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RESEARCH ARTICLE

ROLE OF THE SKIN MICROBIOME IN DERMATOLOGY : A LITERATUREREVIEW

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Abstract

The skin is a complex barrier organ made of a symbiotic relationship between microbial communities and host tissue via complex signals provided by the innate and the adaptive immune systems. It is constantly exposed to various endogenous and exogenous factors which impact this balanced system potentially leading to inflammatory skin conditions comprising infections, allergies or autoimmune diseases. Recently, interest has extended beyond the gastrointestinal microbiome to include the skin microbiome and its impact on various skin diseases. This article aims to provide an overview on the knowledge about the skin microbiota, the microbiome and their importance in dermatology.

Introduction:-

The skin, a primordial organ of the human being, constitutes a favourable environment for the development of micro-organisms. These microorganisms are mostly harmless, and in some ways indispensable to humans.

The first microscopic observations of microorganisms colonising the skin date back to 1683 by Van Leeuwenhoek. But the real research on microflora by culture methods was introduced by Kligman in the 1950s.

In the year 2000, Nobel laureate Lederberg suggested the term 'human microbiome' to refer to the collective genome of our microflora.[1]

The microbiota is present in the various parts of the body in which an epithelium is in contact with the outside world: the digestive tract (stomach and intestines), the skin, the respiratory tract (mouth, pharynx and lungs) and the urogenital system.

It thus forms a complex ecosystem whose composition is the result of a balance between local conditions and the metabolic properties of these microorganisms.

Recently, interest has extended beyond the gastrointestinal microbiome to include the skin microbiome and its impact on various skin diseases.

As skin dysbiosis is frequently observed in dermatological pathologies, the crosstalk between the gut and the skin could offer targeted pathways with obvious therapeutic potential in dermatological practice; probiotics.

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Objectives:-

We present here the current data on the role of the microbiome in dermatology and the interest of probiotics in modulating it.

Our objective is to evaluate whether the data in the literature support the usefulness of oral and topical probiotics for certain dermatological diseases where the microbiota interfere in their pathogenesis.

Method:-

A literature review was conducted in PubMed and Google Scholar databases to find relevant studies with the keywords "microbiome", "microbiota", "dysbiosis", "dermatology", "probiotic", "skin" and "dermatological conditions".

All search terms were used in various combinations and studies were selected for relevance based on their abstracts.

Basic science, in vitro research, animal model studies and clinical trials were included.

Studies written in languages other than English and French were not included.

The cutaneous microbiome and microbiota

The microbiota comprises all living members forming the microbiome[22].

The microbiome is defined as the collective genome of microorganisms. Therefore, the skin microbiome is the genome of the microorganisms present on the skin.

The skin microbiota comprises two groups:

- Resident microorganisms, which are a relatively fixed group (the core microbiota) and recover quickly after a disturbance. This is the basic microbiota considered as commensal.
- Transient microorganisms that originate from the environment and take advantage of a change in habitat to proliferate.

Although microbiota research has so far largely focused on the identification of bacteria, other types of skin colonisers should not be forgotten; yeasts such as Malassezia and arthropods such as Demodex. Viruses remain to date the least known members of the skin microbiota[22].

Temporal and spatial variability of the microbiota

In the skin, the microbiome is variable from one area to another depending on physiological characteristics such as humidity, seborrhoea and the degree of exposure to the external environment[24].

The skin microbiome also varies during life from birth to senescence. The skin of the foetus will be colonised by micro-organisms from the mother from birth[23]. This initial flora is not very diversified and resembles that of the place of delivery, i.e. a vaginal delivery will lead to colonisation by the vaginal flora, whereas after a caesarean section, colonisation will be done by the flora typical of the skin of the belly[23]. This process of colonisation of the skin at the beginning of life is necessary to establish an immune tolerance to commensal microorganisms[23].

