Bacterial Cell Surface Heterogeneity: A Pathogen’s Disguise

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Why Is It Advantageous for Microorganisms to be Able to Disguise Themselves?

All interactions of microorganisms with their environment are surface phenomena, and therewith involve the properties of the microbial cell surface [1] and its possible disguise or hidden identity by an altered appearance. Since appearance is what one initially sees upon first encounter, a disguise always refers to surface properties, like cloths for people and hydrophobicity or charge for microorganisms.

Antimicrobials, for instance, first have to approach an organism and interact with its cell surface before they can become effective. Hydrophobic lactobacilli with a mean water contact angle of 66 degrees were found to be susceptible to nonoxynol-9 (a non-ionic spermicide) and vancomycin, whereas hydrophilic strains with a mean water contact angle of 32 degrees were resistant [2].

Moreover, since adhesion to substratum surfaces depends on the properties of the interacting surfaces [5], the ability of an organism to produce clones with different surface properties will allow a strain to adhere to different surfaces, which may be considered a survival mechanism [6]. Clearly, these are beneficial traits for pathogenic organisms.

How Can We Measure the Surface Properties of Individual Microorganisms or Subpopulations in an Axenic Culture?

In microbiology we like to believe that when we grow an axenic culture, all organisms are identical. This belief is wrong and stems from the fact that measurement of properties of an individual organism or subpopulation of clones is generally impossible, either by lack of a suitable technique or due to statistical limitations. Microscopic analysis of axenic cultures of lactobacilli has shown that part of a population can possess an electron dense, ruthenium red-uranyl acetate stained surface layer, but microscopic analysis, decision to publish, or preparation of the manuscript.

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aqueous phase is measured as a function of the vortexing time. Initial removal of organisms by the hydrocarbon phase is taken as a measure of cell surface hydrophobicity. Interestingly, whereas for some strains, all organisms in the aqueous suspension finally adhere to the hydrocarbon phase after prolonged vortexing indicative of the absence of subpopulations with different cell surface hydrophobicities, for other strains, a sizeable fraction of all suspended organisms remains in suspension, indicative of a subpopulation with lower cell surface hydrophobicity.

Is There Evidence That Cell Surface Heterogeneity Is a Trait of Pathogens and Do Other Strains Exhibit the Same Behavior?

Table 1 summarizes different strains and species for which cell surface heterogeneity in axenic cultures has been found. As can be seen, most evidence stems from particulate microelectrophoresis. Cell surface heterogeneity has been described mostly for pathogenic organisms. Surface heterogeneity can provide a part of a bacterial population with stealth-like properties, allowing at least a number of organisms to escape killing by antimicrobials, which enhances the pathogenicity of the population. Furthermore, since the properties of a microbial cell surface determine the organism’s ability to adhere to a surface, the possession of heterogeneous cell surface properties allows organisms to adhere to a greater variety of surfaces. For T. denticola and E. faecalis, this has been demonstrated to be a clear pathogenic trait, as it allows the organism to adhere with greater versatility to its target substrata. However, also for non-pathogens like lactobacilli, the ability to adhere to a wide range of different surfaces offers an advantage, as adhesion very often is a survival mechanism, stimulating the organisms to adapt a protective, biofilm mode of growth.

How Do Bacteria Regulate Cell Surface Heterogeneity?

Bacteria can adapt quickly to a new environment triggered by environmental signals to change their phenotypic appearance, but it is of apparent advantage that not all clones in a population do so. The genotypic mechanisms and environmental factors controlling surface heterogeneity in axenic cultures are only recently being studied and no general mechanism can yet be forwarded. However, pathogens migrating through the human body encounter different micro-environments, and in response to their environment, virulence genes could be horizontally transferred, up- or down-regulated, or deleted (see Figure 1). Although cell surface heterogeneity was observed in 5% of clinical S. epidermidis isolates [14], it may not be ruled out that in vitro culturing, including medium selection and serial passaging, influences the occurrence of bacterial cell surface heterogeneity.

Bicarbonate may play a determinant role in the development of culture heterogeneity. Bicarbonate as produced by mammalian cells is known to enhance the production of virulence factors in, for example, V. cholera, Staphylococcus aureus, Bacillus anthracis, while in E. faecalis bicarbonate increases pilus formation regulating its colonization of surfaces [15]. In V. cholera, the genes encoding the toxin-co-regulated pilus (TCP) and the cholera toxin (CT) are up-regulated by the excretion of bicarbonate by epithelial cells early in the infection process, causing increased adhesion to these epithelial cells. Significant heterogeneity was subsequently observed late in the infectious process, with a TCP/CT expressing culture heterogeneity. Bicarbonate may play a determinant role in the development of culture heterogeneity. Bicarbonate as produced by mammalian cells is known to enhance the production of virulence factors in, for example, V. cholera, Staphylococcus aureus, Bacillus anthracis, while in E. faecalis bicarbonate increases pilus formation regulating its colonization of surfaces [15]. In V. cholera, the genes encoding the toxin-co-regulated pilus (TCP) and the cholera toxin (CT) are up-regulated by the excretion of bicarbonate by epithelial cells early in the infection process, causing increased adhesion to these epithelial cells. Significant heterogeneity was subsequently observed late in the infectious process, with a TCP/CT expressing culture heterogeneity. Bicarbonate may play a determinant role in the development of culture heterogeneity. Bicarbonate as produced by mammalian cells is known to enhance the production of virulence factors in, for example, V. cholera, Staphylococcus aureus, Bacillus anthracis, while in E. faecalis bicarbonate increases pilus formation regulating its colonization of surfaces [15]. In V. cholera, the genes encoding the toxin-co-regulated pilus (TCP) and the cholera toxin (CT) are up-regulated by the excretion of bicarbonate by epithelial cells early in the infection process, causing increased adhesion to these epithelial cells. Significant heterogeneity was subsequently observed late in the infectious process, with a TCP/CT expressing culture heterogeneity.
comprised in different micro-environments with respect to nutrient availability, oxygenation, osmolarity, and cell density [17], which may all constitute environmental stimuli for phenotypic changes.

What Are the Implications of Cell Surface Heterogeneity for Future Pathogen Control?

Development of new antimicrobials and strategies for pathogen control are usually based on evaluating efficacy at the level of entire populations, discarding the possible existence of heterogeneous subpopulations. We have shown that axenic bacterial cultures in vitro, as well populations of infecting pathogens in vivo, can display heterogeneous surface properties, which puts them at an advantage in comparison with bacterial populations possessing similar phenotypic properties across an entire population. These advantages either include the ability to exert a stronger virulence towards the host or increased possibilities to adhere and survive antimicrobial and other environmental attacks. This implies that in the development of new antimicrobials and strategies for pathogen control, it is important to account for surface heterogeneity, as a disguised subpopulation may form the basis for surviving clones to form more virulent and antimicrobial-resistant strains.

References