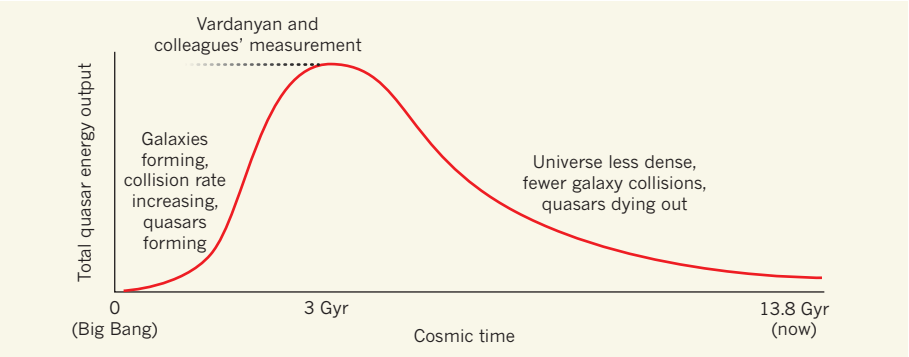

Figure 1 | The energy output of quasars over cosmic time. In the standard picture of quasar evolution, from the Big Bang to the present day, the total energy output of quasars increases to a peak value some 3 billion years (Gyr) after the Big Bang as galaxies form, collide and trigger the activation of quasars. This output then declines steadily as the accelerating expansion of the Universe results in a decrease in the number of galaxy collisions. Vardanyan *et al.*[3] found a surprising 'plateau' (dashed line) from about 1 billion to 3 billion years in the quasars' energy output.

in terms of subjecting them to further scrutiny and exploring their implications for quasar formation if the simplest interpretation — that large numbers of high-luminosity quasars were in place just a billion years after the Big Bang — is indeed correct.

The most exciting potential implication of Vardanyan and colleagues' study is that we need to adjust our understanding of the quasar population, especially how the early quasars formed. Most current models are based on the idea that galaxy collisions trigger quasar activation, so the number of quasars should rise sharply as galaxies form, grow and collide in the early Universe. The authors' results suggest that this link is not so strong, and that the most luminous quasars in particular form more rapidly than astronomers might suspect using simple models of black-hole accretion and galaxy collisions.

The word 'suspect' is appropriate here, because this sort of science really is like detective work, in which indirect clues must be combined with inspired deduction to reach any interesting conclusions. It is remarkable that it is possible to make any kind of inference about black holes that are billions of light years away and have long since ceased to exist as quasars. One ambiguity is that the infrared light being used to assess the quasars' energy output could come from other sources, because any mechanism that heated whatever dust was present in the host galaxy would contribute to this signal. Also problematic is that various corrections to the inferred output of the quasars have to account for the expansion of the Universe: the light seen at any given wavelength here and now has, since its emission, been redshifted by an amount that depends on how distant the source is, and hence how far back in time astronomers are seeing it. Perhaps the most uncertain aspect of all attempts to measure the evolution of the quasar population is deciding how best to account for this effect and how to test whether it has been done correctly. The approach taken by Vardanyan *et al.* is reasonable, but it is easy to imagine future data that would allow these corrections to be improved.

'More data' is something of a mantra in astronomy. Technological developments such as WISE have been one of the main drivers of discovery for the past century, and probably will continue to be in the future. We already have exciting projects such as the Large Synoptic Survey Telescope and the Square Kilometre Array just a few tantalizing years away, and both should tell us a great deal more about the age of the quasars. ■

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MICROBIOLOGY

An integrated view of the skin microbiome

An analysis of the combined genomes of microorganisms inhabiting human skin demonstrates how these communities vary between individuals and across body sites, and paves the way to understanding their functions. SEE ARTICLE P.59

PATRICK D. SCHLOSS

The growing interest in the human body's resident communities of microorganisms has paralleled a growing interest in probiotics and the emerging concept that foods can shape the composition of our gut microbiota and thus our health. At the same time, fuelled by fears of viruses and bacterial pathogens, hand sanitizers have become ubiquitous. The disconnect between protecting the balance of the 10^{14} bacteria that reside within us and destroying the 10^{10} bacteria that live on us is jarring. However, our knowledge of the skin microbiota pales in comparison with that of our gut microbiota. Seeking to fill these gaps, on page 59 of this issue, Oh *et al.*[1] present an analysis of the genetic content of the bacteria, viruses and other microorganisms that live on human skin.