Variation by site

Three microenvironments have been defined:

- Sebaceous regions (forehead, retroauricular folds, nostrils and back) are dominated by Propionibacterium spp. as the main residents of the pilosebaceous unit.
- The moist regions (armpits, elbow creases, umbilicus, inguinal creases and intergluteal creases) are the ecological niches of Staphylococcus and Corynebacterium spp. Indeed, the breakdown of apocrine sweat by Corynebacteria and Staphylococcus is responsible for the odour associated with sweating in humans[25].
- The dry areas (forearms, hands and buttocks) are the site of the greatest microbial diversity with a particular abundance of Gram-negative germs that were thought to colonise the skin only rarely and were considered contaminants of the gastrointestinal tract. In these dry areas, the phylogenetic diversity is greater than in the intestine

and oral mucosa of the same individual. The four phyla (Acinetobacter, Firmicutes, Bacteroidetes and Proteobacteria) are represented in varying proportions[2].

Variations in the mycobiome are also observed depending on the site:
- The central part of the body and the arms are dominated by Malassezia.
- The feet, which are the main site of mycotic infections, are characterised by the diversity of the microbiota and are colonised by Malassezia, Aspergillus, Cryptococcus, Rhodotorula and Epicoccum[26].

Gender variation
Gender also has an impact on the microbiota. From birth, a difference in the lipid composition of the vernix caseosa between male and female newborns appears to influence microbial colonisation. Anatomical and physiological characteristics of the skin (thickness, pH, composition, sebum level and use of cosmetics) could explain the difference between the two genders at the same anatomical site[27].

The skin pH is generally more acidic and sebum secretion higher in males compared to females of the same age.

The study of the microbiota of the hand shows that women have a higher microbiological diversity compared to men[28].

The genitalia of the two sexes also have a different specific microbiome (Lactobacillus and Gardnerella in women, Corynebacterium in men).

Inter-individual variability
Inter-individual variability can sometimes be marked. Indeed, the palm microbiota is so specific to each individual host that it has been proposed to use it as a forensic identification tool. Several extrinsic factors (lifestyle, personal hygiene, location, sun exposure, cosmetics and local or systemic antibiotic therapy) are thought to be responsible for inter-individual variations in the microbiome.[2]

Role of the microbiome
In order to prevent colonisation and invasion by pathogens, commensal germs firstly engage in competitive mechanisms both geographically (competition to occupy the same sites of adhesion) and nutritively (consumption of the same substrates)[30].

P. acnes resident in the sebaceous gland, thanks to its lipolytic enzymes, produces free fatty acids which, together with the sebum, decrease the skin pH and inhibit the proliferation of several germs[30]. Competitive exclusion also involves the production of bacteriocins and antimicrobial factors. For example, some strains of Staphylococcus epidermidis secrete serine protease Esp which inhibits biofilm formation and thus colonisation by S. aureus[31]. On the other hand, S. epidermidis controls the growth and proliferation of P. acnes through glycerol fermentation and succiinic acid production[32, 33].

Stimulation and regulation of the skin's immune system
The skin is home to a large number of effector cells of innate and adaptive immunity.

The primary skin defence system of innate immunity relies on an arsenal of antimicrobial peptides (AMPs) and enzymes (lysozyme, ARNAse and the S100 family of proteins) produced by keratinocytes. The main role of skin peptides and proteins is to inactivate microorganisms by disrupting their membrane integrity or by enzymatic degradation of the cell wall. Cells of the cutaneous adaptive immunity system include antigen-presenting cells including Langerhans cells and lymphocytes[29].

The skin microbiota stimulates innate immunity and the regulation of pathogen colonisation but must in turn escape it to ensure this continued stimulation[29].

The process of skin colonisation in the neonatal period is crucial in establishing this immune tolerance to commensal germs.

The skin microbiota induces an appropriate level of IL 17 and IFN gamma producing T cells and FOX-P3 expressing regulatory T cells.

Early exposure of neonates to S. epidermidis induces specific FOX-P3+ regulatory T cells that contribute to the inhibition of the excessive pro-inflammatory response to commensal bacteria[29].

This exposure also stimulates defence mechanisms against S. aureus by increasing the expression of genes for certain antimicrobial peptides, in particular beta-defensins 2 and 3[29].

Skin dysbiosis

Dysbiosis is by definition an imbalance of the microbiota, the equilibrium state being called eubiosis.

This imbalance is generally linked to a loss of microbiota diversity in favour of an abundance of pathogenic germs. It can therefore occur at different levels, ranging from the taxonomic composition to the functions of these microorganisms.

