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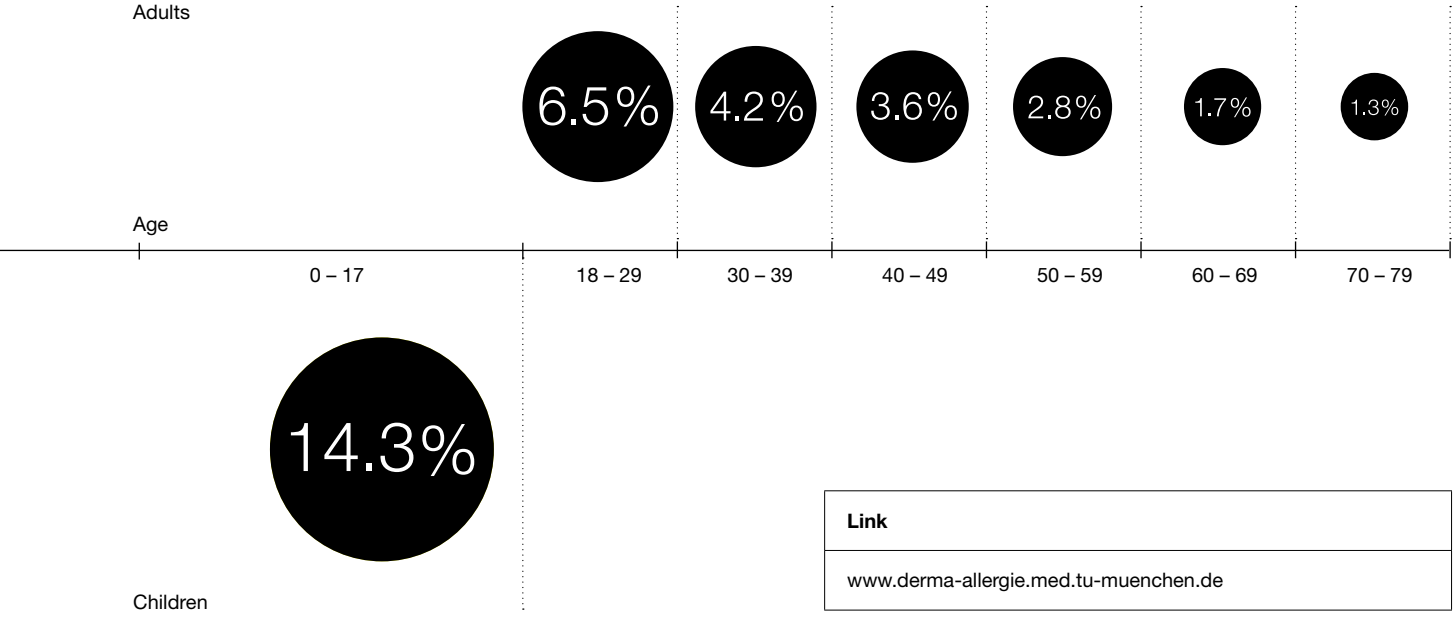

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Tricking
the Immune System

Particularly severe cases of atopic dermatitis, a common inflammatory skin condition, are accompanied by high levels of Staphylococcus aureus bacteria in the affected areas. Allergist and immunologist Prof. Tilo Biedermann has long been grappling with the way these infections aggravate this condition. He recently published some surprising findings in the scientific journal "Immunity." In this interview, Biedermann explains the trick bacteria use to sidestep the immune system in the presence of atopic dermatitis and discusses what is really new about these observations and how they impact his research.

Allergies on the rise: About 30 percent of all adults in Germany suffer or have suffered from an allergic disease. Atopic dermatitis and urticaria rank fifth after hay fever, bronchial asthma, contact eczema and food allergy. (source: DGES study conducted by Robert Koch Institut; Bundesgesundheitsblatt 2013)

Graphics: ediundsepp (source: KiGGS and DGES studies, Germany, Bundesgesundheitsblatt 2014/2013)
Picture credit: Jooss

Before taking over as Chair of Dermatology and Allergology at TUM's Klinikum rechts der Isar last year, Tilo Biedermann headed a research group at the University Hospital of Tübingen's Department of Dermatology. There, he was already investigating the molecular mechanisms that occur in inflamed skin following infection with Staphylococcus aureus.

