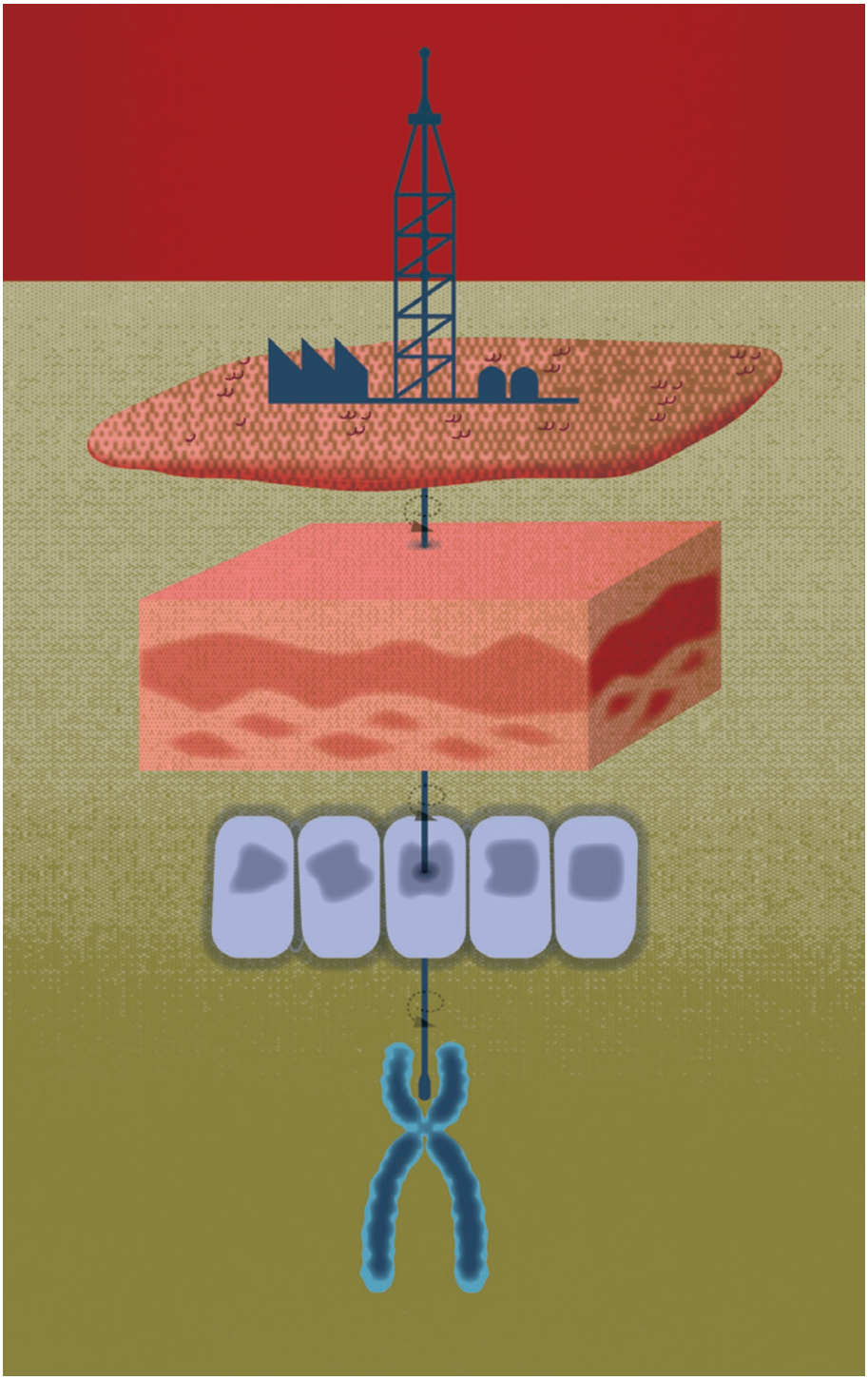

ANDREW BAKER

GENETICS

Deep exploration

Recent discoveries are redefining the role of the immune system in psoriasis, and may help to unravel the mystery of the disease's origins.

BY KEN GARBER

Psoriasis genetics took a big leap last month when the number of genome regions known to confer susceptibility to the disease jumped from 21 to 36. The new regions[1] are pieces in the unfinished puzzle that is psoriasis biology, and how researchers assemble these pieces could change our view of the disease.

