

COMMENTARY

New attempts to improve *in vitro* diagnosis of contact allergy are still far from regular clinical practice

Contact allergy, a state of T-cell mediated hypersensitivity to small chemicals, is associated with allergic contact dermatitis (ACD) when the individual is adequately exposed to the chemical or a chemically related hapten. Patch testing is the gold standard for the diagnosis of contact allergy and ACD, but several *in vitro* tests using patient's peripheral blood mononuclear cells (PBMC) have been tried to document hapten-specific reactivity. These tests measure allergen-specific T-cell proliferation (lymphocyte transformation test – LTT), activation (lymphocyte stimulation tests – LST) or cytokine secretion. Nevertheless, the diagnosis of ACD based on these *in vitro* tests is still far from current practice. Contrary to patch testing, *in vitro* tests evaluate a single allergen at a time, few laboratories have facilities to perform them and there are difficulties in standardization, specificity and sensitivity of the techniques.¹

Characteristics of the chemical and the pathways it activates during sensitization or elicitation and patient's immune status/concomitant diseases, like atopic dermatitis, may influence the sensitivity and specificity. Circulating T cells that specifically proliferate *in vitro* when exposed to cutaneous haptens belong to different phenotypes and produce different cytokines. Even for the same allergen, for example nickel, specific T cells are Th1, Th2, Th17 and Treg. Moreover, many allergens activate the innate immune response which may influence PBMC stimulation results: – nickel stimulates human TLR-4 and NLRP3 inflammasome, other allergens modify hyaluronic acid or ATP, increase alarmins or reactive oxygen species and activate intracellular signalling pathways involved in cytokine secretion and cell activation.² Also, during ACD different T-cell phenotypes (Th1, Th2, Th17, Th22, Th9 and CD8+) infiltrate the skin in distinct proportions eventually influencing the clinics and histopathology of ACD (eczematous, psoriasiform, lichenoid, urticaria, granulomatous, lymphomatoid or erythema multiform-like lesions).³

Therefore, it has been difficult to choose the best technique to document *in vitro* hapten-specific T-cell activation. Summer *et al.* compared LTT with cytokine dosing in the supernatants of Ni-stimulated PBMC in patients with Ni-positive patch tests. IL-5, the only cytokine significantly upregulated, was more evident in patients with atopy (73% of their patients), a condition with a known Th2-imbalance which may have influenced these *in vitro* results. IL-8, which is usually upregulated in *in vitro* evaluation of the sensitizing potential of chemicals in dendritic and THP-1 cells, was inhibited by nickel in this test. Therefore, Summers

*et al.*⁴ calculated the IL-5/IL-8 ratio, a measure which slightly increased the sensitivity of the *in vitro* test, but at the expense of a reduced specificity.

This is not yet the definite answer to resolve the limitations of *in vitro* testing in the diagnosis of contact allergy, but the combination of different *in vitro* techniques with inclusion of measurement of T-cell cytokines may be an important aspect to explore, as observed in non-immediate drug eruptions.

Apart from ACD, a standardized, easily feasible, specific and sensitive *in vitro* test might also be very helpful in the diagnosis of delayed hypersensitivity where the skin is not the main target organ, where allergen-specific T cells may not express the cutaneous homing receptor and patch testing is so not often positive, namely in adverse reactions to metal implants that present as pain, inflammation, swelling or orthopaedic prosthesis loosening,⁵ inflammation and vessel thrombosis with metal stents, or pruritus and dysgeusia in contraceptive metal implants, like the Essure®.

Conflict of interest

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