

Pathogens under stress

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Its not stress that kills us, it is our reaction to it.

Hans Selye (1998)

Introduction

Human bodies may seem like ideal multiplication sites for microorganisms; stable and convenient temperature, sufficient food supply, oxygenated environment, and without any other microbial competitors or predators. However, in fact, the pathogenic life style is probably one of the most stressful ones. To survive and multiply within a host, pathogens are under continuous and different forms of stress. The human immune system and the environment that bacteria live and survive in are limiting the growth conditions of microorganisms in almost any possible way. The defense system of the host is much more than just the adaptive immune system, which traditionally has received most attention. These systems have evolved over millions of years to clear the host from every single invading foreign evader, pathogen or not. In fact, only those microorganisms that can resist these limiting systems can be called pathogens, all other organisms are cleared rapidly.

What we are observing today is adaptations upon adaptations; evolution is never finished, as explained in the red queen hypothesis (Van Valen, 1973). This continuous battle between adaptations in the host and the microorganism makes it that from a microorganism's point of view, stress is always there. The right response to stress will determine whether the pathogen will succeed to successfully infect the host or not. In this ongoing battle, horizontal gene transfer and genome variability is an important weapon, but some pathogens seem to be able to survive without this mechanism. In this special issue, we take a closer look at pathogen stress and stress adaptation. In this volume, we have omitted the topic of stress and the adaptive immune system, as this has been the subject of many reviews before (Herbert & Cohen, 1993; Cláudio *et al.*, 2013). The way our body resists bacterial invasion with physical barriers and limitations and innate immune responses are the subject of this volume.

Stress factors in the host

Extreme environments

The first line of defense of the host is not the immune system, but in fact physical barriers. The outer layer of the skin is mostly dry surface of keratinized dead cells, which are not easy to penetrate. The physical barriers against bacterial invasion are best illustrated by the stomach pH. This acidic environment is the bottleneck that bacteria have to pass to move to

the gut or invade the host. In principle, such an extreme pH is not compatible with most life forms and special adaptations need to be in place in order for bacteria to resist this pH for some time or even to thrive in it. *Helicobacter pylori* is a master in this respect, but is only able to do so by careful adaptation to this highly special niche. After surviving the harsh conditions of the stomach, it will move through the mucus layer to attach itself at the epithelial cell layer, where the conditions are milder. But even then, these cells are frequently shed into the gastric lumen, and therefore, a flexible strategy of attaching and effacing has evolved (Marshall, 2002).

The gut

A special case is the gut. Although not inside the host, this environment, in close proximity to the host, challenges the potential pathogen in a different way. Here, the abundance of food is obvious, but the competition is the big stress factor. Over 3000 species of bacteria compete with each other and benefit from each other at the same time. In recent years, there has been a wealth of information obtained on the composition of the gut microbial communities and we are beginning to understand what the role of the gut microbial communities on the host is. However, the opposite is also true; the host is not a passive bystander, but plays an active role in the composition of the gut microbiota. In particular, the production of bile acids and the innate immune system play a crucial role in controlling gut bacteria. This can be observed best in specific genetic defects. A well-known example in this respect is of course intracellular pattern recognition receptor NOD2 that is a risk factor for inflammatory bowel diseases. But also mice mutated for the flagellin receptor TLR5 have an unstable gut microbial communities composition and are affected in the control of proteobacteria in the gut and, as such, prone to gut inflammation (Carvalho *et al.*, 2012). Invading pathogens therefore not only have to cope with a plethora of competing gut microorganisms, but also adverse conditions imposed by bile acids and the selective pressure of the immune system.

Food

Once microorganisms have managed to invade host tissue and establish themselves at the site of infection, stress-imposing conditions are not any less. The first objective is to obtain sufficient nutrients. Nutrient availability is a double-edged sword. Of course, there is an absolute abundance of nutrients that are needed for host cells to divide and function optimally. These

nutrients are more than sufficient for microorganism too. However, the host has evolved systems to limit these resources (or at least some of them) to eukaryotic cells. Iron acquisition is the most outspoken example of this. Iron availability to microorganisms is so restricted inside the host that this puts severe pressure on the survival of microorganisms and in fact induces severe stress on these microorganisms. Iron availability is normally already low in bodily fluids, but is even more reduced during infections, which can lead to inflammation-induced anemia. The importance of iron can also be seen from the fact that people with hemochromatosis are more vulnerable to both common but also uncommon pathogens. For instance, hemochromatosis is a major risk factor for patients to develop sepsis caused by *Vibrio vulnificus* (Barton & Acton, 2009). Apparently, iron withholding is the major factor controlling such pathogens. Also, other metal ions are crucial spore elements for bacteria, but the host is also aware of the toxicity of these compounds under certain conditions. This is exemplified by the recently identified mechanism of copper accumulation in the phagosomes of macrophages during infections. These amounts of copper generate a lethal accumulation of oxygen radicals within the closed environment of the phagosome. Limitation of nutrient availability is occurring throughout the body but can be very severe depending on the specific site of infection.

The immune system

The biggest threat to invading microorganisms is of course the immune system. Several immunological effector mechanisms such as phagocytes, the complement system, and antimicrobial peptides can kill bacteria in seconds. If ineffective, the host also has the ability to activate the adaptive immune system, a full mobilization of antimicrobial weaponry.

While most other host systems that control microorganisms often rely on limiting growth, the essential difference here is that the immune system is a highly effective bacterial killing machinery with many different, redundant as well as synergistic elements. Therefore, every successful pathogen must have developed a strategy to cope (at least temporarily) with the immune system. Pathogens that use the hit-and-run strategy of infection only have to counteract the innate immune system, whereas pathogens that establish chronic infections have to withstand both the innate and the adaptive immune system.

Bacteria always adapt

One of the lessons in basic biology is that bacteria, given enough time in evolution, always adapt to extreme environments. Stress is the factor that drives evolution in to rapid adaptation. The best example is not an adaptation to a new evolutionary invention of the host, but to medicine; the rapid evolving antimicrobial resistance worldwide. WHO's 2014 report (<http://www.who.int/drugresistance/documents/>

[surveillance/en/](http://www.who.int/drugresistance/documents/)) on global surveillance of antimicrobial resistance shows that antibiotic resistance is not a prediction for the future; it is happening right now. Without urgent, coordinated action, the world is heading toward a postantibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill. This antibiotic resistance is a natural phenomenon. This is what bacteria always do to resist stress that is put upon them. Inappropriate use of antimicrobial drugs, including in animal husbandry (more stress on the bugs), and poor infection prevention and control practices favors the emergence and selection of resistant strains, and their spread. The same bacterial adaptation process is also happening in response to our immune system. In this volume, several of these stress factors and especially the response of microorganism to these stress factors are discussed in detail. Understanding stress factors will teach us how pathogenic bacteria cope with the evolutionary inventions of the host, but will also give us new possible intervention strategies.

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