The new genetic signals strongly suggest a more prominent role in psoriasis for the innate immune system, the body's first line of defence against pathogens. And some of these new psoriasis genes also hint at an answer to a bigger question: where does the disease begin?

AN ARRAY OF RISK

The immune system has two arms, innate and adaptive. The innate immune system reacts quickly and locally to a broad range of invaders, doesn't require prior exposure to them, and lacks memory. Inflammation is an innate response, for example. Adaptive immunity develops over the course of a lifetime. Its long-lived T cells and antibodies are primed from previous exposure to infections, perpetually circulating, ready to strike. Over the past two decades, adaptive immunity had come to be considered the main driver of psoriasis. That conclusion stemmed in part from the abundance of T cells and T-cell-activating dendritic cells found in psoriatic skin, and in part from the effectiveness of drugs that target adaptive immunity, such as ustekinumab (marketed as Stelara by Janssen Biotech of Horsham, Pennsylvania; see 'Silencing psoriasis', page S58). Innate immunity's role in psoriasis was considered secondary.

That's starting to change. Between 2007 and 2011, genome-wide association studies identified 21 psoriasis susceptibility genes, including six involving innate immunity. It was "surprising", says Richard Trembath, a geneticist at King's College London, "how much the genetic evidence pointed towards the involvement of the innate immune system."

To uncover even more susceptibility genes, the Wellcome Trust Case Control Consortium — a group of labs across the United Kingdom — created the Immunochip. This custom genome-sampling device is arrayed with more than 200,000 single nucleotide polymorphisms (SNPs, minuscule genetic changes that vary among individuals) implicated in 12 immune-related diseases. Such diseases were known to have multiple genes in common, and investigators strongly suspected that there were more to be found. More than 10,000 people with psoriasis, along with more than 20,000 control individuals, submitted blood samples for DNA testing.

The Immunochip results hint at an even greater role for innate immunity: at least 5 of the 15 new genomic regions associated with psoriasis risk are involved in innate immunity. (Some regions have not yet been narrowed down to a single gene.) A degree of genetic

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contribution for innate immunity was to be expected, because the skin is a complex, active site of immunity (see 'A many layered thing', page S52). Finding five regions, however, was a surprise, says JT Elder, a geneticist at the University of Michigan, Ann Arbor, and an Immunochip study investigator.

NEXT OF SKIN

Immunochip results also showed that, genetically, psoriasis overlaps most with diseases of the gut. This is not as peculiar as it might seem — skin and the intestines both form a barrier against pathogens and are composed mostly of epithelium. "The skin is epithelium from the outside in, and basically the gut is the same as skin from the inside out," Elder says. "In either case you're dealing with microbes."

Both the skin and the gut marshal similar immunological weapons to repel pathogens. For example, epithelial cells in the intestine and keratinocytes in the skin both release protein fragments called defensins, part of the innate host response to bacterial invaders. Defensins punch holes in bacterial cell walls, eventually killing them, but can also damage host cells if they get out of control. In psoriasis, defensins are produced in vast numbers, causing tissue destruction in the epidermis. As inflammation also stimulates defensin production, this perpetuates a vicious cycle of damage, inflammation and more defensins.

It's not just the Immunochip results that argue for a more important role of innate immunity. In 2011 a French group reported the discovery[2] of the gene responsible for roughly 10–20% of generalized pustular psoriasis, a severe life-threatening form of the disease. The gene, *IL-36RN*, codes for an anti-inflammatory cytokine that normally turns off innate immune pathways in multiple cell types, including keratinocytes (the cells that constitute almost all the epidermis; see 'Psoriasis uncovered', page S50). When both copies of the gene are mutated, the cytokine can't turn these pathways off, leading to unbridled inflammation that can engulf much of the body. Unlike the psoriasis susceptibility genes identified to date that merely increase risk of the disease, *IL-36RN* mutations cause this extreme form of psoriasis outright. This direct connection indicates that dysregulation of innate immunity is sufficient to cause psoriasis.