The list of dermatoses with which a dysbiosis may be associated is constantly growing.

However, it is difficult to confirm whether dysbiosis is a cause or a consequence in these diseases.

Dermatological conditions related to the microbiome

1) Inflammatory conditions:

- Atopic dermatitis

Atopic dermatitis is a chronic inflammatory dermatosis that affects 15-20% of children and 2-10% of adults. Atopic dermatitis results from a complex interaction between genetic susceptibility, skin barrier dysfunction, innate and adaptive immunity and the microbiome.

The study of the microbiota during atopic dermatitis shows that the dysbiosis associated with flare-ups is characterised by a decrease in microbial diversity, with massive colonisation by S. aureus, which can represent up to 90% of the microbiota.

S. epidermidis, a commensal present on healthy skin, appears to be the best antagonist of S. aureus. S. epidermidis is thought to maintain the balance of the skin microbiome by integrating innate immune pathways that control effector T-cell function and by exerting an antimicrobial function through the production of IL-1a by dendritic cells and keratinocytes, thereby limiting the ability of pathogens to establish infections. Clinically, Byrd et al. showed that the least severe atopic dermatitis flare-ups had higher numbers of S. epidermidis while the most severe flare-ups were associated with S. aureus[3].

S. aureus exploits the skin barrier defects associated with atopic dermatitis with a decrease in antimicrobial peptides and the low acidic environment to ensure its colonisation. S. aureus-derived toxins and proteases further damage the skin barrier and induce adaptive and innate immune responses[3].

Malassezia spp.colonisation increases with the severity of atopic dermatitis and has been detected in up to 90% of skin lesions. Its pathophysiological role may be due to the activation of pro-inflammatory cytokines and autoreactive cells that increase the expression of TLR2 and TLR4 through the secretion of immunogenic proteins[3].

Antimicrobial agents eradicate S. aureus, however, they also affect other members of the skin microbiome, disrupting homeostasis between species and generating bacterial resistance.[3]

In addition to dysbiosis, the skin of those with atopic dermatitis is deficient in sphingolipids and potential downstream antimicrobial peptides, even in the absence of clinical symptoms. The sphingolipid pathway, which includes sphingomyelins, ceramides, phospholipids, and arachidonic acid, has been directly linked to atopic dermatitis through its importance in the control of Staphylococcus aureus, epithelial barrier function, and immune regulation[21].

Based on these reports, Ian A. Myles' team hypothesised that defects in lipid production by Gram-negative bacteria might contribute to atopic dermatitis. After modifying previous protocols for culturing sphingolipid-producing bacteria, they presented a method for systematically collecting cultivable Gram-negative bacteria. The most frequently cultured species in healthy volunteers was Roseomonas mucosa[21]. They proposed a topical treatment with R. mucosa which was associated with an improvement in disease severity, an improvement in epithelial barrier function, a reduction in the load of Staphylococcus aureus on the skin and a reduction in the need for topical steroids without serious adverse effects[21].

- Seborrhoeic Dermatitis

Seborrhoeic dermatitis, another common chronic inflammatory dermatosis, is characterised by recurrent oily scales, sometimes accompanied by erythema and itching. Although the exact pathophysiology of the disease is still unclear, current theories point to the role of the microbiota present on the skin surface in the pathogenesis ofseborrhoeic dermatitis.

A dysbiosis in the composition of the bacterial microbiome has been demonstrated in seborrhoeic dermatitis lesions. An increased level of Staphylococcus has been found in lesion sites, and its relative abundance is positively correlated with damage to the epidermal barrier during seborrhoeic dermatitis [4].

- Acne

Acne is a chronic inflammatory disorder of the pilosebaceous follicle that affects over 85% of adolescents and young adults. Its pathogenesis includes increased sebum production, follicular hyperkeratinisation, inflammation, involvement of the skin microbiome, and Cutibacterium acnes.

Acne has been widely associated with the proliferation of C. acnes. However, several authors have found that the abundance and bacterial load of C. acnes do not differ significantly between acne patients and healthy patients. It seems that the severity of acne is associated with a loss of C. acnes strain diversity compared to healthy individuals. Thus, acne would be triggered by the selection of a subset of C. acnes strains, including the IA1 phylotype, which is predominant in facial acne and probably enhanced by a hyperseborrhoeic environment.[17]

C. acnes triggers the release of pro-inflammatory cytokines after binding to TLR-2 that activate NLRP3 inflammasomes and caspase-1, leading to IL-1b secretion, T-cell differentiation and recruitment of lymphocytes and neutrophils into acne lesions.

