Plant Environment Development 4(1):06-13, 2015 (February)
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e-mail: plant.environ.dev@ru.ac.bd

Print ISSN 1994-1501
Online ISSN 2311-3529

Human Skin Bacteria: Innocuous Symbiotic Association, Pathogenic Action and Antibiotic Effect

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Abstract

Bacterial flora found on the human skin is generally considered as commensals and sometimes as pathogen both normally and potentially. Research studies gradually are changing our knowledge on the interaction of host and cutaneous bacteria. Advanced studies in microbiology and immunology have shown that a skin bacterium has a great impact on protection against infection and also on reaction patterns regarding immunity system. The present article mainly emphasized on general features of resident skin bacteria of human and their mode of action along with antibiotic effect.

Keywords: Skin bacteria, Pathogenic action, Symbiotic association.

INTRODUCTION

Human skin bears a characteristic bacterial flora, which are usually regarded as innocuous symbiont or sometimes it may be opportunistic pathogen. The normal skin flora does not have adverse effect except the production of odorous substances (Schlegel, 1993) and these skin bacterial flora derive their nutrition from the human perspiration. The human skin inhibits the invasion of most of the pathogenic bacteria (Chiller *et al*., 2001). The antimicrobial defense mechanism of skin includes mechanical rigidity of the stratum corneum and its low moisture content, lipid content, production of lysozyme, acidity etc. (Harder *et al*., 1997). Skin bacteria become sometimes pathogenic both normally and potentially. Cogen *et al*. (2008) stated that interdisciplinary collaborations at the interface of microbiology and immunology have greatly advanced our understanding of the host-symbiont and host-pathogen relationships. They further stated that very little literature regarding the influence of resident cutaneous microflora in skin health had been evaluated. However, in the last 15-20 years pathogenic roles of microbes present on the human skin have been studied. The present article reviews relevant advanced studies on bacterial skin flora with special reference to innocuous symbionts and potential pathogens in addition to antibiotic effects.

HUMAN SKIN AS HABITAT OF BACTERIA

The human skin is not always good habitat of bacteria, rather it becomes intricate sometimes for many bacteria. The type and density of bacteria on human body depends on anatomic location, local humidity, amount of sebum and sweat production, and the host's hormonal status and age (Aly *et al*., 1991). Microbial flora of skin of three human populations were grouped considering five anatomical skin sites – hands, back, axillae, groin and feet, while significantly larger bacterial populations were found on the back, axillae and feet in individual from the higher temperature and humidity environment compared to the moderate temperature and low humidity environment (McBride *et al*., 1977). However, bacterial flora on normal skin were found as predominantly gram positive and it is assumed that population of gram

negative bacteria is increased there with an increase of either temperature or humidity. Bacterial skin flora are found to be commensal, symbiotic, or parasitic relative to the host, although alterations in host immune status are known to have a significant impact. The type of relation established is often inherent to bacteria (Chiller *et al*., 2001). However, Feingold (1986) reported that stable colony formation becomes possible only due to ability of bacteria to adhere to the skin epithelium and grow there in a relatively dry and acidic environment.

BACTERIAL COLONIZATION AND ITS EFFECTS

Both directly and indirectly commensal bacteria protect the human skin from pathogenic action. Many sorts of effects are shown by this type of bacteria which includes production of bacteriocin and toxic metabolites, induction of a low reduction-oxidation potential, depletion of essential nutrients, prevention of adherence of competing bacteria, inhibition of translocation and degradation of toxins (Chiller *et al*., 2001). Commensal bacteria like *Staphylococcus epidermidis* compete for nutrients and niches, bind keratinocyte receptors and inhibit adherence of virulent *Staphylococcus aureus* (Bibel *et al*., 1983a). Even this commensal bacteria can release antibiotic substances.

There are about 1000 species of human skin flora from 19 Phyla (Grice *et al*., 2009; Papas, 2009). However, the total number of bacteria in an average human has been estimated at 10^{12} (Todar, 2009). The mutualistic bacteria can prevent transient pathogenic organisms from colonizing the skin surface, either by competing nutrients, secreting chemicals against them, or stimulating the skin's immune system (Cogen *et al*., 2008). They also stated that resident microbes can cause skin diseases and enter the blood system creating life threatening diseases particularly in immunosuppressed people. Commensal bacteria release species-specific antibiotic substances known as bacteriocins, with the help of which virulent staphylococcal organisms are inhibited (Peterson *et al*., 1976). Bacteria like *Propionibacterium acnes* can induce the host to enhance antibody production, stimulate phagocytosis and clearance mechanisms, and augment interferon and cytokine production. These bacteria can release fatty acids from lipid breakdown and inhibit growth of *Streptococcus pyogenes* (Hentges, 1993; Chiller *et al*., 2001). Gram negative bacteria more frequently colonize regions of the skin with high moisture content (Elias and Feingold, 2006). However, carbohydrate content, temperature and pH along with moisture are found to identify the colonizing bacteria effectively.

