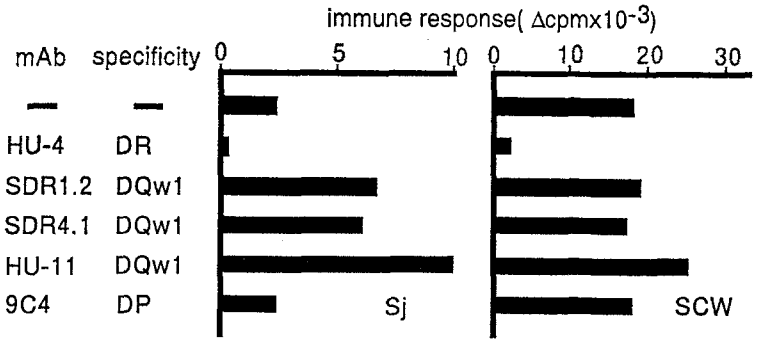

Fig. 4. The effects of monoclonal antibodies on the proliferative response to Sj or SCW of T cells separated from a low responder to Sj. Restoration of immune response to Sj by anti-HLA-DQw1 monoclonal antibodies was observed. Whereas these antibodies had no effects on the response to SCW.

DQw6 (Dw12 halotype) showed strong immune response to Sj after removal of CD8+ T cells, and this response was completely abolished by anti-HLA-DR monoclonal antibody suggesting that *HLA-DR2* on the *HLA-Dw12 haplotype* is acting as the *Ir-gene* for Sj in the nonresponders. Therefore the nonresponse to Sj is not due to the lack of *Ir-gene* but due to the presence of active suppression mediated by

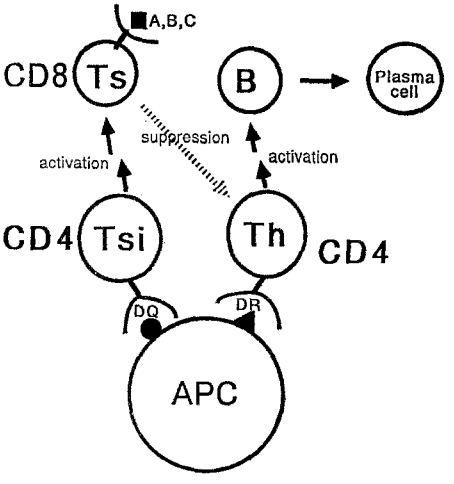

Fig. 5. A possible model for the interaction between antigen presenting cell (APC), CD4+ helper T cells (Th), CD4+ suppressor inducer T cells (Tsi) and CD8+ suppressor T cells (Ts) through the recognition of HLA antigens.

CD8+ T cells which are most likely generated by *HLA-DQw6* as the *immune suppression gene*. Actually monoclonal antibody to HLA-DQw6 restored strong immune response to Sj in this nonresponder.

Because CD8+ T cells, in general, recognize class I histocompatibility antigens but not class II antigens, CD4+ T cells which are activated by DQw6 plus antigen and which can turn on the CD8+ T cells are required in this immune suppression system. Figure 5 illustrates a possible models for the interaction between HLA-DR, DQ, CD4+ T cell and CD8+ T cell. For instance, *HLA-DR2-DQw6 (Dw12)* controls the nonresponse to Sj, even though *DR2* acts as the *Ir-gene* for Sj. *HLA-DQw6* in strong linkage disequilibrium with *DR2* is the *Is-gene* for Sj which controls nonresponse to Sj by activating suppressor pathway, and thus *HLA-DQw6* is epistatic to *DR2* in controlling the immune response to Sj in humans.