There is cause to distrust some of the microbes living on our skin — opportunistic pathogens such as *Staphylococcus aureus* reside there, as do the mixture of microbes that cause atopic dermatitis, psoriasis and acne and that are responsible for the inability of chronic wounds to heal. Yet the vast majority of our resident skin microorganisms are non-pathogenic, and many of these probably contribute to maintaining health. Indeed, earlier work from the group reporting the present study showed that, in healthy individuals, physiologically comparable body sites harbour similar bacterial and fungal communities[2,3], and that shifts in skin communities are associated with development and immune status[4,5]. These results demonstrate that, instead of merely sampling the random bacteria in our environment with which our bodies interact, the skin can differentially select for specific populations.

The researchers have now moved beyond the question of which microbes are present on the skin to assessing what they might be doing. In this study, the authors sampled 15 healthy individuals at 18 sites and sequenced the metagenome — the collection of genomes in an environment — from each sample (Fig. 1). The use of metagenomic sequencing combined with innovative bioinformatic analyses

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enabled them to obtain a more comprehensive taxonomic and genetic characterization of skin microbiota than has been previously attempted. Their results included not only bacteria, but also DNA viruses and microbial eukaryotes (nucleated organisms, such as protists and fungi).

This comprehensive survey revealed that each individual has a unique skin microbiota. The authors used these data to create a classifier, using a random-forest algorithm, that could differentiate between the 15 individuals on the basis of the skin metagenome, with a 19.3% error rate. When the authors attempted to classify the individuals using the bacterial, eukaryotic and viral data separately, the error rates were higher. Interestingly, it was not the dominant organisms, but the low-abundance organisms, that differentiated people. For example, the presence of Merkel cell polyomavirus, *Gardnerella vaginalis* and *Streptococcus pyogenes* were among the key features that could be used to differentiate between the individuals.

Among the more abundant bacterial populations, the researchers identified numerous strains of *Propionibacterium acnes* and *Staphylococcus epidermidis*. Investigating the spatial and personal distribution of these strains, they observed that the distribution of *P. acnes* strains was more individual-specific than site-specific, whereas *S. epidermidis* strains were more site-specific than individual-specific. Future investigations will need to focus on how the distribution of these strains varies over time and with changes in health.

The strength of metagenomic sequencing is the ability to survey the functional potential of microbial communities. To investigate this, Oh and colleagues compared their genomic data from each body site with reference genomes, which contain functional annotation for specific genes. Perhaps the most interesting result of this analysis was the identification of antibiotic-resistance genes that were specific to individuals and body sites. Appreciating the diversity and distribution of such genes across the skin could prove crucial in customizing therapies for the treatment of skin infections. More broadly, the authors were able to identify a strong functional signature between individuals, but found that its composition varied across the body. This result confirms the finding, from taxonomic analyses, that each body site provides a unique niche.

However, the limitation of metagenomic sequencing is that it describes only the functional potential of a community. As the researchers note, transcriptome analysis of the skin microbiota — defining the genes actually transcribed by the microorganisms — will be needed to identify the functional groups that are expressed at each site. It will be interesting to see whether populations such as *P. acnes*, which are found across the body, vary in their gene expression across the range of niches.