INTRINSIC QUALITY OF SKIN BACTERIA

Clinical studies research with special reference to their identification and characterization of bacteria are not extensive. However, Gao *et al*. (2007), Dekio *et al*. (2005), Fredricks (2001), Hadaway (2003), and Roth and James (1989) have stated that existing clinical studies have provided invaluable information about the abundance and types of microbes on the skin.

According to Cogen *et al*. (2008), symbiosis between skin flora and the host falls into three categories: parasitism, commensalism and mutualism. They stated that symbiotic relationship can exist in which only one organism benefited while the other is harmed (parasitism, predation, ammensalism and competition), one organism benefited and other is not affected (commensalism) or both are benefited (mutualism and protoco-operation). Lai and Gallo (2010) stated that skin commensals participate in human protection and provide essential element that protect human from infection and uncontrolled inflammation. They also stated that commensals may be regarded as beneficial to normal healthy host, but can become dangerous to the host with immunodeficiency or disturbed skin integrity.

The surface tissues of the body such as skin and intestinal tract are in direct contact with the external environment and are thus continuously exposed to large numbers of microorganisms. To cope with the substantial microbial exposure, epithelial surfaces produce a diverse arsenal of antimicrobial proteins that directly kill or inhibit the growth of microorganism (Gallo and Hooper 2012). When a bacterium is able to encompass the human defence mechanisms, then the bacterium becomes pathogen. Regarding this sort of pathogenic mechanism in case of cutaneous bacteria, a very little is known (Bibel *et al*., 1983b; Ogawa *et al*., 1985; Cole and Silverberg, 1986). However, several *Staphylococcus aureus* (Foster and McDevitt, 1994) virulence genes have been identified, expression of what is controlled by global regulatory element including *san, agr, xpn* (Cheung *et al*., 1995). These bacteria have been reported as an ideal cutaneous pathogen to study because of its clinical relevance, well-delineated genome, and ability to grow on both liquid and solid media (Cogen *et al*., 2008). Two ubiquitous members of the skin microbiota, *Staphylococcus epidermidis* and *Propionibacterium acnes* are predominant on human epithelia and in sebaceous follicles, respectively (Christensen and Bruggemaun 2014). Their successful colonization is a result of a commensal or even

mutuatistic life style, favouring traits conferring persistency are aggressive host damaging properties.

The skin of human body is a home to a diverse and complex variety of innate and adaptive immune functions (Sanford and Gallo, 2013). Despite potent immune system present at that cutaneous barrier, the skin encourages colonization by microorganisms. They also stated that just as host immunological factors and behaviours shape the composition of these communities, microbes present on the skin greatly impact the functions of human immunity. Thus, their comment is that the skin immune system should be considered a collective mixture of elements from the host and microbe acting in a mutualistic relationship. However, Hooper *et al*. (2012) reviewed advances in understanding the interactions between resident microbes and the immune system, and the implications of the findings for human health. They stated that the large number of microorganisms that inhabit mammalian body surfaces have a highly co-evolved relationship with the immune system. They also reported that the mammalian immune system plays essential role in maintaining homeostasis with resident microbial communities, thus ensuring that the mutualistic nature of the host microbial relationship is maintained.

RESIDENT SKIN BACTERIA AND THEIR INTERACTION

Resident microflora on the skin include bacteria, viruses and many types of fungi. In the present article, literature mainly described bacteria that have been reviewed broadly. The well studied bacterial resident genera isolated from the skin were *Staphylococcus, Streptococcus, Pseudomonas, Corynebacterium* and *Propionibacteriaum.* Todar (2009) described these genera as cutaneous and they all are either common (25%) or nearly 100 percent present on the human body surface. They are also found in different parts of the human body like nose, pharynx, mouth etc. Different species belonging to the above mentioned genera are reviewed and discussed here based on research findings of numerous scientists.