Prof. Biedermann, one of your main focuses as a doctor and a scientist is atopic dermatitis – an inflammatory skin disease that affects one in four children and is also very common in adults. So when someone comes to your clinic with eczema, itchy blisters or other typical symptoms of this condition, how do you proceed?

Essentially, in most cases, atopic dermatitis is diagnosed by clinical presentation, meaning that we do not always need further procedures to confirm the diagnosis itself. Obviously, though, when we are trying to identify the triggering factors exacerbating a patient's atopic dermatitis – finding out what has brought it on, what is making their condition worse – then we need to do more than just examine their skin. ▷

Ausgetrickstes Immunsystem

Unter dem Mikroskop ist Staphylococcus aureus ein hübscher Bursche. Nicht zufällig bedeutet sein Name, der aus dem Lateinischen stammt, frei übersetzt so viel wie „goldene Traubenkügelchen". Der schöne Schein trügt jedoch. Denn bei dem Bakterium handelt es sich um einen höchst gefährlichen Keim, der hinter einer Vielzahl ernsthafter Krankheiten steckt, wie beispielsweise Wundinfektionen, Abszesse, Pneumonien, Nahrungsmittelintoxikationen und nicht zuletzt auch Neurodermitis. So fand man bei etwa 90 Prozent aller Patienten, die an dieser entzündlichen Hauterkrankung litten, eine Besiedelung der Haut mit Bakterien der Sorte Staphylococcus aureus vor. Nun ist es Wissenschaftlern um den Allergologen und Immunologen Prof. Tilo Biedermann gelungen, im Labor, und letztlich auch am Patienten, nachzuvollziehen, wie diese Infektionen die Krankheit zusätzlich verschlimmern. Demzufolge besitzt das Bakterium in seiner Zellwand Proteine, die gegenläufige Reaktionsmechanismen des Immunsystems triggern. „Dadurch wirkt das, was normalerweise als Bremse gedacht ist, plötzlich als Verstärker, der die Situation verschlimmert", erklärt Biedermann, der sich schon vor seinem Amtsantritt im April vergangenen Jahres als Leiter der Dermatologischen Klinik des Klinikums rechts der Isar mit seiner Forschungsgruppe an der Hautklinik der Universität Tübingen mit diesem Thema befasst hat. Wie sich bei den Experimenten im Reagenzglas und an Mäusen zeigte, wird ausgerechnet durch den Versuch, die Entzündung zu beenden, letztlich das Gegenteil erreicht. Interessant sind seine Ergebnisse nicht nur hinsichtlich der Behandlung von Neurodermitis, sondern auch aufgrund der neuen Erkenntnisse über die Mechanismen im angeborenen Immunsystem: Das Wissen, dass dort selbst vermeintlich starre Schlüsselmechanismen und Prozesse nicht zwangsläufig immer binär und linear ablaufen, stellt Wissenschaftler, die sich mit dem vergleichsweise jungen Forschungsgebiet unseres angeborenen Abwehrsystems befassen, vor ganz neue Herausforderungen des Denkens und Arbeitens. *Birgit Fenzel*

One such triggering factor is the bacterium Staphylococcus aureus (S. aureus), which is extremely prevalent on the skin of over 90 percent of atopic dermatitis patients. Along with your research groups, you have been making intensive efforts to determine the correlation between this bacterial load and aggravated inflammation for some time now, recently identifying processes that literally hold the key. But first, the most immediate question: how does S. aureus get onto the affected skin to start with?
Ultimately, up to 60 percent of people carry Staphylococcus aureus in the mucous membrane of their noses without necessarily falling ill. But in patients prone to atopic dermatitis, certain skin functions tend to be compromised – impairing the skin's ability to act as a barrier, for instance. And a weakened barrier makes it easier for bacteria to adhere to the skin in the first place, as well as to subdivide and form colonies.

So in this case, the bacteria itself does not cause the inflammation, but is piggy-backing on another condition. How does it aggravate the atopic dermatitis then?
To understand that, it is important to know a bit about the immune system. Today, we generally divide it into two main branches: innate (or natural) immunity and adaptive immunity. The natural immune system, which is present even in very simple organisms like insects, works by means of specific receptors that detect specific substances or pathogenic materials. These substances fit together with the receptor like a lock and key. So when a pathogen is on the skin, the innate immune system springs into action – switched on by the pathogen so to speak. In our case, toll-like receptors – TLR2, to be precise – sense certain bacterial substances from the surface membrane of the bacterial cells and initiate pathways of inflammation.

