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The latest developments in cutaneous homeostasis

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Abstract

Background: The skin is a major actor of human homeostasis mainly due to its important role in body temperature regulation but also through its role of barrier against any external aggression, and as a transmitter of a lot of information to the brain. It is very important that this vital organ can regulate its own homeostasis to be able to assume its role for the rest of human body. It is commonly admitted that cutaneous homeostasis is more or less the barrier effect but the last discovery for the last decade opens new interesting fields of investigation. Degradation of tight junctions with age are well-known. In rosacea, the water permeation in epidermis sever the cells and break the junctions, it is an open door for microbial infections and dramatic dryness. On atopic mice skin model, Yokushi and al. showed in 2015 that tight junctions of atopic skin are more permeable and this is correlated with the filaggrin protein depletion. If junctions still stop microbials and big molecules penetration, they let small molecules under 30 KDalton to penetrate the epidermis. This could be one of the causes of the inflammatory status of atopic skins and of dryness as water permeation is increased as well.
Conclusions: In conclusion, skin homeostasis becomes more and more complex with the last discoveries about skin microbiota. Interactions between sebum, epidermal lipids, epidermal peptides and microbiota are huge. We have an open field to innovate in new treatment taking into account the capability of billions of living cells on our skin surface which talk with our cells all the time and work together to help our skin assume its defense role of the human body.

Key words: cutaneous homeostasis development.

Introduction

The skin is a major actor of human homeostasis mainly due to its important role in body temperature regulation but also through its role of barrier against any external aggression, and as a transmitter of a lot of information to the brain.

It is very important that this vital organ can regulate its own homeostasis to be able to assume its role for the rest of human body. It is commonly admitted that cutaneous homeostasis is more or less the barrier effect but the last discovery for the last decade opens new interesting fields of investigation.

We will study some of the last developments about 4 skin homeostasis mechanisms:

1. Cell cohesion.
2. The stratum corneum lipids and peptides.
3. The hydrolipidic film.
4. Skin microbiota.

Reminder on cell cohesion

From the basal layer to the stratum corneum, keratinocytes are hung together through tight junctions. Hemi-desmosomes hang cells to the dermis, desmosomes hang keratinocytes together, corneo-desmosomes give sealing to corneocytes until desquamation.

Physiology status

By hanging cells together very tightly, junctions filter the entry of external agents and avoid infections and irritation. In

the other way, they slow down water perspiration and participate in a reduced Trans Epidermal Water Loss (TEWL). They are also a very important pathway for cells communication. At least, thanks to proteases activity, their disappearance allows desquamation on the top of stratum corneum. I won't focus on this topic in this article but it is interesting to notice that they are also involved in some skin dysfunctions.

Pathologic status

Degradation of tight junctions with age is well-known. In rosacea, the water permeation in epidermis sever the cells and break the junctions, it is an open door for microbial infections and dramatic dryness.

On atopic mice skin model, Yokushi and al. showed in 2015 that tight junctions of atopic skin are more permeable and this is correlated with the filaggrin protein depletion. If junctions still stop microbials and big molecules penetration, they let small molecules under 30 KDalton to penetrate the epidermis. This could be one of the causes of the inflammatory status of atopic skins and of dryness as water permeation is increased as well [1, 2].

Stratum corneum. Epidermal lipids and natural moisturizing factors

It is impossible to talk about epidermal lipids without speaking about sebum lipids, as even if they are secreted completely separately they mix together on the hydrolipid film.

Their composition is quite similar with both a high content of Free Fatty Acids (FFA) (about 20 to 25%), cholesterol and its esters (richer in epidermal lipids than in sebum), triglycerides for the sebum and ceramides (glycerides and sphingosides derivate) for the Stratum corneum lipids.

The sebum contains two particular molecules: Wax esters and squalene which are specific for human. You won't find them anywhere else in the human body and they are absent of lot of mammalians sebum including big monkeys (but present in rat and mice sebum).

