Development of Integrated Approaches to Testing and Assessment for Respiratory Sensitization Based on the AOP

Takao Ashikaga
Division of Genome Safety Science, National Institute of Health Sciences Center for Biological Safety and Research, Kanagawa, Japan

Izuru Mizoguchi
Department of Immunoregulation, Institute of Medical Science, Tokyo, Medical University, Tokyo, Japan

Takayuki Yoshimoto
Department of Immunoregulation, Institute of Medical Science, Tokyo, Medical University, Tokyo, Japan

Abstract

The development of in vitro respiratory sensitisation tests demands an understanding of the mechanisms by which chemicals cause respiratory sensitisation. The recently proposed adverse outcome pathway (AOP) for sensitisation of the respiratory tract is useful for gaining such an understanding. The Th2 response induced by a respiratory sensitiser may be related to signals from the airway epithelium, which is known to secrete cytokines (e.g. interleukin (IL)-33 and thymic stromal lymphopoietin (TSLP)) that instruct Dendritic Cells (DCs) to mature; these cytokines also drive Th2 polarisation by upregulating the expression levels of co-stimulatory markers such as OX40L in DCs. Therefore, in vitro methods that involve the coculture of DCs and airway epithelial cells could be useful for recapitulating in vitro the immune responses specific to respiratory sensitisation. Using this co-culture system named DCsens, respiratory senseitisers, skin sensitisers and nons sensitisers were selected from existing information and predictability was simulated using in vitro test results. This hybrid evaluation system by adding DCsens to the existing in vitro skin sensitization tests showed the possibility of classifying chemicals into each group.