TLR-2 activation also stimulates the production of IL-1a, which plays a central role in comedogenesis through the stimulation of keratinocyte proliferation. C. acnes can also form biofilms that increase virulence and resistance to antimicrobial treatments[3].

S.epidermidis inhibits the proliferation of C. acnes by promoting glycerol fermentation and releasing succinic acid. It also reduces C. acnes-induced skin inflammation by producing lipoteichoic acid, which inhibits the production of TLR2, IL-6 and TNFa by keratinocytes. On the other hand, C. acnes inhibits the proliferation of S. epidermidis by maintaining the acidic environment of the pilosebaceous follicle, hydrolysing sebum triglycerides and secreting propionic acid. The loss of balance between them leads to the activation of markers related to inflammation[3].

Malassezia may also play a role in refractory acne. Its lipase, which is 100 times more active than that of C. acnes, attracts neutrophils and stimulates the release of pro-inflammatory cytokines from monocytes and keratinocytes. However, its exact involvement in the pathogenesis of acne remains to be determined[3].

Tetracyclines are the first choice of treatment for moderate/severe acne because they suppress the growth of C. acnes and control inflammation. However, the antimicrobial activity also alters the skin microbiota, which may be beneficial.

Recently, Yang et al. demonstrated in 5 patients with moderate to severe acne that photodynamic therapy increased the diversity of the skin microbiome in acne and shifted the follicular microbiome to the epidermal microbiome, exerting its beneficial effect in part by inhibiting C. acnes and altering the composition and potential function of the skin microbiome in acne.[3]

- Rosacea

Rosacea is a complex facial skin condition combining abnormal inflammation and vascular dysfunction. In addition to known triggers, the role of the microbiota in the development and aggravation of rosacea continues to be of interest. Demodex folliculorum, Helicobacter pylori, Staphylococcus epidermidis, Chlamydia pneumoniae and the Demodex-associated bacterium Bacillus Oleronius are microorganisms that have been associated with rosacea[5].

Pattern recognition receptors (PRRs) expressed on the skin participate in a continuous immune surveillance that allows symbiotic micro-organisms to thrive while eliminating potential pathogens. Two of these PRRs, TLR-2 and the NOD (nucleotide binding oligomerization domain) family receptor, are upregulated in rosacea patients, and their activation by Demodex is thought to trigger inflammation during rosacea[5]. Indeed, chitin (from the mite exoskeleton) can stimulate the pro-inflammatory response of keratinocytes via TLR-2, and mite allergens have been shown to activate NOD-like receptors in vitro.

The microbiota residing on Demodex mites may also be involved in this process: B. Oleronius antigens are reported to induce mononuclear blood cell proliferation in rosacea patients, and to stimulate the production of cathelicidin, MMP-9, tumour necrosis factor (TNF) and interleukin (IL)-8 by neutrophils from healthy subjects[5]. In rosacea patients, this inflammatory state leads to an increase in facial skin temperature. This in turn may affect the growth and balance of the microbiota, and alter the behaviour of S. epidermidis so that it secretes more proteins. In addition, because S. epidermidis antigens are recognised by TLR- 2, the bacteria also participate in skin inflammation. [5]

Psoriasis

Psoriasis is a common dermatosis with a worldwide prevalence of 2%. It results from a complex interaction between genetic predisposition and environmental factors that induce immune dysregulation and trigger rapid proliferation of keratinocytes and infiltration of immune cells with the formation of erythematous and scaly plaques.

The breakdown of immune tolerance to skin microorganisms has been implicated in the pathogenesis of psoriasis. Bacteria found on psoriasis plaques include Firmicutes, Actinobacteria and Proteobacteria.

Several studies have shown an increase in the number of Staphylococcus in the skin of a psoriatic subject compared with the skin of healthy individuals.