Difference in structure, expression and contribution to MLR between HLA-DR and DQ

Because there seems to be difference between *HLA-DR* and *DQ* in regulating immune response to certain antigens, it is interesting to ask if there are any differences in structure and in some other features between *HLA-DR* and *DQ*. *HLA-DR* and *DQ* belong to the *HLA-D* multigene family, together with *DP*, *DO* and *DN*. The α chains of DR and DQ exhibited a 64% homology in amino acid sequence and the β chains of DR and DQ exhibited a 68% homology (Auffray *et al.*, 1984; Long *et al.*, 1984). The majority of DQ β chains are eight amino acids shorter in the cytoplasmic tail due to base substitution from G to A right before exon 5, in comparison to DRβ or β chains of mouse I-A and I-E (Larhammar *et*

al., 1983; Boss and Strominger, 1984) even though DQ β chains from *HLA-Dw12*, *Dw9*, and *DB7* utilize exon 5 because of no base substitution (Tsukamoto *et al.*, 1987).

Expression of the DQ molecules on B cells, macrophages and activated T cells is much less than that of DR molecules (Fujisawa *et al.*, submitted), a finding which may be explained by the base substitution in the promoter region of *DQA gene;* one base substitution from C to T in the X box and from G to A in the Y box within the 5′ flanking region which controls expressivity of the *DR* and *DQ genes* (unpublished observations).

In the allogeneic mixed lymphocyte reaction (MLR) DR is the major element related to stimulation, with DQ contributing little, if at all (Sone *et al.*, 1985; Hirayama *et al.*, 1986). On the other hand, when the frequencies of precursor T cell reactive to class II molecules are estimated in the presence of recombinant IL-2, utilizing murine L cells transfected with *HLA class II genes* and a limiting dilution analysis, the frequencies of precursor T cells reactive to autologous or allogeneic DQ molecules were unexpectedly as high as that of precursor T cells reactive to allogeneic DR molecules (Fujisawa *et al.*, submitted). Because the expressivity of HLA-DQ on B cells and monocytes is smaller than that of HLA-DR, the contribution of HLA-DQ molecules in allogeneic MLR becomes smaller than that of HLA-DR molecules, despite the high frequency of DR reactive precursor T cells. Thus, *HLA-DR* and *DQ* possess significant differences in structure, expression and function. At this stage, however, it is not possible to relate these differences to the difference in immune regulation between *HLA-DR* and *DQ*.

Distinct role of HLA-DR and DQ in immune regulation

To investigate directly the role of *HLA-DQ* in the low responsiveness to SCW, antigen specific T cell lines were generated from high and low responders, as described (Sone *et al.*, 1985; Hirayama *et al.*, 1986). The restriction molecules of these T cell lines were identified using murine L cells transfected with *HLA-class II genes.* In high responders, DR molecules were mainly recognized in the context of SCW by T cell lines. On the other hand, DQ molecules as well as DR molecules were used as restriction molecules in low responders and $CD4^+$ T cell lines were a mixture of T cell lines restricted by *DR* or *DQ* molecules. In low responders, a small proportion of $CD8^+$ T cells was also found.

These T cell lines from low responders were co-cultivated with SCW, IL-2 and irradiated allogeneic PBL which shared *HLA-DR* or *DQ* with the donor of the T cell lines, to establish T cell lines restricted by either HLA-DR or DQ. After this selection, T cell lines were co-cultivated with irradiated autologous PBL as the source of antigen presenting cell (APC). The $CD3^+$ $CD4^+$ $CD8^-$ and $CD3^+$ $CD4^-$ $CD8^+$ T cells were propagated in the HLA-DQ restricted T cell lines. The irradiated DQ restricted $CD4^+$ T cell subpopulation stimulated the $CD8^+$ T cell subpopulation to proliferate in the presence of SCW and autologous APC. The irradiated $CD8^+$ T cell subpopulation had a suppressive activity. On the other hand,

CD4+ T cells dominated and CD8+ T cells disappeared in the HLA-DR restricted SCW specific T cell lines.

