Synopsis of Original Research Paper

Development of in vitro evaluation system of allergenic sensitizing potential of chemicals

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Recently, several in vitro assays to predict the respiratory sensitizing potential of chemicals were developed, because the use of animal models in safety testing of chemicals is significantly limited. However, these alternative methods cannot distinguish chemical respiratory sensitizers and skin sensitizers, although the risk management systems for them are quite different. Therefore, in the present study, we aim at developing a novel in vitro assay, which can discriminate chemical respiratory sensitizers from skin sensitizers by taking advantage of the fundamental differences between their modes of function; development of helper T (Th) 2 immune responses, which is critically important for respiratory sensitization.

We have established a novel 3-dimensional (3D) coculture system using scaffold, which consists of human airway epithelial cell line, immature dendritic cells (DCs) derived from human peripheral blood $CD14^+$ monocytes, and human fibroblast cell line. The present results indicate that this DC coculture system can discriminate the respiratory sensitizing potential of chemicals from their skin sensitizing potential by means of more enhanced expression of key costimulatory molecule OX40 ligand, which is important for Th2 differentiation, as a marker in DCs. Moreover, we have also developed a novel DC/T coculture system, which consists of the sensitized DCs and allogenic naive $CD4^+$ T cells. In this system, we have great advantage that IL-4 up-regulation can be used as a marker for the prediction of respiratory sensitizing potential. Indeed, our data suggest that selective up-regulation of IL-4 was observed by the stimulation with respiratory sensitizer as compared to that with skin sensitizer.

Taken together, the present results suggest that our 3D coculture systems consisting of epithelial cells, DCs, fibroblast cells, and T cells would be useful for in vitro evaluation of allergenic sensitizing potential of chemicals. We are currently trying to further improve the versatility of these systems by using iPS technology.