S. aureuscolonises psoriatic lesions in 35% of patients[20] and up to 60% secrete enterotoxins and toxic shock syndrome toxin-1. Colonisation by S. aureus is thought to trigger a Th17 inflammatory response responsible for the perpetuation and proliferation of keratinocytes.

S. pyogenes is also frequently identified as a trigger for both the development and exacerbation of psoriasis. Pharyngeal infection with S. pyogenes induces activation of superantigens and thus of T4 cells.

The association of Malassezia with psoriasis is unclear. Its presumed involvement is based on the ability of Malassezia to invade keratinocytes, which in turn increase the expression of TGFb, integrin chains and heat shock protein 70, which induce keratinocyte hyperproliferation. In addition, through the secretion of chemotactic factors, Malassezia attracts neutrophils to psoriasis lesions[4].

Candida albicans has been linked to the persistence and worsening of skin lesions, particularly in reverse psoriasis. The mechanism remains unknown, however, it may be mediated by superantigens[4].

With regard to viruses, patients infected with human immunodeficiency virus or human papillomavirus show more severe features of psoriasis related to the secretion of substance P, which stimulates keratinocyte proliferation. [4]

- Maskne

"Maskne" is a new term that emerged during the COVID-19 pandemic. It refers to a subset of mechanical acne, which merits consideration for widespread use of reusable cloth masks to control the pandemic worldwide.

The pathophysiology of this entity is directly related to the new skin microenvironment and textile-skin friction created by mask wearing.

The occlusive microenvironment leads to a dysbiosis of the microbiome, which is linked to various dermatological conditions such as acne, but also perioral dermatitis, rosacea and eczema by creating a new wet intertriginal zone favouring the proliferation of certain microbial communities such as Staphylococcus and Corynebacteria. [10]

2) Autoimmune diseases:

- Bullous pemphigoid

The study of the microbiota in patients with bullous pemphigoid shows a significant difference in the microbiological profile at the peri-lesional sites compared to the same location in healthy controls. In these sites there is a decrease in acinobacteria and proteobacteria, and a significant increase in firmicutes. [12]

It is unclear how dysbiosis may contribute to the pathogenesis of bullous pemphigoid. In this regard, it is interesting to note that complement gene expression in keratinocytes is not regulated by bacteria. In addition, S. aureus is a known inducer of proteases and elastases, expressed in human keratinocytes and eosinophilia, which process basement membrane structural proteins and mediate pruritus. Interestingly, S. aureus can also produce these enzymes by itself. Despite these considerations, we cannot exclude that dysbiosis in bullous pemphigoid is the consequence and not the cause of the disease. There is growing evidence to support a role for commensal bacteria in modulating the immune system, including the production of antimicrobial peptides (AMPs), activation of Toll-like receptors (TLRs) and induction of complement gene expression. On the other hand, the breakdown of the epidermal barrier makes the skin particularly susceptible to colonisation by many bacteria. [12]

- Systemic lupus erythematosus

The correlation between systemic lupus erythematosus and microbiota colonisation has received much attention in recent years. Variations in the abundance of the genus Staphylococcus have been identified, in particular Staphylococcus aureus and Staphylococcus epidermidis, colonising skin lesions in systemic lupus erythematosuspatients, which may effectively distinguish systemic lupus erythematosus skin lesions from healthy skin[11].

Several studies have shown the association of variations in the skin microbiome with specific lupus involvement; renal tropism, complement consumption, etc.

The presence of nasal colonisation by Staphylococcus aureus is associated with renal manifestations and autoantibody positivity in systemic lupus erythematosus, indicating that regional change in the skin microbial community may affect not only the local immune microenvironment but also the whole system of systemic lupus erythematosus patients.[11]

- Vitiligo

All studies agree that there is no significant difference in the richness and uniformity of the microbiota in vitiligo lesions, but rather differences in community composition.

Either a significant increase in Streptomyces and Streptococcus in vitiligo lesions[19] or depletion of Staphylococcus and Acinetobacter versus enrichment of pathogenic Paracoccus (Proteobacteria) in lesional skin[18].

