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> ONE MONTH, ONE PROTEIN <

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zips, necklaces and mobile telephones

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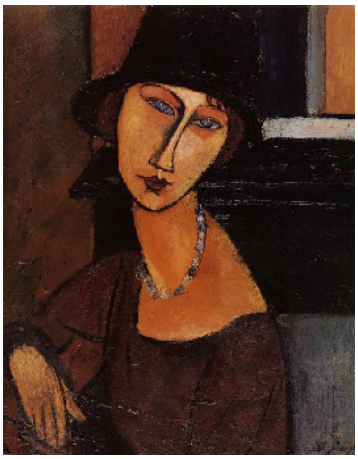
I would hate to leave the house without the odd necklace hanging round my neck. But I happen to be fortunate. Millions of other people are not. That is because a lot of jewellery contains the silvery-white metal known as nickel, which can cause disagreeable skin conditions. If nickel were confined to jewellery, things would not be so bad but it is also frequently found in zips, coins and mobile telephones for instance. And who, in our society, can easily dispense with any one of these items? 65 million people in Europe suffer from nickel allergy; that is a large part of the population. Nickel ions are able to creep off a necklace or a coin – following sweat or rubbing for example – and sink through the first layers of skin where they will trigger off an immune response resulting in dermatitis. But why does it happen in some people and not in others? The answer seems to reside in a very small region of a protein known as the toll-like receptor 4, or TLR4, which has been shown to be at the heart of nickel allergy.



Jeanne

Amadeo Modigliani (1884-1920)

Why is an organism allergic to anything in the first place? Self-defence would be the answer. Over time, our bodies have learned to discern what it believes is good for us from what it imagines is bad. Allergies are just a way of saying it out loud. This said, is there really any point in being allergic to dairy products or wheat for example? No. Not really. Allergies are frequently a case of something potentially harmless which is seen as being harmful, so the body responds accordingly in self-defence, causing all sorts of discomfort. Nickel is not harmless. However, nickel poisoning caused by wearing an earring or answering your mobile telephone must surely be extremely rare. So what is it that causes the swelling, itches, redness and even blisters on the skin of so many people?

Much of the second half of the 19th century and the first half of the 20th were devoted to understanding the nature of an allergy on the molecular level. In the event of a skin allergy for example, there has to be something from the outside that triggers something off in the inside. In other words, there has to be some kind of molecular receptor on our skin, or under it, that can recognise an "intruder" and subsequently set off the alarm. The existence of toll-like receptors (TLRs) was mentioned for the first time in the mid-1950s. Since then, TLRs have turned out to be part of a large family of receptors – from drosophila to humans – that recognise a variety of different pathogens, mainly of microbial and viral origin.

TLR4 is one such receptor. During the course of microbial contact, it identifies pathogen lipopolysaccharides (LPS) which – once bound to the receptor – spark off an immune reaction. Nickel is an inorganic compound which is able

to do the same. And even more. Unlike other pathogenic compounds, nickel acts directly on TLR4, that is to say without the upstream assistance of adaptor proteins or even the initial presence of pathogenic LPS. So far, this is the first time that a ligand of inorganic nature is able to stimulate the innate immune system directly.

What is involved? TLR4 is a transmembrane protein which usually acts with a TLR4 twin partner thus forming a homodimer. When a nickel ion comes floating in TLR4 vicinity, it spots a part of the receptor which presents two histidines in close proximity, and binds to them. This causes the twin TLR4 to lean over and bind to the same nickel ion via the matching histidines, thus forming a true homodimer. This new TLR4 architecture constitutes the basis for an immune response and is at the very beginning of the cascade reaction following which hordes of third party macromolecules are set into motion.

The intriguing part is that scientists discovered that the histidine pocket consists in six histidines – three on each side of the homodimer. When one histidine is blocked, nickel ions are still able to bind and create an allergy. When more than one is blocked, the nickel ions do not bind and there is no immune response. This probably means that people who are spared nickel allergy lack these particular histidine residues on their TLR4s. Of greater interest for researchers: LPS is still able to elicit an immune response despite the status of the histidine pocket. This suggests that LPS is recognised by another part of TLR4 and that scientists should be able to find a site-specific treatment against nickel allergy which would not hinder an immune reaction via LPS, caused by microbial pathogens for example.

One drawback: mice are no good as a model for nickel allergy because their TLR4s do not present the histidine pocket. Which is why it took so long to understand what was going on. This also highlights the difficulty there is in considering mice as humans… However, human TLR4 has been introduced into mice, who subsequently developed nickel allergy. So researchers will be able to carry out their work. The molecular basis of immunity with regards to TLR4 is also very intriguing: here are agents which are pathogenic to certain organisms, and not to others. Take HIV for instance, to which humans and chimps are susceptible, but not New World monkeys… Could infection all be brought down to the existence – or not – of a few residues? Most probably not. However, in the case of nickel allergy, finding a way to mask the histidine residues will make life easier for millions of people. Not only for zipping up their trousers but also where cardiovascular stents or dental implants are involved. Apparently TLR4 has something to do with binge drinking too. But that's another story…

Cross-references to UniProt

Toll-like receptor 4, *Homo sapiens* (Human) : O00206

References

1. Schmidt M., Raghavan B., Müller V., Vogl T., Fejer G., Tchaptchet S., Keck S., Kalis C., Nielsen P.J., Galanos C., Roth J., Skerra A., Martin S.F., Freudenberg M.a., Goebeler M.
   Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel
   Nature Immunology 11:814-820(2010)
   PMID: 20711192

2. Roediger B., Weninger W.
   How nickel turns on innate immune cells
   Immunology and Cell Biology 89:1-6(2011)
   PMID: 20938456

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