What usually happens then, in terms of immune response?
The skin's innate sentinel cells are then activated. They take in material from their environment and translate the signals derived from the innate sensing into biological information, which they transport to the lymph nodes and present to the immune system there. The immune system then determines whether it can mount an appropriate response. And this process in the lymph nodes involves the second branch of the immune system – adaptive immunity. Here, the lymph nodes can generate specific immune cells, for example, which then migrate back to the skin to combat the pathogen. ▷

"I always say that research is like stepping into the fog and trying to find a path that may or may not exist, because you are the first to explore that route."

Tilo Biedermann

Picture credits: Jooss

Picture credit: Jooss; graphics: ediundsepp (source: TUM)

And to start with, when the skin is infected with Staphylococcus aureus, everything takes its normal course. The substances in the bacterial cell membrane fit into the lock of the TLR2 and so the immune system mounts a resistance against the microbes. Yet somehow, the bacteria are still able to continue proliferating on the skin, aggravating the inflammation. What is going wrong?

That is because another process is triggered simultaneously – with exactly the opposite effect. Not only does Staphylococcus prompt a simple immune response via TLR2, it is evidently able to trigger a cascade of reactions at the same time, resulting in increased formation of myeloid-derived suppressor cells (MDSCs).

Those cells that are actually there to suppress or stop the immune reaction?

Exactly. Because, of course, every inflammatory response needs to end sometime. Inflammation does not just draw to an automatic close, like a wave washing up on the shore, but would simply continue to advance if the immune system did not actively shut it off again at some point.

And how do the bacteria take advantage of this mechanism?

The mass formation of MDSCs also leads to a reduction in the skin's antibacterial immune response. This allows the bacterial population to increase, and their growing numbers exacerbate the inflammatory process further. Unfortunately, it just keeps escalating. The more severe someone's condition, the worse affected they are by this mechanism.

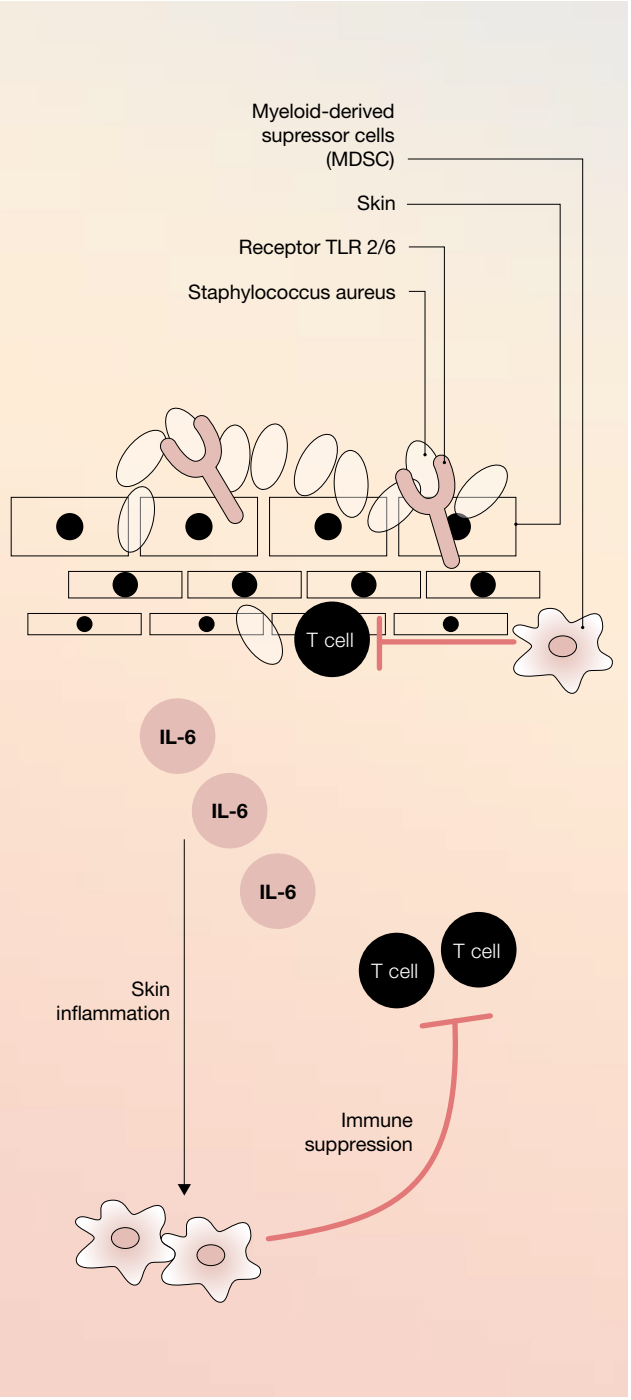
What are the therapeutic implications of these findings?