From these observations we confirmed the model for the activation of CD8+ suppressor T cells as was shown in Fig. 6. The classical CD4+ helper T cell (TH) which activates B cells to produce immunoglobulin recognizes antigen in the context of the DR molecule. On the other hand, CD4+ suppressor inducer T cell (Tsi) which activates CD8+ suppressor T cells (Ts) to suppress the proliferative response of CD4+ T cells recognizes antigen in the context of DQ molecules. CD8+ T cells, in general, recognize class I major histocompatibility antigens (Ratnofsky *et al.*, 1987). Therefore, CD8+ suppressor T cells may recognize self or non-self antigens in the context of class I antigen expressed on CD4+ T cell or APC to sup-

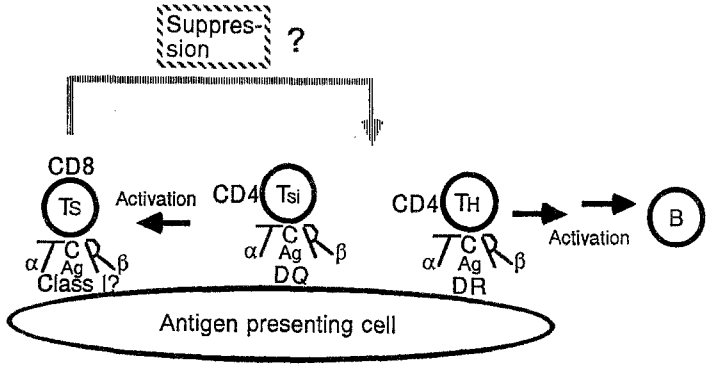

Fig. 6. A probable model for the interaction between antigen presenting cell (APC), CD4+ helper T cells (Th), CD4+ suppressor inducer T cells (Tsi) and CD8+ suppressor T cells (Ts) through the recognition of a self or non-self antigen (Ag) in the context of distinct HLA antigens.

Table 3. Association between HLA and autoimmune disease.

Disease	HLAs	
	Susceptible	Resistant
Graves' disease	A2-Cw11-Bw46(DRw8) (Bw54)-(DR4)-DQw4	(A24)-(Cw)-(Bw52)-(DR2)-DQw6 (A24)-(Cw7)-B7-DR1-DQw5
Hashimoto's thyroiditis	(DR4)-DRw53-DQw4-(Dw15) (DR9)-DRw53	(A24)-(Cw7)-(B7)-DR1-DQw5 DRw6 (DR2)-DQw6
Insulin dependent diabetes mellitus	Bw54-DR4-DQw4	DR2-DQw6
Rheumatoid arthritis	Cw1-(Bw54)-DR4-DQw4	(DR2)-DQw6 (DRw8)-DQw6

[a] HLA haplotypes associated positively or negatively with diseases were indicated. HLA alleles increased or decreased in the patients group without statistical significance were indicated in parenthesis.

press the proliferative response of $CD4^+$ T cell. Taken together we suggest that *HLA-DR* upregulates the immune response and *HLA-DQ* downregulates it through induction of $CD8^+$ suppressor T cells by DQ restricted $CD4^+$ suppressor inducer T cell. The immune suppression gene may be a particular allele(s) of the *HLA-DQ locus* and *HLA-DQ* might be epistatic to *HLA-DR* in the regulation of immune response and disease susceptibility in humans.

Is-genes control susceptibility or resistance to disease

Table 3 summarizes the statistical association between *HLA* and diseases. *HLA-DQw6* controls resistance to postschistosomol liver cirrhosis through controlling nonresponse to Sj (Fig. 1 and Table 2). There is no doubt that immune response is inevitable to the host to prevent from infectious disease, however, it is also true that immune response has an adverse effect on the host. Multigene family and extremely high degree of polymorphism of the *HLA class II genes* may have been maintained through the long history of evolution by exerting up or downregulation of immune response to a large variety of environmental pathogens. Resistance to Graves' disease, Hashimoto's thyroiditis, insulin dependent diabetes mellitus and rheumatoid arthritis determined by *HLA-DQw6* in the Japanese population may also be explained by the immune suppression, however, we have to wait until "the responsible antigen" involved in the pathogenesis of these autoimmune diseases is identified.

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