Synthesis of epidermal lipids

On the granular layer of epidermis, the granular keratinocytes show some granules called the lamellar bodies. Those granules are issued from the Golgi corpus and are released very classically by exocytosis. As shown in figure 1, they contain ceramides, and cholesterol. But what it is very interesting to note is that they contain not only the precursors of epidermal lipid such as phospholipids, glucosylceramides, sphingomyelin and cholesterol, but also the enzymes that will transform them after liberation in the extra cellular space. But those granular lipids are real tool boxes as they contain proteases that will act in the stratum corneum and also antimicrobial peptides which will regulate the skin microbiota [3, 4].

Synthesis of natural moisturizing factors (NMF)

In the granular keratinocytes, we found also keratohyalin granules which contain profilaggrin, which is transformed into filaggrin. Filaggrin links to keratin to build the corneocyte cytoskeleton and to involucrin to build the corneo-desmosomes. Filaggrin will at least give birth to the NMF.

The life circle of filaggrin is also a very good example of finest regulation of skin homeostasis. Keratohyalin granules contain profilaggrin. This huge protein (more than 400 KDalton) is made of 10 to 12 filaggrin attached together, and 2 uncomplete filaggrin at each end (one N-terminal and one C-terminal). The N-terminal peptide is separated by enzyme under Ca^{2+} signal. This peptide goes to the nucleus and it is probably one of the signals which lead the keratinocyte into apoptosis. The filaggrin is then dephosphorylated by enzymes. This allows them to link to other proteins (keratin and involucrin). By linking with keratin, they constitute the cytoskeleton of the corneocyte, and by linking to involucrin, they participate in the corneo-desmosmoes which attach corneocytes together and seal the stratum corneum. By these both actions they contribute to decrease TEWL. But it is not their only role, on the last stage of stratum corneum, some new enzymes will deiminate the filaggrin. It allows some other protease to cut the protein into amino acids and acids such as urocanic acid, lactic acid, and urea. These molecules are released into the intercorneocyte space, they are called the Natural Moisturizing Factor (NMF) and they have a key role in cutaneous homeostasis. They have the capability to capture

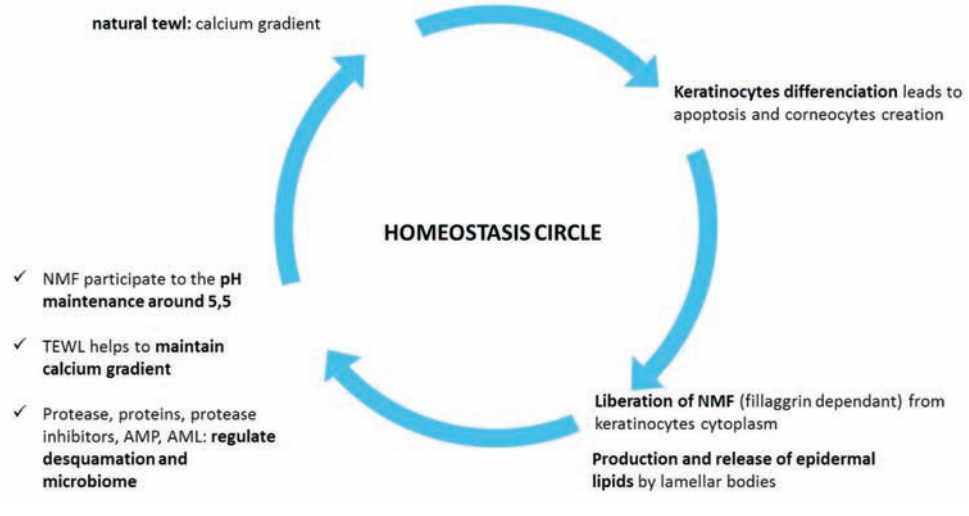

Fig. 1. Homeostasis Circle. Hydrophobic lipid cement decreases TEWL and participates in skin moisturisation. Free fatty acid gives the skin a pH 5.5 and enables the life of commensal bacteria. Fillagrins participates in cell cohesion. The PRO fillagrin triggers apoptosis.

water molecule and, doing that, they will another time reduce the TEWL. As they are low acids, they mix with epidermal and sebum fatty acids, and this mix gives to the skin its very robust buffered pH around 5, 5. This pH is very important as we will see further that it allows the life of commensal bacteria of the skin microbiota. The last but not the least some of these peptides have an antimicrobial action against pathogeneous bacteria, such as *S. aureus* [5, 6].