Streptomyces can produce a variety of metabolites such as decomposition enzymes and anti-biomass for various substances[19]. Tacrolimus is derived from streptomycin and is currently a calcineurin inhibitor, which plays an important role in the treatment of vitiligo either as monotherapy or in combination with phototherapy[19]. Recently, the efficacy of topical application of tacrolimus 0.1% twice weekly in the prevention of vitiligo recurrence has been reported[19]. Assuming that Streptomyces can produce certain immunosuppressants, similar to tacrolimus, which slow down the disease process, their increased population in active vitiligo lesions could be a mechanism of skin self-regulation or be involved in the pathogenesis of vitiligo[19].

The study by Bzioueche H. et al highlighted the interaction between mitochondria and microbiota. It has been shown that mitochondrial genotype modulates both reactive oxygen species (ROS) and microbiota during vitiligo[18].

Thus this study reported significant mitochondrial damage in the lesional skin of patients[18].

The change in the microbiome only in biopsy samples with mitochondrial DNA strongly supports a mitochondrial stress-induced change in the microbiome. Interestingly, the genus that was almost completely absent in patients with mitochondrial DNA in the skin is Bifidobacterium, which is well known to have protective effects and to decrease activation of innate immune cells[18].

Bzioueche H. et al were able to demonstrate that primitive mitochondrial stress in some patients with vitiligo could be responsible for changes in the skin microbiome. This skin dysbiosis could then trigger the innate response via PAMPs and lead to the production of IFNs and chemokines[18].

3) Infectious diseases:

- Leishmaniasis

The study of the role of the microbiota in cutaneous leishmaniasis has shown that infection by leishmania-type parasites leads to a decrease in the bacterial diversity of the skin, characterised by communities dominated by Staphylococcus spp. and/or Streptococcus spp.[13] This suggests that disease-associated changes in the skin microbiota ("dysbiosis") contribute to the genesis of lesions and dermal cellular responses, including immune and inflammatory responses to L. major infection. The dysbiosis induced by leishmaniasis is not limited to the site of infection, but occurs globally on the skin with the possibility of being transferred to uninfected subjects living in cohabitation.

- Opportunistic infections

Although commensal microorganisms generally live peacefully in our bodies, many have the ability to cause infections in the right context. S. epidermidis, despite its many beneficial roles as described above, is a common cause of infections, including nosocomial deep tissue infections involving indwelling medical devices such as catheters.[3] In addition, many bacteria present in the normal skin microbiome frequently cause infections in chronic wounds with delayed healing, which frequently occur in diabetic patients and the elderly.[3] While many factors in host biology contribute to the impaired healing of these wounds, it should be noted that the immune response to these commensal germs in previously sterile tissue, which leads to prolonged inflammation, exacerbates the problem and creates a vicious circle.[3]

4)Neoplasia:

- Non-melanocytic

Since the global incidence of skin cancers is increasing exponentially, a question frequently arises; how an individual's microbiota, which is ten times more numerous than human cells, can influence skin cancer risk and subsequent response to therapy.

As microbial dysbiosis is linked to chronic inflammation, inflammation-mediated carcinogenesis processes and immune evasion, it is not surprising that the microbiota is associated with the development of specific cancers[7].

Such a mechanism is possible in the case of cutaneous squamous cell carcinomas because

S. aureus infection triggers inflammation-related signalling and the release of cytokines such as tumour necrosis factor-alpha, which has already been identified as being involved in squamous cell carcinogenesis. Thus, numerous studies have found a strong association of

S. aureus DNA with skin squamous cell carcinoma. This association is stronger than what has been found for squamous cell carcinoma and HPV[7].

The increased prevalence of S. aureus DNA also in actinic keratosis biopsies (compared to seborrhoeic keratosis) is interesting because actinic keratosis is considered a precursor to the development of squamous cell carcinoma, which might suggest that increased S. aureuscolonisation is observed already at the beginning of the carcinogenic process[7].

S. aureus is not normally able to infect an immunocompetent person unless the normal barriers have been broken, for example by surgery or burns, which are known to promote squamous cell carcinoma[7].

- Melanocytic

For melanoma, current studies only concern the pig skin microbiome because of its high similarity to that of human skin[7]. Thus, significant differences were found in bacterial compositions and microbial diversity between melanoma and normal skin samples[7]. The abundance of Fusobacterium and Trueperella was higher in melanoma skin samples than in controls [7]. In addition, increased abundance of Fusobacterium nucleatum was associated with disease progression. Among Fusobacterium, Fusobacterium nucleatum can potentiate tumour proliferation by inhibiting NK cell cytotoxicity through the interaction of Fusobacterium Fap2 protein and T cell immunoglobulin and ITIM domain[7].