i. *Staphylococcus*

Two species under this genus viz., *S. epidermidis* and *S. aureus* are found commonly and abundance of *S. epidermidis* is very high. On the contrary, *S. aureus* is found as potential pathogen. *S. Epidermidis*, the most common clinical isolates of the cutaneous microflora, is gram positive bacterium, found in clusters and despite its innocuous nature generally, it has been reported as a frequent cause of nosocomial infections (Cogen *et al*., 2008). This bacterium infects primarily the compromised patients like drug abusers, patients with acquired immune deficiency syndrome (AIDS), premature neonates and patients with an indwelling device (Domingo and Fontanet, 2001; Cogen *et al.*, 2008). Catheters and implants play important role for entry of these infections (Tacconelli *et al*., 1997) and thereafter, the virulent strains of *S. epidermidis* form bioflims that partially shield the dividing bacteria from the host's immune system and exogenous antibiotics (Cogen *et at.* 2008). However, biofilm formation reduces the excess of antibiotics to the bacteria and often necessitates the removal of indwelling devices (Hoyle and Costerton, 1991). However, once systemic, *S. epidermidis* can cause sepsis, native valve endocarditis, or other subacute or chronic conditions in the patient risk group (Caputo *et al*., 1987; Overturf *et al*., 1990). For *S. epidermidis* infection medical treatments range from systemic antibiotics to device modification and removal (Cogen *et at.* 2008). and research suggests that bacterial attachment to materials is dependent on the physicochemcial properties of the bacterial and plasitc surfaces (Cerca *et al*., 2005; van der Mei *et al*., 1997; Vacheethasanee and Marchant, 2000).

Many strains of *S. epidermidis* produce lantibiotics, which are lanthionine containing antibacterial peptides, also known as bacteriocins (Cogen *et al*., 2008). The identified bacteriocins are epidermin, epilancin K7, epilancin 15x, Pep 5 and staphylococcin 1580 (Bierbam *et al*., 1996; Ekkelenkamp *et al*., 2005; Sahl, 1994). Additional antimicrobial peptides on the surface of the skin have been identified as originating from *S. epidermidis* (Cogen *et al*., 2007). This bacterium may also promote the integrity of cutaneous defence through elicitation of host immune responses (Cogen *et al*., 2008). Their preliminary data suggest that *S. epidermidis* plays an additional protective role by influencing the innate immune response of keratinocytes through Toll-like receptor (TLR) signalling. This way against harmful pathogen skin's immune system may play an important role in defence.

S. aureus is the most causal agent of cutaneous and systemic infections. It may transiently colonize the skin of newborn baby and the skin of atopic patients (Strange *et al*., 1996). Skin infections caused by this bacterium include impetigo, folliculitis, furuncles and subcutaneous abscesses, and through the production of exfoliative toxins, staphylococcal scalded skin syndrome (Iwatsuki *et al*., 2006). This bacterium also causes septic, arthritis, osteomyelitis, pneumonia, meningitis, septicaemia and endocarditis (Iwatsuki *et al*., 2006; Foster 2005; Lowy 1998). This bacterium is also reported to act as cutaneous

pathogen in HIV-infected patients, causing superficial and deep dermal pathology that can lead to life threatening complications (Berger, 1993).

Viale and Stefani (2006) stated that *S. aureus* infections are treated with antibiotics and the removal of infected implants is necessary. But Foster (2004) and Hiramatsu (2001) reported that there has been a dramatic rise of antibiotic resistant strains such as methicillin resistant *S. aureus* (MRSA), vancomycin-intermediate and vencomycin-resistant *S. aureus* strains (VISA and VRSA). This might be due to acquisition of a transferable DNA element called staphylococcal cassette chromosome *mec* (SCC*mec*), a cassette (type I-V) carrying the *mec*A gene, encoding penicillin-binding protein (PBP) 2a (Ma *et al*., 2002; Hiramatsu *et al*., 2001; Foster *et al*., 1994).

However, *S. aureus* is relatively resistant to killing by cationic antimicrobial peptides produced by the host epithelial cells and phagocytes (Cogen *et al*., 2008). They also stated that the most key mechanism for this resistance involves alterations in the charge of the bacterial cell surface and effective opsonization of this bacterium is inhibited by polysaccharide capsule, the surface expressed clumping factor and protein A. Liu *et al*. (2005) stated that the eponymous golden caroteniod pigment protects *S. aureus* against neutrophil killing *in vitro* by scavenging oxygen free radicals. Peacock *et al*. (2001) and von Eiff *et al*. (2001) suggested that *S. aureus* may be considered a normal component of the nasal microflora, despite of its cutaneous habitat. It is estimated that about 33% people of the world are colonized with *S. aureus* (Mainous *et al*., 2006). Among the population, 20% are persistently colonized, 60% carry intermittently colonized and 20% are never colonized (Peacock *et al*., 2001). However, this was found on healthy human skin and in nasal passages in commensal effect, rather than a pathogenic effect. Hale and Hinsdill (1975) stated that certain strains of *S. aureus* were found to produce bacteriocins such as staphylococcin 462, a peptide responsible for growth inhibition of other *S. aureus* strains.