By considering keratinocyte apoptosis, stratum corneum cohesion, TEWL regulation, living condition of skin microbiota, we can say that profilaggrin and its metabolites are a key factor of skin homeostasis.

In the following drawing, you will find a summary of the regulation role of epidermal lipids and peptides in skin homeostasis (fig. 1).

This is a robust and efficient mechanism, as it is able to repair the barrier function disruption. After a barrier disruption, the brutal change in calcium gradient induces a massive liberation of lamellar bodies. This activates the proteins SREBP and they induce the gene coding for enzymes involved into lipids synthesis such as (HMG-CoA reductase, HMG-CoA synthase, fornesyl synthase, squalene synthase). Following this activation, Free Fatty Acids, cholesterol are synthesized and fill new granular bodies. At the same time, AMP synthesis is also increased to help the epidermis to fight aganst bacterial invasion.

Pathology

Atopy is the more related disease with epidemic lipids and peptides. On human chromosome 1, we find the locus 1q21 with the epidermic differentiation complex. It contains a lot of genes involved into keratinocytes differentiation including seven genes coding for S100 fused Type proteins (SFTPs) and for filaggrin I and II.

A non-sense mutation on filaggrin genes (Kesic and al, Front biosc, 2014) has been shown on Caucasian atopic patient.

A non-sense mutation on Fillggrin-2 gene has been associated with the persistence of atopic bursts on Afro-American patients (Margolis and al., J Aller clin Immunology, 2014).

In addition, the lamellar organization of lipids into lamellar bodies is degraded.

In psoriasis, a lot of genes deficiencies have been observed resulting in abnormal filaggrin expression, excess of involucrin (protein involved into desmosomes) in psoriasic lesions and persistence of cholesterol receptors in upper layer of keratinocytes. All these anomalies show a barrier effect deficiency including both epidermic protein and lipids.

Hydrolipidic film

The hydrolipidic film is a mix between sweat and sebum. Sweat is mainly excreted by eccrine glands. They are mainly present on feet sole and hand palm, armpit and forehead. Apocrine glands always link with hair which is less involved into sweat excretion.

The composition of sweat is very complex and is one of the way for the body for evacuate wastes. It contains a lot of amino-acids, sugars, and urea.

Sebum is excreted by sebaceous glands. These glands are mainly present on head, face, upper chest and back. The composition of sebum is quite similar to epidermal lipids with free fatty acids, triglycerides, cholesterol and its esters. But it contains 2 types of molecules: wax esters and squalene. These types aren't present in other parts of human bodies (fig. 2).

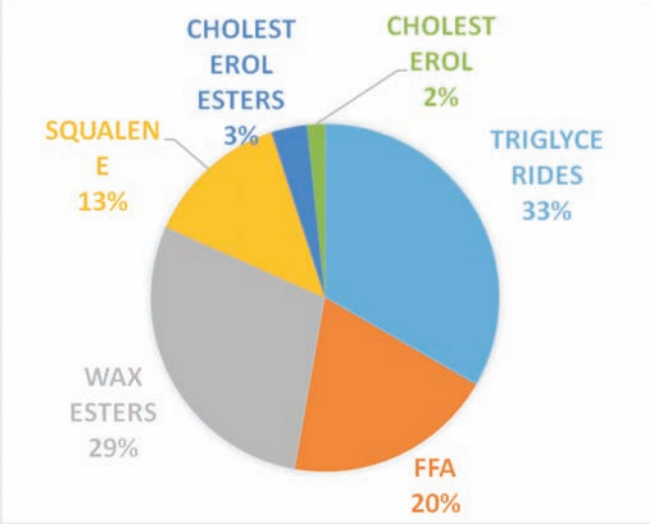

Fig. 2. Hydrolipidic film composition.

