Table 4 Cytokine production profiles of Cry j 1-specific T-cell lines obtained from the pollen allergic donors

Antigens	Patients									
	AR-1	AR-2	AR-3	AR-4	AR-5	AR-6	AR-7	AR-8	AR-9	
Cry j 1 protein	174/877[a]	437/1410	39/34	550/509	393/316	665/131	59/20	204/46	49/15	(pg/ml)
p13–32		82/127								
p61–80			269/46							
p71–90								37/ < 10		
p81–100			39/32							
p86–105			73/ < 10							
p108–125	116/638									
p115–132		< 8/109			480/218					
p127–143				23/118						
p201–220	36/87									
p206–223	51/80			18/27	95/ < 10		27/12			
p230–250	51/58									
p261–280			57/35							
p271–290								91/ < 10		
p301–321				127/115						
p337–353	44/36			127/214		131/98			203/93	

[a] The values indicate IFN-γ/IL-4 production, respectively.

ods (24, 48, and 72 hours), and at which times culture supernatants were collected for the determination of cytokine concentrations. These two T-cell lines failed to produce IL-4, while producing large amounts of IFN-γ and undergoing considerable proliferation throughout these three incubation periods (data not shown). Moreover, cultures using various peptide concentrations (2.5, 5, and 10 μM) were also performed, however; the same patterns of cytokine production were observed (data not shown). These results suggest that p86–105 and p271–290 are likely to be Cry j 1-derived Th1 epitopes.

DISCUSSION

Allergen-specific immunotherapy is a highly effective treatment in patients with IgE-dependent diseases including insect venom anaphylaxis and allergic rhinitis. However, the administration of natural allergen extracts might occasionally give rise to adverse events due to severe IgE mediated reactions, therefore; several new strategies have been developed to reduce the potential to cross-link IgE on mast cells while still containing the relevant T-cell epitopes. As a new approach, synthetic peptides corresponding to T-cell epitopes of the allergen have been evaluated in various studies for peptide-based immunotherapy. More recently, a clinical immunotherapy trial that used synthetic peptides of allergens was also reported.[8,19,20] One of the advantages of peptide-based immunotherapy may be related to the insufficient length to cross-link IgE on the surface of mast cells, thereby eliminating the risk of induction of anaphylaxis. Another advantage is that immunotherapy can be accomplished within a shorter period of time using a relatively high-dose injection of antigenic peptides. Fellrath *et al.* have designed a double-blind, placebo-controlled phase I clinical trial in patients hypersensitive to bee venom using 3 long synthetic overlapping peptides mapping the whole sequence of phospholipase A2, a major bee venom allergen, and demonstrated that there was peptide-specific T-cell hyporesponsiveness and an increase of IL-10 and IFN-γ secretion by stimulation with peptides in the peptide group.[20] On the other hand, Kay A.B. and colleagues have demonstrated that 12 synthetic overlapping peptides encompassing most of the T-cell epitopes of the major cat allergen Fel d 1 can induce T cell tolerance in animal experiments and these peptides have been shown to decrease the amount of proliferation as well as cytokine production in cat allergic patients.[6,7] Moreover, this treatment has also been reported to have potential for inhibiting upper and lower airway outcome measurements in a pilot study.[8] Thus, peptide-based immunotherapies have been shown to be effective for bee venom and cat allergen.

In the present study, we demonstrated that four peptides of Cry j 1 (p61–80, p115–132, p206–225 and p337–353) activated more than one T-cell line. Furthermore, T-cell lines generated from eleven out of twelve donors reacted with at least one of these four peptides. Therefore, a mixture of these four peptides may be a useful cocktail for peptide-based immunotherapy for patients sensitive to Cry j 1. To date, Hirahara *et al.* and Sone *et al.* have reported on the benefit of the hybrid or polypeptides consisting of Cry j 1-derived T cell epitopes for the development of peptide-base immunotherapy.[12,15] These hybrid pep-