ii. *Streptococcus*

Streptococcus species are known as notorious pathogen for human skin and based on M-protein serotype, *Streptococcus* species belong to different groups. M-protein is a virulence antigen that confers bacterial resistance to phagocytosis (Chiller, 2001). One of the important species of *Streptococcus* is *S. pyogenes* belongs to the group A. This species is said to be cutaneous resident, but not typical and it is carried asymptomatically in the throat of school aged children (Bisno, 1995). This species is reported to cause tonsilitis pneumonia and endocarditis and some of the diseases caused by this bacterium lead to rheumatic fever or nephritis (Todar, 2009), ultimately damaging the heart and kidney.

Three different dermal infections viz., erysipelas, cellulitis and necrotizing fasciitis are caused by *S. pyogenes*. Erysipelas is an acute infection caused by this bacterium involving the dermis and dermal lymphatics (Jorup-Ronstrom, 1986). Cavernous sinus thrombosis is a devastating complication of erysipelas (Wortman, 1993) and cellulitis, unlike erysipelas, involves the subcutaneous tissue (Hook *et al*., 1986). Two forms of cellulitis are found to occur in children. Perianal cellulitis is observed in young children as perianal erythema, which are associated with painful defecation and blood-tinged stool (Barzilai and Choen, 1998). Necrotizing fasciitis is a potentially life threatenting infection of the subcutaneous fascia (Tharakaram and Keczkes, 1988). *S. pyogenes* produces also several toxins that can cause localized destruction or systemic symptoms (Hackett and Stevens, 1993). *S. pyogens* is also reported to cause scarlet fever just shortly after an episode of pharyngitis (Stevans, 1992). It reflects now that *S. pyogens* is known for causing superficial infections as well as invasive diseases.

Superficial infections differ with age and cutaneous morphology, and pyoderma prevails in infants and children (Cogen *et al.,* 2008). The post infectious nonpyogenic syndrome rheumatic fever can follow throat infection and post-streptococcal glomerulonephritis can follow either skin or throat infection (Hahn *et al*., 2005). Extensive skin infected patients are treated with oral antibiotics such as penicillin, erythromycin or clindamycin (Montagnani *et al*., 2006). However, invasive infections require systemic antibiotics and intensive support (Schroeder and Steinke, 2005).

iii. *Pseudomonas*

A gram negative species named *P. aeruginosa* is found in non sterile areas of healthy human beings. This species is well known for its ability to produce fluorescent molecules, including pyocyanin, pyoverdin and pyorubin, and its grape like sweet odour allow for easy identification of *P. aeruginosa* from other gram negative bacteria (Cogen *et al*., 2008). They also stated that infections of this bacterium occur primarily through compromised skin and transmission occurs through contamination of inanimate objects. On human skin, *P. aeruginosa* causes dermatitis, and it occurs when skin comes contact with infected water.

P. aeruginosa secrets extracellular fibrous polysaccharide matrix called alginate, protecting the bacterium from phagocytic killing and potentially from antibiotic access (Lam *et al*., 1980). This bacterium also produces a variety of toxins and enzymes including lipopolysaccharide, elastase, alakaline protease, phospholipase C, rhamnolipids and exotoxin A, to which the host produces antibodies (Stainslavsky and Lam, 1997). They reported that virulence factors of this bacterium is regulated in a complex way and thus, contribution of many of the toxins to bacterial virulence is still controversial and the toxin lacking strains exhibit virulence in murine models of infection. Wu *et al*. (2005) stated that *P. aeruginosa* is able to sense the immene response and upregulate the virulence factor type 1 lectin (*lec*A). It is interesting that *P. aeruginosa* is found sometimes to protect the human host from a variety of infections and in such case by-products of *P. aeruginosa* become so potent that several of them are turned into commercial medications (Cogen *et al*., 2008). *P. aeruginosa* was found to produce a peptide called PsVP-10, which has antibacterial activity against *Streptococcus mutans* and *S. sorbinus* (Padilla *et al.*, 2006).

iv. *Corynebacterium*

The bacterial species belong to this genus are gram-positive, non motile and facultative anaerobic in nature. The members of skin flora are divided into two species: *Corynebacterium diphtheriae* and non- diphtheriae corynebacteria, *C. Jeikeium*, which is normal inhabitant on human skin.