If we compare both sweat and sebaceous glands distribution (see below), it is easy to understand that the composition of the hydro-lipidic film will be different regarding the considered part of the body.

On head, it will be richer in sebum, on hand palm and armpit, it will be richer in sweat. In regions poor in both types of glands, the hydro-lipidic film will be the result of the spreading from the wet region giving more or less dry parts of body, and these regions will be more or less richer in sebum or sweat.

But some parameters will be unchanged on body surface: temperature between 32 to 35 °C and a buffered pH around 5.5. This pH is the result of the acidity activity of free fatty acids and weak acids from the NMF (lactic acid, urocanic acid) and molecules of sweat. As this mix has a buffered effect, the pH is relatively stable even when the rate between sebum and sweat changes.

This will have an influence on the efficiency of the barrier effect but a big impact on the last component of skin homeostasis; the microbiota.

Skin microbiota

Cutaneous skin microbiota is a part of human microbiota (mainly located in stomach and gut). Cutaneous microbiota is made of 10^{12} (thousand billions) of bacteria for more than 200 different species. Human microbiome excesses human genoma in cells number and DNA size: 10^{16} microbial DNA copies versus 10^{14} human DNA copies.

This microbiota is a biofilm made of bacteria but also micro-fungis, micromites and micro-nematodes. This biofilm is symbiotic with the skin: it protects the skin from pathogeneous aggression, skin provides nutrients (cellular wastes) and pH around 5,5 which permits life for non-dangerous

