Karolinska Dermatology Symposium, 2017 "The Microbiome in Health and Disease – Focus on SKIN"

Photo: John Sennett

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Introduction

The Karolinska Dermatology Symposium is a longstanding yearly tradition in our department. This year the theme was "The microbiome in health and disease – focus on SKIN", highlighting the recent understanding of the expanded role of bacteria, viruses and funghi in health and disease. The symposium gathered more than 100 dermatologists and skin researchers from all over Sweden. This year the symposium was generously sponsored by Novartis.

Professor *Mona Ståhle* and Associate Professors *Maria Bradley and Liv Eidsmo*, Karolinska Institutet and Karolinska University Hospital, greeted everyone welcome and introduced the exciting field of the disease modulatory effects excerted by our microbiome. The microbiome is currently attracting much attention in the pathophysiology of the gut, or "interior skin". In dermatology we are just in the beginning of unravelling its impact on the skin, which warrants for an exciting future development.

The Karolinska Dermatology Symposium 2017 spanned from the role of commensals in skin biology and the effect of skin microbiome on odor to fecal transplantations and cutting edge genetic methods to study microbiota.

Human microbiome in health and disease

Staffan Normark, Senior Professor, Karolinska Institutet, Stockholm

Professor Normark made an elegant introduction to the field. He described how humans have co-evolved with microbial partners and reminded that we have much more microorganisms in our body than our own cells. Since we are unable to culture many of these microorganisms the development of deep sequencing technologies has been instrumental to advance our understanding of the complexity of the microbiota in our bodies.

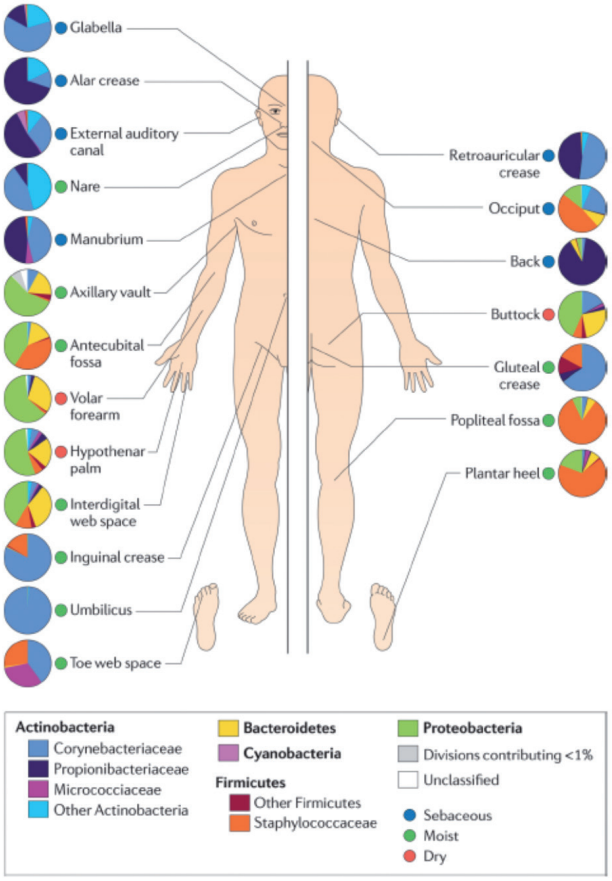


***Fig. 1.* Topographical distribution of bacteria on skin sites.** The family-level classification of bacteria colonizing an individual subject is shown, with the phyla in bold. The sites selected were those that show a predilection for skin bacterial infections and are grouped as sebaceous or oily (blue circles), moist (typically skin creases) (green circles) and dry, flat surfaces (red circles). From Grice EA, Segre JA, Nat Rev Microbiol 2011; 9: 244–253. Reprinted by permission from Macmillan Publishers Ltd.

It is now clear that the diversity of the human microbiome varies between individuals and is strongly influenced by the microbial habitat such as the skin, the oral cavity, the nose and the gastrointestinal tract. The microbiome is also different at different sites within the same tissue, for example there is a

gradual decrease in number of microbes in the lower parts of the respiratory tract, possibly due to differential production of antimicrobial peptides (Fig. 1).

Professor Normark also reviewed studies in which normal and germ-free mice were fed with high fat diet and the normal mice consequently became obese, but not the germ-free mice. A fecal transfer from the obese mice to the germfree lean mice however rendered them fat, pointing towards a role of the commensals in obesity. In line with this, obese humans also have an altered bacterial flora with much less of the bacteriodes compared to firmicutes, and the bacterial ratio can be altered upon dietary changes.

