Physical Stress and Bacterial Colonization on Human Skin and Stomach: Review

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ABSTRACT
Bacterial surface colonizers are subject to a variety of physical stresses. During the colonization of human epithelia such as on the skin, bacteria mainly have to withstand the mechanical stress of being removed by fluid flow, scraping, or epithelial turnover. To that end, they express a series of molecules to establish firm attachment to the epithelial surface, such as fibrillar protrusions (pili) and surface-anchored proteins that bind to human matrix proteins. Furthermore, many bacteria produce multi-layered agglomerations called biofilms with a sticky extracellular matrix, providing additional protection from removal. This review will give an overview over the mechanisms human bacterial colonizers have to withstand physical stresses with a focus on bacterial adhesion.

Keywords: Adhesion, colonization, biofilms, Helicobacter pylori.

INTRODUCTION
In their natural environment, bacteria have to cope with a variety of physical stresses. Most bacteria live in a surface-attached form. During colonization they thus first need to make sure that attachment is established. Later on, they must defend themselves against forces that may detach them from the surface, such as mechanical stresses exerted by fluid flow or any kind of scraping. To that end, many bacteria “encapsulate” themselves in a sticky matrix called biofilm [1]. Bacteria that live in the environment or on abiotic man-made surfaces often establish attachment only by hydrophobic or electrostatic interaction. Bacteria that colonize animal or human tissue additionally use specific mechanisms of adhesion to host proteins or other macromolecules for attachment. The molecular factors underlying the subsequent cellular agglomeration phase are in principle similar between colonizers of animals and those of abiotic surfaces and involve molecules that cause intercellular aggregation. In multi-species communities, they may include interaction with the surfaces of other colonizing organisms [2]. Other physical and physico-chemical stresses that may be harmful to bacteria during the colonization of surfaces are osmotic stress, ultraviolet radiation, and shifts in pH value. Bacteria living in environments with sun exposure need mechanisms to withstand UV rays, while skin bacteria often experience shifts in salt concentration [3]. Extreme pH values may be encountered for example by bacteria living in the stomach. In this review, molecular mechanisms that bacteria have developed to withstand physical stresses during colonization will be reviewed.

Colonization of the skin
The skin is the largest human organ and is colonized by a wide variety of microorganisms [4]. Many occupy specific niches that differ in many aspects, such as regarding humidity and the chemical composition of host-produced secretions. The skin environment is in general dry and acidic, but more moist conditions are found in glands and hair follicles. The surface of the skin is composed of keratinocytes, which are terminally differentiated at the most exposed layers. This surface is disrupted by invaginations – sebaceous, apocrine and eccrine (sweat) glands and hair follicles [5]. Eccrine glands secrete water and electrolytes, and contribute to the acidification of the skin. Apocrine glands, found mostly in the
Armpits and anogenital regions, produce viscous secretions. Sebaceous glands are connected to hair follicles and produce sebum. Sebum is an oily/waxy matter containing for example triglycerides that are degraded by propionibacteria to produce free fatty acids, which also contribute to the acidic pH of the skin surface [6]. Notably, the density of glands differs significantly between different areas of the skin; and those with low density such as arms and legs are in general dryer and contain a lower density of bacteria. In addition to moisture, differences in temperature may lead to differences in the degree of bacterial skin colonization. The skin is host to a wide variety of colonizing bacteria. According to both classical, culture-based studies as well as recent metagenomic investigations, Propionibacterium ssp. dominates in sebaceous sites and staphylococci and corynebacteria in moist areas [7]. 16S rRNA metagenomic sequencing analyses revealed a great variety of bacteria colonizing the dry areas of the skin, which includes many Gram-negative species. However, bacterial colonization in these areas is overall lower than at the moist sites. Among the propionibacteria, Propionibacterium acnes is the most important skin colonizer, together with Propionibacterium avidum and Propionibacterium granulosum [8]. It is well known as a contributor to the development of the skin disease, acne, although the mechanistic details of how P. acnes promotes acne are not well understood and P. acnes may not be involved in all cases of acne [9]. In addition to acne, P. acnes may occasionally be involved in opportunistic infections such as endocarditis or osteomyelitis [10]. These may involve biofilms, judging from the observation that P. acnes is able to form biofilms in-vitro [11]. The molecular components of P. acnes biofilms, however, are largely unknown. Notably, P. acnes is also attributed a beneficial role in skin colonization, as its acidic fermentation products lower the skin pH, thereby preventing colonization of harmful pathogens such as Staphylococcus aureus [12]. Staphylococci are widely regarded as the most important colonizers of the human skin, both in terms of frequency and sources for infection [13]. There is a certain preference of specific coagulase-negative staphylococci (CoNS) species for the site of colonization [14]. The main species colonizing various areas of the skin are Staphylococcus epidermidis and Staphylococcus hominis. CoNS are opportunistic pathogens and S. epidermidis, for example, is the most frequent cause of catheter-related infections [15]. However, the involvement of CoNS in such infections may be regarded “accidental” rather than representing a clear pathogenesis program, and is likely due chiefly to the sheer abundance of CoNS on the skin and their extraordinary capacity to colonize tissue surfaces, as will be discussed in detail further below. In contrast, the coagulase-positive species S. aureus is commonly regarded as a major and dangerous human pathogen, although about one third of the population is colonized non-symptomatically by S. aureus in the nares and rectal areas [16]. Of note, S. aureus non-symptomatic colonization is correlated with a higher chance of subsequent infection. Except for the species Corynebacterium diphteriae, corynebacteria are commonly innocuous bacteria found widespread in nature; some species may colonize humans [17]. Occasionally, some corynebacterial species may cause opportunistic infections in immune-suppressed patients. Several studies have addressed a potential bacterial competition between S. aureus and corynebacteria in the human nose. In general, there appears to be a negative correlation between the abundance of corynebacteria as well as P. acnes and S. epidermidis and S. aureus colonization, indicating bacterial interference [18].