What we have established here is relevant for patients whose condition is severe, with large areas of skin affected. Our findings confirm the risk and underline the danger these patients are in. We simply need to admit these patients for more intensive therapy, including systemic treatment with antibiotics where appropriate, to reduce the concentration of bacteria.

Antibiotic-resistant Staphylococcus is a major problem. The important thing is not to treat the skin with antibiotics, to which the bacteria can develop a specific resistance, but with antiseptic agents, to which the bacteria cannot develop resistance. Many decades ago, we regularly used antiseptic dyes in dermatology. Then they were frowned upon, and now they are making a comeback.

What was the most exciting result for you as a scientist?

We actually drew two interesting conclusions. First, we were surprised to find that colonization of the skin with ▷



How Staphylococcus aureus bacteria sidestep the immune system in the presence of atopic dermatitis: The natural immune system identifies the bacteria on the skin surface via toll-like receptors (TLR/6). The adaptive immune system produces immune cells (T cells), which migrate to the skin and combat the pathogen. However, S. aureus also triggers the production of interleukin 6 (IL-6), which regulates the inflammatory response. The immune system produces myeloid-derived supressor cells (MDSC), which block the activation and the effect of the T cells. As a consequence, the bacterial population increases and the inflammation is exacerbated further.

"The important thing is not to treat the skin with antibiotics, to which the bacteria can develop a specific resistance, but with antiseptic agents, to which the bacteria cannot develop resistance."

Tilo Biedermann

S. aureus is in itself sufficient to trigger these mechanisms. In sepsis cases, we know that a very similar mechanism of the innate immune system plays a major role in making patients so critically ill. There, too, a great deal is determined by a specific receptor for a specific sub-species of bacteria – the latter going on to spread in the blood. In sepsis, though, the receptor is TLR4, rather than TLR2 as in atopic dermatitis.

What is really striking in this case is our observation that it clearly suffices if the skin is infected, without the microbes penetrating further into the body (or our model). Both cases lead to massive up-regulation of the pro-inflammatory messenger interleukin 6. In atopic dermatitis, this results in accumulation of MDSC production, in turn triggering the whole counter-reaction and increasingly vicious circle.

And the second lightbulb moment?

That was the realization that, although innate immunity is a relatively rigid system in itself, the same receptor can be used both to suppress and to amplify it. The receptor is the lock, so to speak, and the ligand the molecular key. And when the key fits into the lock, that sets the alarm. But, as we have seen here, the same key can have a completely different impact on the immune system. So it is not the case that we can only turn it either on or off – obviously both at once is possible, too. For me, that is the most exciting finding from these efforts over the past few years – that we need to think in much more complex terms to grasp that not every model that appears to be binary actually works that way.

Is that not sometimes exasperating though?

It can be. I always say that research is like stepping into the fog and trying to find a path that may or may not exist, because you are the first to explore that route. So you do sometimes feel you have lost your way. On the other hand, if your curiosity and inner drive are strong enough, that is exactly what keeps you going forward despite it all.

So going forward in this case means widening the focus?

The innate immune system has always been investigated in very linear terms to date. You take a receptor and a ligand – a lock and a key – and A happens, and then maybe B. But we now know it doesn't work that way. Innate immunity is highly complex and integrates a large amount of data at once, which can lead to totally conflicting output. It depends what information about the immune system's environment is available at the point when the key is placed in the lock – inflammation levels, for instance, or other input signals that affect the immune system. In the end, it's a combination of data that influences the end result. And that's biology. It is actually quite logical, but you do have to get there.

The interview was conducted by Birgit Fenzel

Picture credit: Jooss