Skin microbiota in health and disease

Shruti Naik, Postdoctoral researcher, Rockefeller University, New York

Dr Naik shifted the focus from gut to skin microbiome. We learnt that skin microbiota represents the most diverse niche, with around 1,000 species and 19 phyla, and that microorganisms reside not only on the skin surface, but also in hair follicles and in sebaceous glands. Perhaps this is the reason for the skin microbiome being remarkably stable over time and largely unaffected by external stress such as bathing and application of skin creams. Skin resident microorganisms show high tropism to certain habitats of our body, favoring either for example dry or oily skin, and there is more intra-individual than inter-individual diversity in the skin microbiome.

During her work as a graduate student in the Belkeid lab, Dr Naik made major contributions to our understanding of the effect of microbiome on peripheral immunity. In the gut it was previously known that the balance between T effector cells and T regulatory (T reg) cells was altered towards more T reg cells in germ-free mice and normalized when commensals were given to the mice. Dr Naik and colleagues infected germfree mice with gut or skin tropic bacteria and found that gut tropic bacteria specifically rescued the immune system in gut, and skin tropic bacteria the immune system in skin through an IL-1 dependent pathway.

Her work also revealed great differences in the immune modulatory impact by different strains and commensal specific immune effects. For example, certain strains of *S. epidermidi*s uniquely causes induction of CD8b+ T cells. Such T cells are interestingly found in psoriasis and squamous cell carcinoma where they represent long lasting IL-17A+ CD8b T cells.

Commensal microbiota – a radical defender in times of stress

Rolf Lood, Researcher, Lund University

Dr Lood discussed the intriguing concept of human-microbiota symbiosis and put forward the hypothesis that this is not merely achieved by the absence of virulence factors but also the presence of unknown promoting factors.

Much of Dr Lood's work and interest is centered around *P. acnes*, which is found mainly in sebaceous glands. *P. acnes* is associated to acne and in patients with psoriasis and AD a reduction in *P. acnes* has been observed.

Dr Lood raised the question about the possible role of *P. acnes* in these diseases. He identified a very conserved protein called "RoxP" that is unique to *P. acnes*. One function of RoxP is to bind heme, reduce free radicals and prevent damage caused by oxidative stress. Several skin diseases are either initiated by or progress through oxidative stress, caused by for example UV radiation. Dr Lood thus speculates that *P. acnes* and RoxP reduce the risk of developing certain skin diseases.

Anaerobic human intestinal microbiota and fecal transplantation – clinical applications

Elisabeth Lissa Norin, Associate Professor, Karolinska Institutet, Solna

Associate Professor Norin introduced and reviewed her interesting work with the anaerobic cultivated human intestinal microbiota (ACHIM), to use instead of fecal transplantation.

The ACHIM originates from fecal material and has been cultivated for more than 20 years. Benefits of ACHIM over fecal microbiota transplant (FMT) is that it is carefully monitored

and does not require further screening for possible infections or gastro-intestinal diseases among the donor etc. Since the original fecal donation to generate the ACHIM is from the 1990 when antibiotic resistance was less wide-spread, fewer resistance genes are also transferred to the patient.

The ongoing studies by Norin and colleagues focus on treating patients with Clostridium difficile diarrhea and irritable bowel syndrome (IBS) with ACHIM. In both these diseases the commensal ecology is unbalanced and available treatment options often insufficient.

Methods for studying microbiota

Björn Andersson, Professor, Karolinska Institutet, Solna

In the EU consortium "microbes in allergy and autoimmunity related to the skin", MAARS, skin from patients with psoriasis and AD is compared in search for differences in the microbiome. The sampling and methods included in this ambitious project include 16s rRNA PCR + sequencing, swab + biopsy, microbiome sequencing and virus screening.

Professor Andersson is one of the responsible scientists for the MAARS project, and he reviewed the experimental approaches of the project. One novel technique is for example "shotgun sequencing", where everything in the sample undergoes deep sequencing without selection. This approach has helped identifying additional organisms but the data analysis is challenging. The recent review in J Invest Dermatol regarding standardization of methods to perform studies of skin microbiome is recommended for anyone with a particular interest in the methodology (J Invest Dermatol, Research Techniques Made Simple, 2015–2016).

Some yet unpublished interesting findings of the MAARS study were also reviewed, where differences were found in skin from patients with AD compared to skin from healthy subjects and patients with psoriasis and also in AD non-lesional vs lesional skin. Compared to AD, psoriasis displayed a more complex pattern, involving more different types of bacteria.