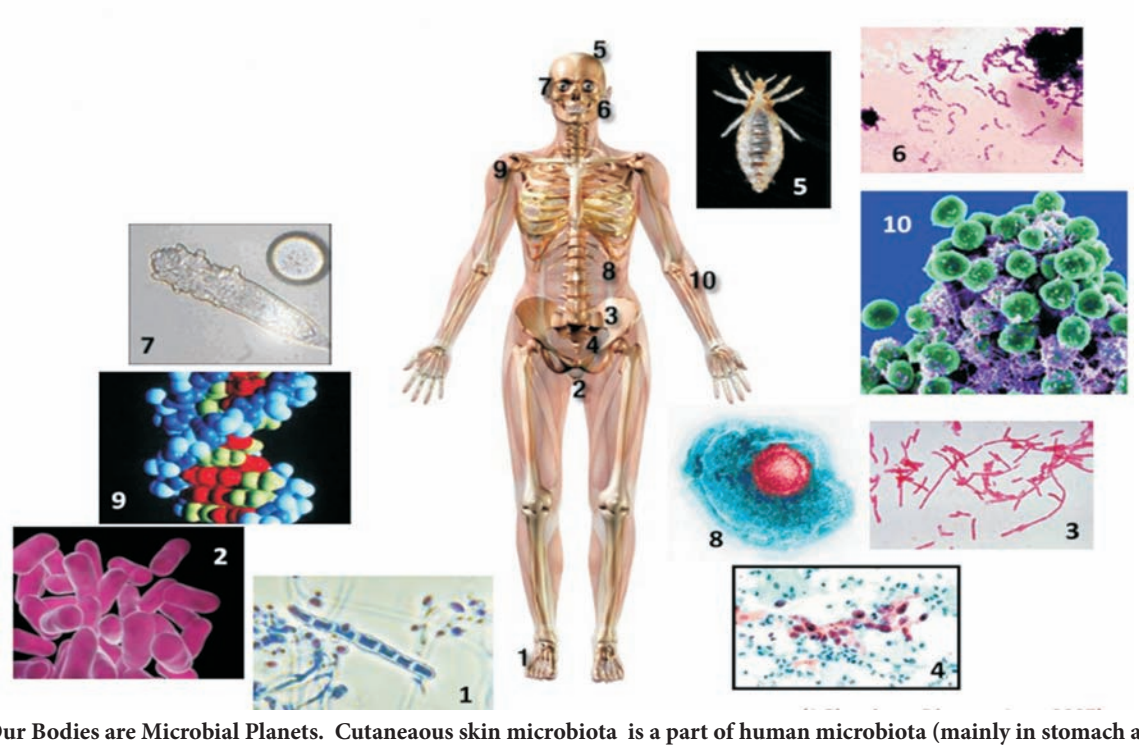

Fig. 3. Our Bodies are Microbial Planets. Cutaneaous skin microbiota is a part of human microbiota (mainly in stomach and gut). Cutaneous microbiota is made of 10^{12} (thousand twelve billion) of bacteria for more than 200 different species. Human microbiome exceed human genoma in cells number and DNA size: 10^{16} microbials cells versus 10^{14} human cells.

bacteria [7, 8]. So we can say that: Our Bodies are Microbial Planets (fig. 3).

The composition of this biofilm evolves all along the skin life from birth to death. It is different for each person and varies with age, sex, activity, and environment. It is also different from one part of the body to another: hand, scalp, armpit, forehead, arm, leg and back are respectively richer in bacteria. Grice and Segre have shown all the parameters modifying the microbiota composition (fig. 4).

Scharschmidt and al. [8] have studied the uptake into the hydro-lipidic film of each bacteria phylum. So knowing that the film composition changes all over the body, it is easy to understand that the composition of bacteria's population will change in the same way (tab. 1).

Table 1

The composition of bacteria's population

Genus	Phylum	Primary nutrient sources in skin
Staphylococcus	Firmicutes	Sweat : Urea, ammonia, AAs, glucose Sebum: AAs SC: peptides
Corynebacterium	Actinobacteria	Sweat : Urea, ammonia, vitamins, glucose Sebum: lipids SC: lipids
propionibacterium	Actinobacteria	Sweat : AAs, glucose Sebum: lipids, AAs SC: peptides, lipids

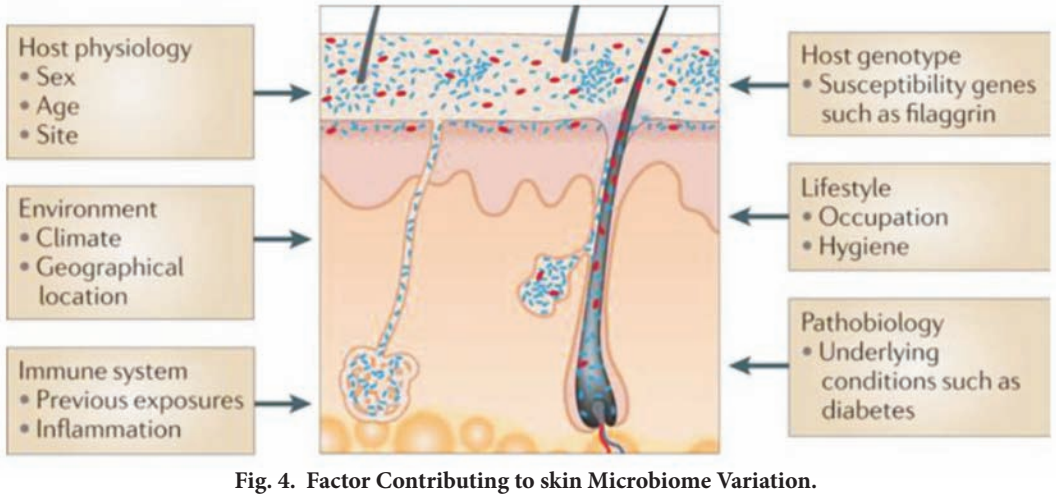

Fig. 4. Factor Contributing to skin Microbiome Variation.

But giving an accurate living temperature and nutrients is not the only role of hydrolipidic film for the microbiota. After millions years of evolution, our microbiota and our immune system have learned to live together. At the early stage of childhood, there will be a lot of exchanges between the bacteria colonization and the innate immune system. Commensal bacteria are presented to immune system inducing a tolerance versus these bacteria.

