



Research on the effects of chemical substances on children, elderly people, and those with gene disorders

Title of Research:

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Establishment of in vitro evaluation system for the prediction of respiratory sensitizing potential of chemicals

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Summary of Research:

Recently, several in vitro assays to predict the respiratory sensitizing potential of chemicals have been 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.

In this year, we have established an immunocompetent 3D co-culture system of human upper airway, which consists of human airway epithelial cells, immature dendritic cells (DCs) derived from human peripheral blood CD14⁺ monocytes, and human fibroblast cells cultured in individual scaffolds. Then, these scaffolds were assembled into a 3D multi-cell tissue model, which more closely mimics the in vivo situation. Then, three typical chemicals for respiratory and skin sensitizers were added on the 3D co-culture system. The present results indicate that this 3D co-culture system can predict the respiratory sensitizing potential of chemicals by means of enhanced expression of key costimulatory molecule OX40L, which is important for Th2 differentiation, as markers in DCs (1). Moreover, to improve the versatility, we have next utilized iPS cell-derived DCs based on published protocols, although this efficacy is not good. Therefore, we are currently trying to establish a novel method to generate infinitely growing myeloid progenitors by stimulation with various cytokines and incorporation of genes related to cell cycle and survival. In addition, we are also trying to develop a novel 3DC/T system, which consists of sensitized DCs and allogenic naive CD4⁺ T cells. In this 3DC/T system, IL-4 up-regulation could be the best marker for the prediction of respiratory sensitizing potential of chemicals.

Timeline:

March 1, 2017-February 28, 2018

Topics:

The 5th Annual Meeting of The Japan Chemical Industry Association LRI, poster presentation "Establishment of a novel in vitro evaluation system for the prediction of respiratory sensitizing potential of chemicals" (The Tokyo Shoken Building, August 25, 2017)

Publications:

1. Mizoguchi I, Ohashi M, Chiba Y, Hasegawa H, Xu M, Owaki T, Yoshimoto T. Prediction of chemical respiratory and contact sensitizers by OX40L expression in dendritic cells using a novel 3D coculture system. *Front Immunol.* 8, 929, 2017 (IF=6.429).
2. Ohashi M, Mizoguchi I, Chiba Y, Hasegawa H, Xu M, Yoshimoto T. Prediction of chemical respiratory and contact sensitizers by OX40L expression in dendritic cells using a novel 3D co-culture system. The 46th Annual Meeting of The Japanese Society for Immunology, oral poster presentation in English (Sendai, December 12-14, 2017)