Finally the potential role of polyoma viruses in skin disease was discussed, as an increased shedding of polyoma virus is observed in several dermatological conditions. It may however be too early to firmly establish a causative role for polyoma virus and an alternative explanation may be that there is an increased shedding of virus particles generally in diseased skin.

Gene environment interplay in health and disease

Harri Alenius, professor
Karolinska Institutet and Helsinki University

Professor Alenius started by explaining how the immune system has developed during evolution and how environmental biodiversity, human microbiota and allergy are interrelated. Some immune responses remain against pathogens no longer present in modern civilization and may be involved in causing pathology instead.

Professor Alenius reviewed his research on the relationship between skin microbes and expression levels of immune genes in peripheral blood, showing that dermal exposure to Acinetobacter protects from allergic inflammation.

In another interesting study Finnish and Russian school children in Karelia were compared with respect to nasal microbiota and gene expression. Approximately 100 genes were differently expressed between the groups, many of which are related to innate immunity. This led to the conclusion that microorganisms somehow affect genes and pathways, possibly through expansion of effector cells during an infection.

In light of recent findings discussed throughout the Karolinska Dermatology Symposia Professor Alenius philosophically asked: "Are we more microbe than man?"

Cutaneous microbiome and atopic dermatitis

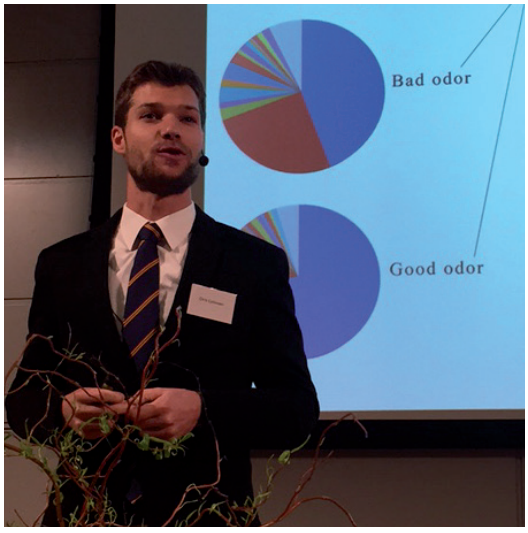
Thomas Volz, Senior Dermatologist and Researcher, Munich Technical University, Munich

Dr Volz described the pathophysiologic vicious circle in atopic dermatitis (AD), with dry skin, impaired cutaneous barrier, reduced resistance to environmental influences and the microbiome lead to disease. Immune alterations associated with AD are skewing towards a Th2 immune response, with increased levels of the cytokine IL-4, and colonization with *S. aureus*. The effects of IL-4 include reduction of barrier functions and suppression of the cytokines IL-17 and IFNγ.

In acute flares of AD there are changes in the cutaneous microbiome leading to an overabundance of Staphylococci that decline in patients post-flare. The post-flare microbiome however never reaches the composition of control subjects. There is also evidence that non-pathogenic bacteria could modulate inflammation. Dr Volz and colleagues therefore performed a double-blind placebo-controlled randomised prospective study on non-pathogenic bacteria as therapy. A cream with a lysate of the gram negative bacteria *Vitreoscilla filiformis* was used to treat patients with AD. The cream showed efficacy in a one-month follow up and the underlying mechanisms were explored in experimental models.

Skin microbiome and body odor

Chris Callewaert, Postdoctoral Researcher, University of California, San Diego, Ghent University, Belgium



Dr Callewaert is interested in malodor and the microbiome of the armpit. In humans the armpit microbiome mainly constitutes of staphylococci and corynebacteria.

To understand the link between microbes and axillary malodor Dr Callewaert and colleagues have collected clinical material from the armpit of 200 people and performed odor panels and assessed psychological impact. Key finding from these yet unpublished studies are that higher microbial diversity and an altered pattern of microbiota are linked to malodor. Other factors that are studied in relation to body odor are body mass index (BMI) and age.

As many bacteria are localized deep inside the skin, for example in hair follicles and sweat glands, showering may not help to completely clear malodor since it does not affect the deep microbiome.

Dr Callewaert and colleagues are now working on a solution through bacterial transplantation of bacteria from unsmelly people on the armpits of people that suffer from heavy body odor.

Outlook

This concluded an entertaining and educative day. We learnt many new things about the fascinating interplay between the microbiome and the skin, in health and disease. The speakers of the Karolinska Dermatology symposium 2017 spanned a wide field and successfully managed to explain complex matters in great details. The symposium also generated several intriguing new questions to be solved in the future.