C. diphtheriae is categorized by biotypes *gravis*, *mitis*, *belfanti* and *intermedius*, as defined by colony morphology and biochemical tests and this species is further divided into toxigenic and non-toxigenic strains (Cogen *et al*., 2008). Highly lethal diphtheria toxin is produced by toxinogenic *C. diphtheriae* and on the other hand, non-toxinogenic *C. diphtheriae* is capable of producing septicaemia, septic arthritis, endocarditis and osteomyelitis (Austin and Hill, 1983; Barakett *et al*., 1993; Poilane *et al*., 1995). Both the types can be isolated from cutaneous ulcers of alcoholics, intravenous drug users and from host with poor hygiene standards (Harnisch *et al*., 1989; Coyle *et al*., 1989). However, in most developed countries immunization has successfully reduced the prevelence of diphtheria (Prospero *et al*., 1997).

The non-diphtherial corynebacteria, *C. jekeium* is considered to be normal inhabitant of epithelium and found frequently on human skin. This bacterium causes infections in immune-compromised patients in conjunction with underlying malignancies and in skin-barrier defects (Coyle and Lipsky, 1990). It has been suggested by Jucgla *et al*. (1995) that this bacterium causes papular eruption with histological features of botryo-mycosis and once the bacterium penetrates the skin barrier, sepsis or endocarditis is caused (van der Lelie *et al*., 1995). *C. jeikeium* treatment varies from other gram positive bacteria due to its resistant characters to various antibiotics and this character stems from a variety of factors.

When *C. jeikeium* is cultured from hospitalized patients, colonization is seen in axillary, inguinal and perineal area (Larson *et al*., 1986; Wichmann *et al*., 1985). Like *S. epidermidis*, this species of *Corynebacterium* is ubiquitous and largely innocuous, that indicates *C. jeikeium* is definitely a commensal (Cogen *et al.*, 2008).

v. *Propionibacterium*

Only the well studied species of this genus is *P. acnes*, which resides in the sebaceous glands. It is anaerobic and gram positive bacterium. *P. acnes* derives energy from fatty acids of sebum and susceptible to ultraviolet radiation due to the presence of endogenous porphyrins (Ashkenazi *et al*., 2003). This bacterium is implicated in a variety of manifestations resulting in endocarditis (Jakab *et al*., 1996; Homma *et al*., 1978). In sebaceouos gland, this bacterium produces free fatty acids as a result of triglyceride metabolism and these by-products can cause to irritate follicular wall and induce inflammation (Coenye *et al*., 2007), which due to host tissue damage by *P. acnes* leads to cutaneous infection (Miskin *et al*., 1997; Jappe *et al*., 2002). Callegan *et al*. (2002) stated that *P. acnes* causes endopthalmitis i.e.; inflamation of the interior of eye causing blindness weeks or months after eye surgery and this delayed infection might be due to low virulence phenotype of this bacterium.

Fagundes *et al*. (2011) reported that the indigenous microbiota colonizes exposed surfaces and aids their host in several physiological activities. They also reported that the transition between a non-colonized to a colonized state is associated with modification on the pattern of host inflammatory responsiveness. However, various medications are employed based on the presentation of disease by *P. acnes*. Tropical retinoids such as tretinoin and adapalene reduce inflamation of follicular keratinocytes and may interfere with *P. acnes* infection (Webster, 2005). A compound related to retinol (vitamin A) is prescribed as the only treatment that leads to permanent remission (Layton *et al*., 1993).

CONCLUSION

A human body is covered by a few square meters of skin and most of the bacteria are found in the superficial layers of the epidermis. The upper part of the hair follicles is suitable for gram positive bacteria. The *Staphylococcus, Corynebacterium, Propionibacterium, Streptococcus, Pseudomonas* etc. are considered to be commensal, although mutualistic and parasitic as well as pathogenic roles by them have been reported. However, sometimes potentially pathogenic bacteria are found on the face and hands of human, and these are nasal carriers. But in most of the cases, the pathogenic bacteria are inhibited by the toxic metabolites of resident skin flora. Thus they potentially play an opposite role by protecting the host. Interactions between host and bacteria that occur on human skin shows most of the time beneficial role as reviewed in this article. Even they have been found to participate in inflammatory diseases, causing no infection. The human skin as a poor media supports the growth of both commensals and pathogenic bacteria. Thus, the use of antibiotics should not be enormous. Extensive and overuse of antibiotics have the chance to disrupt the balance of cutaneous bacteria and this may allow the skin to be more susceptible to pathogens. The present article finds that human skin bacteria benefit the host mainly and pathogenicity rarely.

ACKNOWLEDGEMENT

Authoress acknowledges her father Dr. Golam Kabir, Professor of Botany, University of Rajshahi for going through the manuscript and valuable suggestions.

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