At the same time commensal microbiota and epidermis will produce a lot of different molecules which will be well-tolerated by commensal bacteria (mainly composed of gram – bacterias) but with anti-microbial activity versus pathogeneous bacterias (mainly composed of gram + bacteria).

These peptides are called Anti-Microbial Peptides (AMP), synthesized by the epidermis and conveyed through the lamellar bodies. It is interesting to note that these AMP are also synthesized by the commensal bacteria. So, microbiota and epidermis work together to avoid pathologic bacteria colonization (tab. 2).

Table 2

Antimicrobial peptides action

AMP	ACTION
Defensines (human β defensin (HBD), human neutrophil peptide (HNP), α defensin and θ defensin	Antimicrobial and anti viral activity
Dermicidine	Stimulate keratinocytes for chemokines and pro inflammatory cytokines production Stimulate neutrophile cells
Psoriasine (S100A15)	
Cathelicidin (LL37)	
Rnase 7	Chemoattractive for lymphocytes, mastocytes and neutrophile cells
Chemokines (CXCL-1)	
Proteins (lactoferrin, lysosime)	

Fats into the hydrolipidic film come mainly from sebum, but also from epidermal lipids synthesized by the lamellar bodies which spread into the film. It has been recently shown that lots of ceramides and sapienic acid (a free fatty acid specific of human sebum) have also an anti-microbial activity which helps the AMP action. It is a new link between microbiota and epidermal components (tab. 3).

Table 3

Antimicrobial lipids action

AML	ACTION
Sphingosine	Inhibits C.albicans, E.coli, S.aureus
Dehydrosphingosin	Inhibits C.albicans, E.coli, S.aureus
Phytosphingosin	Inhibits C.albicans, E.coli, S.aureus
Sapienic acid	Inhibits S.aureus

The last but not the least, we discover during the last decade that the neuro-mediator involved into the stress response or into inflammatory chain reaction has an influence on skin microbiota. It could be a link between inflammatory status and microbial infection and new pathway for treatment in future.

A very interesting example of adaptation between the film and microbiota is the psoriasin. Called psoriasin because it was found in psoriasis lesion at first, psoriasin is a common AMP of healthy skin which has an anti-E.coli activity. It is known that E.coli is a commensal bacterium for gut but could be pathologic for the skin. The way of contamination is mainly provided by the hand and feet. As hands touch the face more than hundred times a day the risk of contamination is high for face as well. If we measure the rate of psoriasin in hydrolipidic film, concentration is ten times more important on hand palm, feet sole and face where the possibility of contamination by *E. coli* is the highest.

We can summarize the balance between hydrolipidic film and microbiota in the following figure. In healthy condition, both systems influence themselves until reaching a balance status. Film provides nutrients to commensal bacteria. Using these nutrients, bacteria reject their wastes in the film. These wastes are mainly polyunsaturated fatty acids which enrich the lipidic film composition and they have usually an anti-microbial action against pathologic bacteria.

But if this balance status is destroyed (for internal reasons that change the composition of hydro-lipid film) or external environmental reasons that change the microbiota composition; this homeostatic circle could be destroyed. Once the pathologic bacteria start to colonize the skin, the wastes given back to the film change with the bacteria species. Opposite to the commensal ones, pathologic bacteria of polyunsaturated fatty acid have an inflammatory effect making the virtuous circle becoming a vicious circle leading to disease and inflammation [9, 10, 11].

The human microbiota has been studied for less than ten years. In 2008, the project human microbiota was launched on the way to explore the composition of this biofilm. The first DNA analysis made after blade sampling showed a majority of human DNA due to cells from stratum corneum removed by the blade. Nowadays, microbiota sampling is made with swabs which allows a mild sampling of bacteria.