5) Capillary pathologies:

- Folliculitis decalvans

Folliculitis decalvansis a primary scarring alopecia whose pathophysiology is unclear. Arguments for a link between bacterial communities and disease development are based on the fact that S. aureus is often cultured from lesion swabs, and that in most cases the response to antimicrobial therapy is temporarily good[9]. In addition, biofilm-like structures consisting of C. acnes have been identified in hair follicles from biopsy samples (species confirmed by in situ hybridisation) and in plucked hair follicles (bacterial species suspected on the basis of their morphology) from some folliculitis decalvans patients[9]. Although such structures have also been found in plucked hair follicles of healthy individuals, the biofilm hypothesis is quite convincing[9].The persistence of the disease despite transiently effective antibiotic therapy, the infiltration of neutrophils on histology, which destroy the follicle but are not able to destroy the biofilm, and the normal immune background of the patients, are listed among the supporting arguments. The current hypothesis is that an initially non-pathogenic biofilm can spread and develop into a pathogenic form causing inflammation[9]. Antibiotic treatment can kill the planktonic form of the bacteria released by the biofilms and even temporarily remove the symptoms, but the remaining biofilm cells are the nest of the chronic infection[9].

- Androgenetic alopecia

Androgenetic alopecia is characterised by a shortening of the anagen phase and a miniaturisation of the hair follicle that progresses slowly over time. Infiltration of mononuclear cells and lymphocytes is detected in about 50% of skin samples[9]. This microinflammation occurs in the upper third of the hair follicle, where a large number of microorganisms are harboured[9]. In addition, complement-stimulating porphyrins produced by Cutibacterium spp. were identified in the pilosebaceous canal of 58% of the androgenetic alopecia patients compared to 12% of the control group[9]. These arguments, together with the improvement observed after the application of antimicrobial agents, may suggest a possible link with the skin microbiota[9].

- Alopecia areata

Alopecia areata is a non-scarring alopecia with an incidence of 2% and a higher prevalence in paediatric populations.

The pathogenesis of alopecia areata remains incompletely understood. Autoimmune-mediated hair follicle destruction, upregulation of inflammatory pathways and loss of immune privilege in the hair follicle are thought to be involved in the development of this condition. Genetic predisposition, environmental factors and, recently, the skin microbiome have been linked to autoimmunity in alopecia areata[3].

The microbiota of the hair follicle is located near the bulge (stem cell niche) and the bulb (site of cell division), which are considered immune privileged sites[3].

Changes in the hair follicle microbiome may be related to the loss of homeostasis, modulation of immune responses and intense peribulbar inflammation in hair loss[3].

The symbiosis of Corynebateriaceae, Propionibacteriaceae, Staphylococcaceae and Malassezia is linked to a healthy scalp, whereas dysbiosis can cause pathological conditions. Pinto et al. found microbial changes in people with alopecia, with over-colonisation by

C. acnes and reduced abundance of S. epidermidis, but it has not been determined whether these differences are the cause or consequence of the disease. The role of CMV in the initiation of alopecia was suggested after finding DNA sequences in skin biopsies from alopecic areas[3]. Rudnicka et al. hypothesised a possible relationship between colonisation of the scalp by Alternaria spp. and alopecia after its culture from skin scrapings in patients[3].

6) Genodermatoses

- Netherton syndrome

Netherton syndrome is a severe ichthyosis characterised by desquamative skin inflammation, elevated IgE levels, extensive allergic sensitisation, neonatal growth retardation and recurrent bacterial skin infections[6]. It is an autosomal recessive disease characterised by mutations in the serine protease inhibitor type 5 (SPINK5) gene resulting in uninhibited protease activity and thus a barrier defect and constant inflammation of the skin with increased levels of pro-inflammatory cytokines and the type 17 T helper pathway[6].

The skin inflammation of Netherton syndrome resembles that of atopic dermatitis and hyper-IgE syndrome. Microbiota diversity is reduced and S. aureus is frequently isolated from skin lesions and during disease flares[6].

