

Healthcare industry BW

Mystery of nickel allergies solved

Researchers from the University of Gießen and the Mannheim Medical Faculty along with colleagues from Freiburg, Münster and Munich, have made a fundamental contribution to deciphering the biological mechanisms behind nickel allergies. The results, which might be of great importance for developing innovative preventive and therapeutic approaches, have now been published in the current edition of "Nature Immunology".

Allergies are more common than ever. People with allergies often exhibit contact dermatitis that causes itching, redness and desquamation. Nickel is the most common allergen: In Europe alone, current estimates suggest that 65 million people have allergic reactions to this metal, which can be found in many day-to-day objects, including costume jewellery, watches and coins. However, the mechanisms that lead to the development of nickel-related contact dermatitis are not yet understood in detail.

Under the overall management of the work group led by Prof. Dr. Matthias Goebeler and Dr. Marc Schmidt (Centre for Dermatology, Venerology and Allergology at the University of Gießen), who worked at the Department of Dermatology, Allergology and Venerology at the Mannheim Medical School (MMA) until recently and carried out the majority of the research published in Nature Immunology, the researchers have deciphered the biological mechanisms behind nickel allergies that cause skin inflammation, an allergic reaction that precedes the development of visible signs of dermatitis.

The researchers showed that nickel activates a receptor, which signals the immune system to initiate intracellular signalling pathways. The immune response involves the production of proinflammatory messenger substances, which activate the specific immune system, which in turn leads to allergic responses (contact dermatitis) mediated by T-lymphocytes.

The researchers also found that nickel induces an immune response by binding to a protein called Toll-like receptor 4 (TLR4). This protein was discovered in 1998, but up until now has only been known to act as a target structure for proinflammatory bacterial substances (lipopolysaccharides). TLR4 plays a key role in the defence of bacteria where it prevents the excessive proliferation of bacteria by activating the innate immune system.

The researchers found for the first time ever that nickel induces inflammatory reactions by binding to TLR4. They also found that nickel binds to a different molecular recognition site than that used by bacterial lipopolysaccharides. This finding might lead to a breakthrough in the treatment of nickel allergies that are currently difficult to treat. In principle, the findings open up the possibility of developing specific TLR4 inhibitors to block an allergic reaction to nickel without interfering with TLR4's natural ability to fend off bacterial infections.

The researchers were surprised to find that nickel activates TLR4 receptors in humans, but not in mice. They found that the mouse receptor lacks the amino acids that are crucial for enabling nickel to bind to TLR4 and concluded that this might be a possible explanation as to why mice do not develop nickel allergies and why it has previously been impossible to establish an experimental mouse model for contact nickel allergies.

In cooperation with the research groups led by Prof. Dr. Stefan Martin (Department of Dermatology, University Medical Centre Freiburg) and Prof. Dr. Marina Freudenberg (Max Planck Institute of Immunobiology, Freiburg), the team of researchers succeeded in establishing a mouse model that possesses the human TLR4 receptor rather than the mouse TLR4 receptor. These data not only show that conclusions derived from animal models can only be transferred to the situation in humans to a limited extent, the researchers also identified nickel as the first allergen to be able to directly trigger the immunologically important TLR4 receptor of the innate immune system.

The findings reported in Nature Immunology provide further evidence for the assumption that allergies are essentially misguided immune responses. Prof. Goebeler's and Dr. Schmidt's research project was funded by the German Research Foundation and the Baden-Württemberg Foundation.

Publication

Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel.

Schmidt M., Raghavan B., Müller V., Vogl T., Fejer G., Tchapchet S., Keck S., Kalis C., Nielsen P., Galanos C., Roth J., Skerra A., Martin SF, Freudenberg M, Goebeler M.

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Press release

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