DNA is extracted and amplified with 16S RNA. A very rich collection of primer is available and these primers could be specific of the phylum, the genius, the order or the bacteria specie. So thanks to them, it is possible today to make a phylogenetic analysis of each human microbiota. If sampling and sequencing aren't very difficult to do, the more critical in these studies is the data analysis. Knowing that the microbiota of each of us changes from one part of the body to another, that it changes every day according to the environment or our health condition, it needs a lot of sampling and a very fine statistical analysis to obtain relevant results.

We told previously that the hydrolipidic film changes according to glands distribution as shown by Verhulst and al. and that influences the microbiota composition.

Grice and al. showed in 2009 that this hypothesis is true. They study human microbiota on 10 subjects in three areas: sebaceous, moist and dry.

Unsurprisingly, in sebaceous areas a majority of Propionibacterium has been found except on subject 6 who showed a very low level of this genus. In other areas it is more difficult to find a majority genus and the disparity is higher. In these areas we can see the high differences that could occur among people (see especially subject n°5) and this could explain the susceptibility of subjects to diseases.

Following this study, many other researches have been done and we get to know better and better the microbiota composition.

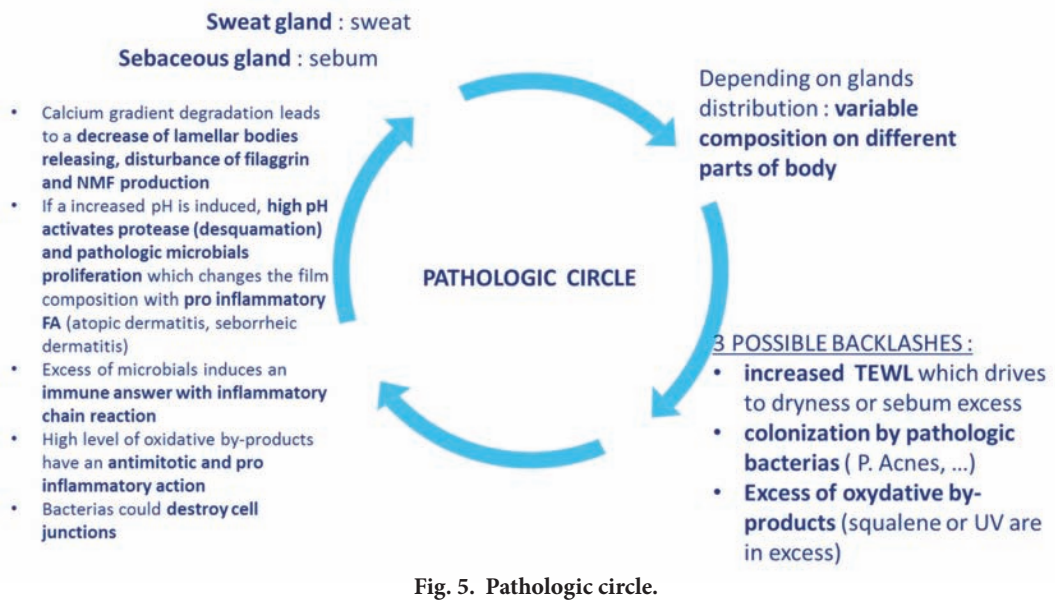

Fig. 5. Pathologic circle.

It is now possible to define that the phyla are more or less specific of a body area and relatively constant from an individual to another one (Spor, 2011; Grice, 2009), even if there is a high interindividual disparity in gender, species and genus are high [12, 13].

What about fungi?

We talked a lot about bacteria but they are not alone in our microbiota. Micronematodes and mites such as Demodex are, of course, present on our skin and important in some pathology such as rosacea. In 2010, Gao and al. made a study to analyze both bacterial and fungal microbiota populations. They confirm the diversity of bacteria's phyla but when we look at fungi, we can see that they are composed of more than 90% by Malassesia spp in humans.

We saw the huge diversity of bacteria species in different parts of the body and in different people but what about the shift occurring in skin diseases.

We can summarize the interactions between hydrolipidic film and microbiota and their results on skin barrier homeostasis (fig. 5).

Pathologic status

In the following figure, you will see the difference between a healthy skin and psoriasic lesions where we can notice a big decrease into Propionibacterium population (fig. 6).

