Bacteria with a split personality outsmart the immune system

Bacteria, whether beneficial or harmful, must adapt to changes in their environment in order to survive. This is especially true for bacteria that reside within the human respiratory tract. The bacterium nontypeable *Haemophilus influenzae*, or NTHI, asymptomatically colonizes the human nasopharynx (upper part of the throat behind the nose). However, NTHI can transition into other areas of the respiratory tract (usually when people have a viral 'cold') and thus cause diseases, such as otitis media (ear infection), bronchitis, and complications in patients with cystic fibrosis (CF) or chronic obstructive pulmonary disease (COPD). In order for these bacteria to survive they must be able to adapt to changing conditions within the respiratory tract and escape the natural defenses of the human immune system.

One method of adaptation used by several respiratory pathogens is called the 'phasevarion', or phase variable regulon. The phasevarion allows a single bacterium to switch between one of two distinctly different forms (or phenotypes), similar to the way Dr. Jekyll switches into Mr. Hyde, yet is the same person. Thus, within a population of NTHI bacteria, there will be a subpopulation of each of these phenotypes, which are referred to as either the ON population or the OFF population.

In this study, we assessed the ability of each phasevarion subpopulation, ON or OFF, to survive killing due to toxic reactive oxygen species (ROS). ROS are highly reactive derivatives of oxygen that can damage DNA and proteins, and lead to cell death if uncontrolled. We first tested a clinical NTHI otitis media isolate for resistance to killing by hydrogen peroxide (H_2O_2), a common ROS encountered in the respiratory tract. Hydrogen peroxide is produced by human immune cells as well as some species of bacteria, as a mechanism to kill harmful bacteria. We found that the OFF population of bacteria are significantly more resistant to killing by H_2O_2 compared to the ON population, which was killed in the presence of H_2O_2. As an additional experiment, because immune cells, such as neutrophils, produce numerous types of ROS in order to control bacterial infection we incubated NTHI subpopulations in the presence of neutrophils isolated from the blood of healthy adults. Neutrophils were able to kill significantly more NTHI from the ON population compared to the OFF population. When an equal mixture of both the OFF and ON populations was exposed to ROS from human neutrophils, the ON population was killed and the OFF population was able to survive. These data indicated that the OFF population is better adapted to survive in the presence of high levels of ROS and thus may survive better during initial stages of infection.

Several other human pathogens also use a phasevarion to adapt and survive throughout the airways or gut, dependent on the bacterium. This adaptability allows these bacteria to evade the immune system and antimicrobial treatments, making diseases due to these bacteria difficult to treat or prevent. Because of this adaptability, vaccines or therapies that target a single subpopulation of bacteria are not likely to be as effective at killing all of the bacteria. Greater understanding of how the phasevarion allows bacteria to adapt and survive in the human body will allow us to better target both populations and thereby more effectively treat, or ideally, prevent

disease.

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