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Chromium Allergy - Clinical and Cellular Studies

Summary

Chromium salts can cause severe allergic contact dermatitis. Chromium is a transition metal that shows several different oxidation states ranging from -II to +VI. However, only the trivalent Cr(III) and the hexavalent Cr(VI) oxidation states are sufficiently stable to act as haptens. Most studies investigating chromium allergy have been performed with Cr(VI). However, real exposure to chromium from leather products may include both Cr(III) and Cr(VI). The aim of this PhD thesis was to characterise different aspects of allergic contact dermatitis to chromium in previously sensitized patients.

In study I, we performed dose response studies in order to determine the minimum eliciting threshold (MET) concentration for Cr(III) and Cr(VI) in Cr(VI)-sensitive patients. A total of 18 chromium-allergic patients were patch tested on the back with a dilution series of potassium dichromate (Cr(VI)) and chromium trichloride (Cr(III)). The MET concentration eliciting an allergic reaction in 10% of the patients was calculated from dose response curves to be 0.18 $\mu\text{g Cr(III)/cm}^2/48\text{h}$ (6 ppm Cr(III)) and 0.03 $\mu\text{g Cr(VI)/cm}^2/48\text{h}$ (1 ppm Cr(VI)). We concluded that although Cr(VI) was confirmed as being the most potent hapten, Cr(III) also demonstrated a significant capacity to elicit allergic reactions at low concentrations. Thus, both Cr(III) and Cr(VI) may play a role in chromium-induced dermatitis.

In study II, we investigated the relation between the content of Cr(VI) and soluble Cr(III) in leather and the ability of the leather to elicit eczema in chromium-allergic patients. A group of 15 chromium-allergic patients with a history of foot dermatitis and leather exposure was exposed to a selection of 14 chromium- and 1 vegetable-tanned leather samples on the upper back. No relation was observed between the measured content of Cr(VI) and soluble Cr(III) in the leather and the elicitation of eczema. Additionally, a prolonged exposure study demonstrated that an extended exposure period might reveal allergenic potential of a leather sample not otherwise identified using an ordinary 48h-exposure period. We concluded that to evaluate the safety of a leather sample in relation to preventing allergic skin reactions, other, more clinically relevant methods reflecting the actual bioavailable Cr(III) and Cr(VI) fractions should be developed.

In study III we investigated the reactivity to both Cr(VI) and Cr(III) in consecutive patients in order to analyse the clinical pattern in relation to foot eczema and reactivity to Cr(III). Among the 2211 consecutive patients patch tested, 3.2% had a positive reaction to Cr(VI) of which 44% also had a positive Cr(III) reaction. No Cr(VI) negative patients had a positive reaction to Cr(III). An increased risk for foot dermatitis was found in Cr(VI) positive patients with a concomitant positive or doubtful reaction to Cr(III) compared to Cr(VI) positive patients with no reactions to Cr(III). The increased risk was not due to a higher degree of sensitivity to Cr(VI) but other shoe allergies were more common in the group reacting to both Cr(III) and Cr(VI).

Study IV was a cellular study aiming at finding gene transcripts suitable as *in vitro* diagnostic markers for allergic contact dermatitis. We used the microarray technology in the identification of differentially expressed genes in allergen-stimulated peripheral blood mononuclear cells (PBMC) from chromium-allergic patients versus healthy controls. A total of 26 genes were differentially expressed by more than twofold ($p < 0.01$, $q < 9\%$) in allergen-stimulated PBMC from patients compared with controls. Three genes (CASP8, CISH, ETS2) were selected for real-time RT PCR measurements. Analysis of the gene expression in an extended patient/control population indicated that the differential gene expression depended on a proper proliferative response to the allergen *in vitro*. Thus, the three gene transcripts may not provide more information than the traditional proliferative *in vitro* assay on allergic contact dermatitis.