An association of skin microbiota diversity with specific subclasses of lymphocytes and NK cells has been demonstrated, the same cells that are altered in patients with Netherton syndrome and correlate with the frequency of skin infections and increased antibiotic use[6].

What about probiotics?

Modification of the microbiota through the use of faeces has been described for over 500 years, but the use of specific strains of bacteria to achieve a specific clinical impact has only been of interest for the last 50 years. In fact, the first definition of probiotics was described in 1965 by Lilly and Stillwell and was limited to substances produced by bacteria that promote the growth of other bacteria. In 1989, the notion of a living microbial supplement appeared, although this definition was still linked only to nutritional health. The latest, current definition considers probiotics as living micro-organisms that must be ingested in sufficient quantities to have a positive effect on health that is not limited to nutritional effects. These three definitions allow us to understand how probiotics can have an impact on health: by acting on the resident microbiota, the cells of the intestinal epithelium and, globally, on the immune system.

The microbiota acts in a web-like interaction to suppress virulence-related genes and promote genes associated with commensalism; by producing bioactive molecules, the microbiota influences the development of appendages, tumorigenesis, ageing, sensory nerve function and the innate immune system.

Probiotics are known to block the release of inflammatory cytokines and signalling pathways and thus help reduce skin inflammation and restore skin barrier function. As we have seen, the state of the barrier is fundamental to skin defence and immune guidance. Restoration of the barrier is associated with improved clinical outcomes.

Oral probiotics may improve skin health through a gut-brain-skin axis that reduces systemic and brain inflammation. The GBS axis improves nutrient absorption, which promotes barrier synthesis. Oral ingestion of Lactobacillus reuteri reduces perifollicular inflammation. Other probiotics targeting skin disorders have improved atopic dermatitis, healing of burns and scars in general, and even skin aging.

As shown by the example of psoriasis, where oral administration of Lactobacillus pentosus significantly reduces erythema, desquamation and thickening of the epidermis.

The reduction in the expression of inflammatory cytokines, namely TNF-α, IL-6 and pro-inflammatory cytokines in the IL-23/IL-17 cytokine axis, upon administration of probiotics suggests a possible therapeutic modality to manage psoriasis.

Topical application of the probiotics L. bulgaricus,L. acidophilus or L. plantarum improves the outcome of acne by reducing Cutibacteriumacnescolonisation of the skin.

Soluble pro-inflammatory molecules, such as substance P, associated with the spread of skin inflammation are reduced after topical application of L. paracasei, and keratinocyte expression of the NF-kB pathway is inhibited after topical application of

Streptococcus salivarius K12. Similarly, production of the anti-inflammatory molecule IL-10 by dendritic cells is increased after topical application of Vitreoscillafiliformis extracts on atopic dermatitis. As well as topical application of R. mucosa, which is associated with a significant improvement in atopic dermatitis lesions[21].

Topical probiotics have also entered the world of skin care with their use in photoaging and skin aging. Although clinical trials are underway, one study has shown that probiotics slow down the photoaging process, reduce oxidative stress and improve the skin's barrier function. Researchers found a significant improvement in the severity of wrinkle depth, hyperpigmentation of the forehead and glabella in the group receiving a high topical concentration of probiotic[14].

Conclusion:-

Molecular approaches to defining microbial diversity have changed our understanding of the skin microbiome and raised several questions regarding host-microbe interaction and its relevance to skin diseases. Current knowledge has shown that bacterial, fungal and viral species are under- or over-expressed in several dermatoses compared to healthy skin.

To date, the pathogenic role of several species has been suggested in various skin diseases, such as C. acnes in acne or S. aureus in atopic dermatitis. However, the paradigm of the microbiome related to certain skin diseases has shifted from the proliferation of one or more microorganisms to the loss of diversity among several microorganisms in the production of disease.

Finally, as antimicrobial treatments directed against pathogens associated with skin diseases also eradicate the beneficial flora, research efforts have been directed towards maintaining the homeostasis of the skin microbiota through the use of probiotics, prebiotics, symbiotics and faecal transplants. In the near future, their real therapeutic effectiveness will certainly be established.

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