Title of Research:

15_S03-01-1

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

Principal Investigator:

Takayuki Yoshimoto, PhD (Professor, Tokyo Medical University, Institute of Medical Science)
6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-8402, Japan
(tel)+81-3-3351-6141 Ext. 431, (e-mail) yoshimot@tokyo-med.ac.jp

Collaborators:

Izuru Mizoguchi, PhD (Research Associate, Tokyo Medical University, Institute of Medical Science) 6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-8402, Japan
(tel) +81-3-3351-6141 Ext. 448, (e-mail) imizo@tokyo-med.ac.jp

Summary of Research:

Although the number of patients with occupational asthma has recently been estimated to be as high as approximately 15-18% of that with adult asthma, there is no established diagnostic methods for it and no standard, validated and regulatory-accepted methods to identify potential respiratory sensitizers and distinguish them from skin sensitizers. This is in marked contrast to the situation of contact hypersensitivity, where there are highly sophisticated, established diagnostic methods. Testing assays for assessment of chemical sensitizers including GPMT and LLNA, which utilize guinea pigs and mice, respectively, were previously developed. However, the use of animal models in safety testing will be significantly limited due to introduction of 3Rs principles of refinement, replacement, and reduction of animal experimentations in research wherever possible. Therefore, several in vitro assays including DPRA, KeratinoSense, h-CLAT, and IL-8 Luc Assay have been developed. However, these alternative methods cannot distinguish chemical respiratory sensitizers and chemical skin sensitizers, although the risk-management countermeasure is markedly different between them.

Therefore in the present study, we aim at developing a novel in vitro assay, which can discriminate chemical respiratory sensitizers from chemical skin sensitizers by taking advantage of the fundamental differences between their modes of function (AOP: Adverse outcome pathway); development of type 2 helper T (Th2) immune responses, which is critical for respiratory sensitization.

Using the Alvetex® Scaffold from Reinnervate, we have established an immunocompetent 3D co-culture system of human upper airway. It consists of a human airway epithelial cell line, human immature dendritic cells (DCs) derived from peripheral blood $CD14^+$ monocytes, and a human fibroblast cell line cultured in individual scaffolds and then assembled into a 3D multi-cell tissue model, which more closely mimics the in vivo physiological situation. The present results indicate that this 3D co-culture system has great potential to contribute to the establishment of in vitro evaluation system for the prediction of respiratory sensitizing potential of chemicals by means of enhanced expression of molecules critical for induction of Th2 differentiation and immune responses such as OX40L and IL-10 as markers.

Timeline:

March 1, 2015-Feberary 29, 2016

Topics:

The 3th Annual Meeting of The Japan Chemical Industry Association LRI, poster presentation “Development of a novel method for in vitro assessment of chemical respiratory sensitizers” (Tokyo, August 28, 2015)

Publications:

The 28th Annual Meeting of The Japanese Society for Alternatives to Animal Experiments, Japan Chemical Industry Association LRI Symposium, oral presentation “Development of a novel method for in vitro assessment of chemical respiratory sensitizers” (Yokohama, December 11, 2015)