Yet more evidence that the innate immune system is responsible for psoriasis comes from work over the past two decades by Anne Bowcock, a geneticist at Washington University in St Louis, Missouri. In 1994 Bowcock found that a region on chromosome 17 was linked to a rare, hereditable form of psoriasis. In terms of biological understanding, however, that knowledge was of limited use: this region, says Bowcock, encompasses more than 70 different genes. To find the specific genetic culprit, Bowcock needed to sequence DNA for the entire region in both affected individuals and controls. In 2012 her work paid off when she reported[3] that *CARD14* was the chromosome 17 psoriasis gene. Lab experiments showed that two mutations in *CARD14* cause psoriasis by activating *NF-kB*, a master gene for inflammation. "It's important because we now have two genetic mutations in psoriasis [*IL-36N* and *CARD14*], both involving the innate immune system", that cause psoriasis, says Michelle Lowes, a dermatologist at the Rockefeller University in New York who worked with Bowcock.

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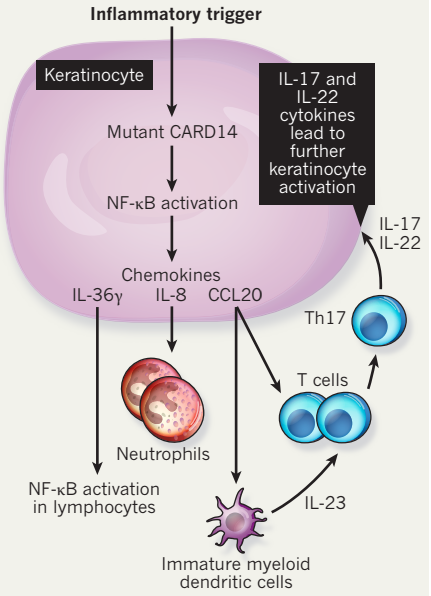
INNATE IMMUNITY GONE AWRY

In this model, a skin insult triggers activation of the NF-κB pathway via the CARD14 protein. Signalling proteins cause widespread inflammation, recruitment of T cells and thickening of the skin, all amplified in a feed-forward loop.



Bowcock's team also found a third *CARD14* mutation in a patient with early-onset pustular psoriasis who had no family history of the disease[3]. This led Bowcock to suspect that, beyond these rare families, *CARD14* might be involved in psoriasis more generally.

Evidence for this broader role emerged from the recent Immunochip psoriasis association study[1] in which *CARD14* was one of the 15 genes identified. "That says that *CARD14* and its pathway are important in the classic form of psoriasis as well," says Bowcock. "What proportion of the classic form isn't clear. But certainly it's part of one of the pathways leading to common psoriasis."

CARD14 is mainly expressed in keratinocytes — a fact that Bowcock says sheds light on the origins of psoriasis. "It's the first instance where we can show that the keratinocyte is likely to play a major role in the development of the disease, and possibly be where the trigger resides," she says.

STARTING POINTS

Despite the identification of these disease-linked genes, no one knows where psoriasis starts. Some evidence points away from the skin. For example, the first onset of psoriasis often coincides with infection of the throat and tonsils by *Streptococcus* bacteria. The theory is that in priming T and B cells against these invaders, the adaptive immune system confuses some bacterial protein for a host skin protein. (Variants in genes that code for parts of the antigen-presentation machinery have been linked to a predisposition to develop psoriasis, supporting this idea.) This misidentification then leads to an influx of T cells to the skin and hence the autoimmune attack that characterizes psoriasis lesions.

But the many innate immunity genes recently implicated in psoriasis are shifting attention back to the skin. Researchers have found[4] that most people with psoriasis lack at least one copy of two related genes involved in differentiation of epidermal cells. It is possible that people lacking these genes are unable to properly repair damage to their skin, resulting in a leaky barrier that microorganisms easily pass through. This finding is consistent with the recent Immunochip results. The nature of the innate immunity genes associated with psoriasis, notes Trembath, "tends to suggest the involvement of microbes, particularly viruses".

It's also possible that physical trauma might set off an inflammatory response in keratinocytes that escalates, or that a virus causes an innate immune response and collateral damage to the skin. Both scenarios would involve a cascade of damage and inflammation (see 'Innate immunity gone awry'), accentuated by genetic factors, that draws in the adaptive immune system. "What we're dealing with is a threshold effect for inflammation," says Bowcock. "If the level is too high you will get enhanced immune activation that cannot be turned off."

So attention turns back to the keratinocytes as a potential site for the origin of psoriasis, where a burst of innate immunity later brings in adaptive immunity. "The 'which comes first in psoriasis: abnormalities of keratinocytes or of the immune system' is an ongoing lively debate," says Lowes. "The pendulum has swung in both directions for years." As the genetic profile of psoriasis comes more into focus, the pendulum may be swinging back to the skin. ■

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