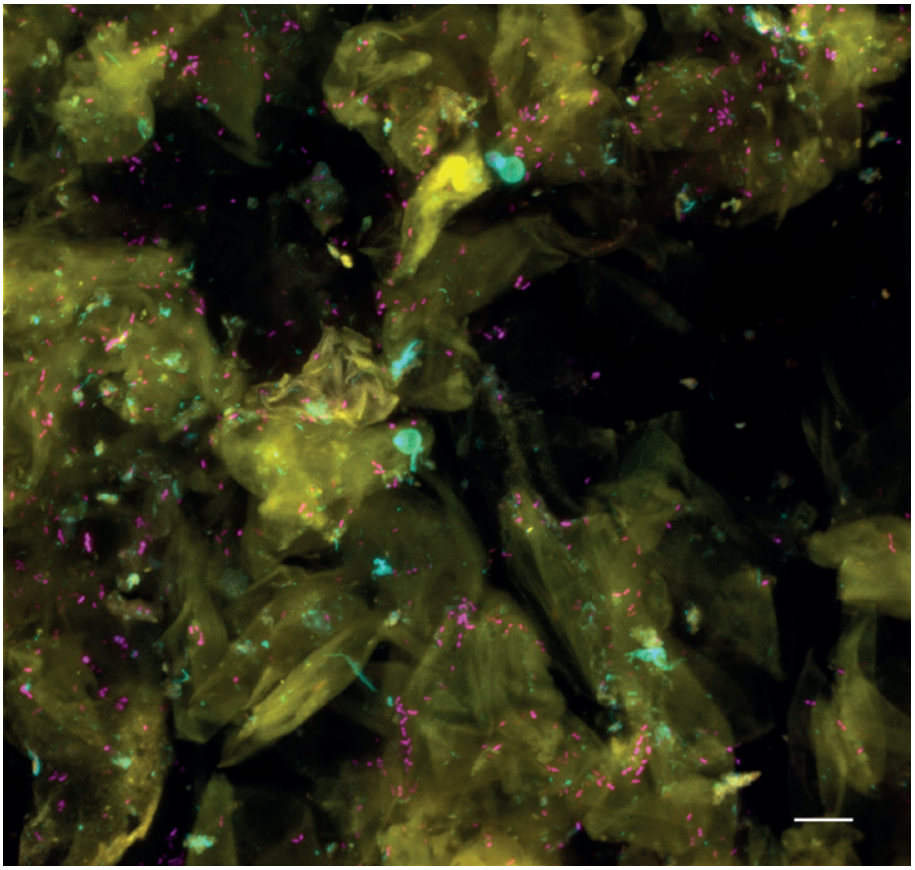

Figure 1 | Skin partners. Healthy human skin (cells shown in yellow) is colonized by a diverse array of microorganisms, including bacteria (magenta) and fungi (cyan). Scale bar, 10 μm.

A frustrating but also exciting result of this analysis was the realization that between 2% and 96% of the sequence reads in each sample did not map to any of the reference genomes. Furthermore, many of the reads that did map could not be assigned a function on the basis of known genes. These results only underscore the individuality of the skin microbiota and beg for further cultivation and genome sequencing of skin-associated microbial populations. As comprehensive as this study was, the results demonstrate the need for a 'multi-omic' approach and time-series data. Sampling an individual over time would allow us to see how their particular microbiome varies in its composition and gene expression during transitions between health and disease. As this study indicates, cross-sectional studies are challenged by the enormous heterogeneity in the composition of the skin microbiota between individuals. Changes observed during such health–disease transitions might provide a better understanding of the relevance of these unknown sequences, which the researchers refer to as metagenomic dark matter. It is probable that this dark matter contains genes crucial to the functions that are unique to each niche and individual.

According to the 'hygiene hypothesis', our modern, sanitized world has fostered the spread of autoimmune disorders such as allergies and asthma, by decreasing exposure to microorganisms during early life and thereby impeding the normal development of the immune system[6]. Just as probiotics and fibre (as a prebiotic) have emerged as consumer products designed to promote gut bacterial populations that are associated with health, it is tempting to interpret the data from Oh and colleagues as a call to develop similar products. For example, the presence of lipophilic *Corynebacterium* and *Malassezia* populations in the healthy people in this study suggests that moisturizing creams could be acting as a prebiotic to feed these organisms. With such knowledge, instead of reaching for a hand sanitizer that kills such populations, we might soon be able to reach for a product that fertilizes our skin microbiota to improve its ability to resist the colonization by potentially pathogenic organisms. ■

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