tides or polypeptides would have superior potential for inducing T-cell proliferative responses as compared with a mixture of the T-cell determinants. However, the clinical efficacy in immunotherapy using these peptides has yet to be reported. Hirahara *et al.* and Sone *et al.* have selected a total 4 different peptides, p108–120, p211–225, p235–247, and p312–330 from T cell-epitopes identified in the Cry j 1 sequence. In our study, p206–225 inducing T-cell proliferative responses in 4/12 (33.3%) was the identical peptide which they selected. Alternatively, 2 other peptides, p61–80 and p337–353 have also been shown to induce proliferative responses in relative high frequency, 3/12 (25.0%) and 4/12 (41.7%), respectively. Hori *et al.* have demonstrated a significant positive association between Japanese cedar pollinosis and HLA-DPB1*0501 (79.2% in patients versus 60.6% in controls).[14] Furthermore, they found that p214–222 was the minimal antigenic site of the immunodominant peptide for the HLA-DPB1*0501 restricted T cells. Similar to p206–225, the p61–80 peptide has also been reported to be presented in the context of HLA-DPB1*0501 alleles as T-cell defined epitope.[11] HLA-DPB1*0501 is one of the most frequently expressed HLA-DP common alleles in the Japanese population, therefore; these two peptides may be useful for peptide-based immunotherapy. It is noteworthy that T cell lines generated from some DPB1*0501 negative donors were able to proliferate in response to p61–80 or p206–225 peptides, suggesting that these two peptides may be recognized in the context of any other HLA class II. With respect to another peptide, p337–353, the restriction element remains unknown. Ikagawa *et al.* showed that Cry j 1 p335–346 was presented in the context of HLA-DRA + DRB3*0301, however; the frequency of HLA-DRB3*0301 is less than 20% in the Japanese population.[13] Therefore, the p337–353 peptide may also be an immunodominant T cell epitope that is presented by multiple HLA class II molecules. Another possibility is that the p337–353 peptide may be more immunogenic among Cry j 1-derived T cell epitopes. Thus, for development of a broadly applicable peptide-based immunotherapy, universal T cell epitopes that are immunogenic in individuals of many HLA haplotypes should be identified, selected, and used.

In general, it is accepted that PBMC of allergic patients preferentially induce Th2 rather than Th1 responses under stimulation with certain allergens; however, proteins or longer peptides containing multiple epitopes may induce various T-helper responses, and the extent of T-helper responses to each epitope may also vary. Actually, Sone *et al.* indicated that the p191–205 peptide presented by HLA-DRB1*0901 and HLA-DQB1*0602 molecules could preferentially induce Th2 and Th0, respectively.[11] Gardner *et al.* demonstrated that high dose allergen stimulation of T cells induced expansion of IFN-γ + T cells, apoptosis of CD4+IL-4+ T cells and T cell anergy in house dust mite allergic patients.[21] Thus, other factors such as HLA class II allele, the allergic status of the donor, type of antigens and their concentration, might also influence immune responses in individuals. Interestingly, Cry j 1-specific T-cell lines obtained from AR-3 and AR-8 showed Th1 responses to p86–105 and p271–290, respectively. These T-cell lines secreted IFN-γ, but not IL-4 regardless of the time course and antigen concentrations. Th1 cells have inhibitory effects on Th2 function and have been shown to prevent airway inflammation in mouse models.[22] Alternatively, Szabo *et al.* have demonstrated that Th1-associated transcription factor, T-bet not only induced Th1 development but also actively suppressed Th2 differentiation in vitro.[23] Thus, allergen-specific Th1 cells appear to have a suppressive function to Th2 responses to allergen, however; it remains unclear how allergen-specific Th1 cells are interrelated to other regulatory T cell subsets including naturally occurring CD4+CD25+ T cells, Tr1, and Th3 cells, in allergic disease. Furthermore, there is little information regarding the relation between the nature of the peptide and the clinical efficacy in peptide-based immunotherapy. A better understanding of the nature of peptides and the specificity of Cry j 1-specific T cell responses in allergic patients is necessary to better design, and develop more effective peptide-based immunotherapy in the future.

Taken together, our data indicated that four Cry j 1-derived peptides (p61–80, p115–132, p206–225 and p337–353) may be considered to be the immunodominant T-cell epitopes of the Cry j 1 molecule, and can be useful for the design of broadly applicable efficacious peptide-based immunotherapy for the management of Japanese cedar pollinosis.

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