Microbiota has been studied in other skin diseases. It is now well known that Atopic dermatitis is linked with Staphylococcus aureus proliferation.

In acne, microbiota studies have shown that Propionibacterium acne is mainly commensal bacterium. Only on strain of *P. acne* are produced inflammatory fatty acids. It seems that

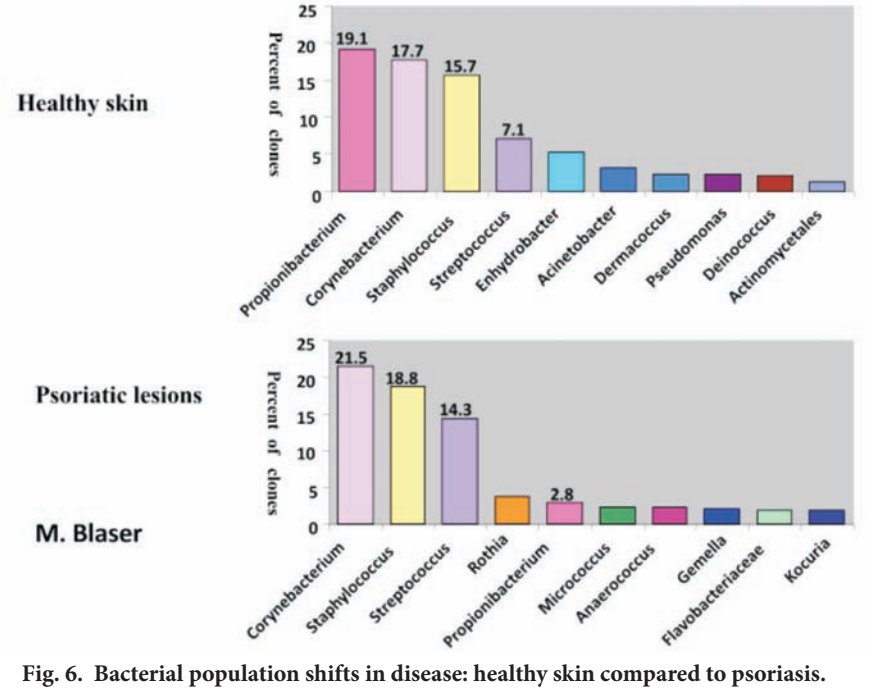

Fig. 6. Bacterial population shifts in disease: healthy skin compared to psoriasis.

it is the combination of this particular strain of *P. acne* with an important production of sebum and oxidized squalene which leads to acne.

In rosacea, Demodex invasion is known for a long time. Recent study (2012) showed that Demodex destroys epithelial cells and allows staphylococcus epidermidis to penetrate into the epidermis and cause pustular rosacea. But we can find lots of other bacteria on Demodex which could be involved into rosacea infections (*P. acne, S. epidermidis, Corynebacterium kroppenstedtii, S. mitis, P. granulosum ans S. anvi*).

For a new therapy

We saw that modified microbiota is involved into a lot of skin diseases. A new way of cure could be to restore microbiota balance. It has been tried in gut with good results. But knowing the complexity of interaction between microbiota and other skin barrier components, and the impossibility to control the environment of skin, adding commensal bacteria to take place of pathologic bacteria won't be a good solution.

But it is possible to influence the microbiota. Seite and al. showed in 2015 that restoring the barrier function by adding an emollient cream leads to a restoration of microbiota balance regarding staphylococcus.

Dr. Reygangne has shown that it is possible to reduce dandruffs caused by Malassesia by food supplemented with lactobacillus paracasei strain NCC2461, ST11.

Conclusions

In conclusion, skin homeostasis becomes more and more complex with the last discoveries about skin microbiota. Interactions between sebum, epidermal lipids, epidermal peptides and microbiota are huge. We have an open field to innovate in new treatment taking into account the capability of billions of living cells on our skin surface which talk with our cells all the time and work together to help our skin assume its defense role of the human body.

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