Colonization of the Stomach
The mucosa of the stomach is coated with a thick, continually secreted layer of mucus to protect surrounding tissue from the acidic conditions inside the stomach.
This creates an environment that is very harsh for bacteria to colonize. Therefore, the stomach has for a long time been believed not to contain bacterial colonizers, until the microaerophilic Gram-negative bacterium H. pylori was identified to live in that environment [19]. Later on, more bacterial colonizers of the stomach were identified, such as Deinococcus radiodurans [20], but here there will be a focus on H. pylori, as this bacterium is far better studied. In some populations, the frequency of H. pylori colonization can reach 80%; and ~ 50% of all people are thought to be colonized with H. pylori. H. pylori colonization can be considered an infection, although most people are asymptomatic [12]. The majority of H. pylori cells are found in the gastric mucus, but similar to pathogens of the lower intestinal tract - adhesion to epithelia is considered a prerequisite for infection. Several H. pylori adhesion proteins have been described. The best-characterized is BabA, which attaches to the fucosylated Leb blood antigen [10]. SabA, another H. pylori adhesin, mediates binding to sialylated glycoconjugates expressed during inflammation in gastric tissue [6], but also to the matrix protein laminin and to neutrophils and erythrocytes. H. pylori contains further adhesins, whose role in attachment are not as well understood and whose interaction partners have not yet been identified. The most intensively studied H. pylori virulence factor, the Cag type IV secretion system with its effector molecule CagA subverts intracellular host signaling, leading to changes in cell growth, motility, and alteration of tight junctions, thus in principle similar to mechanism described in Figure 1, used by pathogens of the lower intestinal tract [17].

The pH of the stomach is about 2.0; therefore, H. pylori needs efficient mechanisms to cope with acid stress [10]. The most important such mechanism is the production of an extraordinarily potent urease, whose catalytic capacity exceeds those of other bacteria, which is likely why H. pylori has the almost unique capacity to colonize the human stomach [6]. As further acid resistance systems, H. pylori also has two amidases (AmiE, AmiF) that produce ammonia and an arginase producing urea and ornithine from arginine hydrolyzation (RocF) as shown in Fig. 1. All those H. pylori ammonia-producing acid resistance systems are up-regulated by low pH via the ArsSR two-component system [8]. Other than H. pylori.

**Fig 1:** H. pylori mechanisms important during colonization of the stomach [17].
pylori, several enteropathogenic bacteria show considerable acid resistance to be able to pass through the upper intestinal tract. In *E. coli* and some other gamma proteobacteria such as *Vibrio* or *Salmonella*, acid resistance systems are mainly amino acid decarboxylases [14]. These systems consist of the decarboxylase, which is induced by low pH and removes carbon dioxide from the gastric cavity. The proton export of the decarboxylation product with the concomitant import of the amino acid educt effectively removes that proton to the cytoplasm and transports it to the periplasmic space [19].

**CONCLUSION**

To overcome the problem of mechanical removal from human tissues, often exacerbated by epithelial turnover (except for on the teeth), bacteria have invented a series of adhesion mechanisms. These range from initial interactions by non-specific physical forces to long-range adhesion by protrusions such as pili and short-range, firm interactions mediated by bacterial surface proteins. Aggregation and encapsulation in an extracellular matrix (biofilm formation) further helps to prevent removal. In addition, many bacteria use internalization to persist in epithelial cells and thereby withstand epithelial shedding. In specific environments, bacteria also need to cope with additional stresses, such as a highly acidic environment in the stomach. While we have a fairly good understanding of bacterial adhesins and biofilm formation as it occurs in vitro, the in-vivo relevance of many findings is still unclear, owing to the fact that colonization of many human epithelia is often difficult to mimic in animal infection models. Frequently, we need to extrapolate from the ex-vivo analysis of the binding capacities of adhesins to immobilized matrix proteins or from infection models (such as in the case of staphylococcal infections), which may not correctly represent asymptomatic colonization. Furthermore, it is becoming increasingly clear that in most situations, bacteria not only interact with human epithelia during colonization, but also with sometimes up to thousands of other bacterial species. For example, we are only beginning to understand how interactions between the surface molecules of different bacteria can strengthen a bacterial multi-species biofilm or how “probiotic”, benign bacteria prevent colonization with potential pathogens.

**REFERENCES**


