REVIEW ARTICLE

Life history tradeoffs of pathogens and the treatment principle of antibiogenesis

Rui-An Wang

Department of Pathology, Shenzhen Hospital, Southern Medical University, Shenzhen 518100, China

Abstract   There are no eternal individual lives so life continues by relaying with reproduction. Consequently, lifespan and fecundity are two essential genetic traits of life. The life history tradeoffs theory holds that there is an inverse relationship between lifespan and fecundity. This paper proposes two new concepts, i.e., "lifespan of pathogens" and treatment of infections by "antibiogenesis". The lifespan of pathogens is the time limitation of those tiny lives just as other large creatures. Notably, the lifespan of bacterium is the time interval from the cell division by which it is produced to next division by then its life ends and transforms to two new lives, or dies. Antibiogenesis means inhibiting generation of new lives. By the principle of life history tradeoffs, the lifespan of pathogens determines the speed of their proliferations and consequently the modality of infection. The treatment principle of antibiogenesis requires the duration of treatment to be determined by the lifespan of infected pathogens. The life history tradeoffs theory and the two concepts are helpful to understanding the pathobiology and shaping the clinical aspects of infectious diseases.

Significance of the paper

For the first time the paper answers the following questions. 1) Are bacteria immortal? How are their lifespans defined? 2) Why is the latent period of hepatitis A, SARS, plague infections very short and why are there no chronic infections of these pathogens? 3) Why does the treatment of tuberculosis and leprosy take a long time? 4) Why, in the case of hepatitis B, does immunotolerance not result in rampant proliferation of the virus? The tradeoff between the lifespan and fecundity is the law of conservation in biology. If a species has a long lifespan with high fecundity, the biological system would not exist; similarly, if it has a short lifespan with low fecundity, the species would not exist.

Introduction

It is well-known that no eternal individual life exists in the biosphere. However, life continues by relaying from generation to generation with reproduction. Thus lifespan, the time limitation of an individual life, and fecundity, the efficiency with which an individual life can multiply or propagate, are the two essential genetic traits of life. The life history tradeoffs evolution theory holds that there is an inverse relationship between the two.[1] Figuratively, the relationship between the lifespan and fecundity is just like the diagram of Taiji (Fig. 1). Lives with long lifespan have a lower fecundity, and vice versa.[12] The tradeoffs between lifespan and fecundity are universal in the biosphere, ranging from microorganisms to plants and to animal kingdom, including humans.[2–6] While the mechanisms of the tradeoffs are still an enigma,[7] it is critically important to maintain the diversity and balance of the biosphere for the existence of species. The tradeoffs not only exist between species[8] but also are important adaptation mechanism for a given species. It has been shown that when lifespan extended in model animals, the fecundity inevitably weakened. Sir2 in yeast was shown to be a balancer between the longevity of parent cells and the number of progenies produced by a parent cell.[3] The life history tradeoffs in viruses and cancer cells have also been noticed in recent years.[9–11]

The tradeoffs between lifespan and fecundity are the key to the balance of biosphere. They are like two variants in an equation. If both of them decrease, i.e., short lifespan with lower fecundity, this life cannot exist. Conversely, if both of them increase, i.e., an organism with long lifespan and robust fecundity, such as the fictitious creature of the Darwinian demon, this life will dominate the ecosystem and the whole system will collapse immediately.

Microorganisms and parasites are highly important in medicine. Except for some worms, the pathogens are generally tiny lives. Interestingly, although we have a better knowledge of how long a specific type of worm lives, we rarely think about the lifespan of bacteria and viruses. Nonetheless, the lifespan of these pathogens is critical for understanding their biological properties and the diseases they cause.

Figure 1 Interrelationship between lifespan and fecundity is depicted by the Taiji diagram. The fecundity increases as the lifespan shorten. Reversely, when the lifespan prolongs, the fecundity decreases.

The lifespan of bacteria

Lifespan of bacteria is from one division to next division or death

Bacterium is a special type of life generally deemed to be immortal, because they reproduce by division. When a cell divides, it is hard to know where and when the life will end. If they keep on dividing, the life seems to be limitless. Based on the same principle, tumor biologists deem that cancer cells are immortal. However, there is no eternal individual life in the philosophical sense. The trick is when a cell divides, its original life no longer exists, and instead it is transformed into two new lives. So the lifespan of a bacterium or any cell which reproduces by division is from one division to next division or death. The immortality of the bacteria and cancer cells is just a mirage without metaphysical reasoning.

Why is *M. tuberculosis* so difficult to grow and *M. leprae* never grown on a plate?

Defining the lifespan of bacteria not only settles a contradiction but also is critically important for understanding the biology of bacteria and many other related issues in medicine. For example, *M. tuberculosis* is a slowly growing bacterium. Professors of microbiology often describe *M. tuberculosis* as "lazy" (reluctant to grow), "hard" (nutritiously more demanding) and "tough" (their infections are difficult to treat) in class teaching. Yet there is no logical and metaphysical explanation to all these phenomena. A more difficult bacterium is *M. leprae*. It has never been successfully grown in the lab ever since it was discovered about one and a half centuries ago.

With the concept of bacterial lifespan, we understand that since the *M. tuberculosis* has a longer lifespan than most of common bacteria such as *E. coli*, they inevitably grow slower. The generation time of *E. coli* is about 18–20 min and the generation time of *M. tuberculosis* is around 18 h *in vitro*. The generation time is considered as surrogate average lifespan of the bacterium under specific conditions. No one knows the generation time of *M. leprae* since it has never been successfully grown *in vitro*. The explanation is that *M. leprae* has such a long lifespan that a colony will not show up for months, or even years.[12]

The lifespan of pathogens determines the infection type they cause

As lifespan holds an inverse relationship with fecundity, pathogenic bacteria with short lifespans proliferate very fast and tend to cause acute infections in a short latent period (Fig. 2, curve A). In contrast, those pathogenic bacteria with long lifespans proliferate very slowly and cannot generate large amounts of pathogens in a short time so they usually cannot cause acute infections (Fig. 2, curve C). The latent period of diseases caused by long living pathogens is also very long. In addition, when antibiotics are applied, the short living bacteria soon die out so that acute infections get cured in a short time (Fig. 3). However,
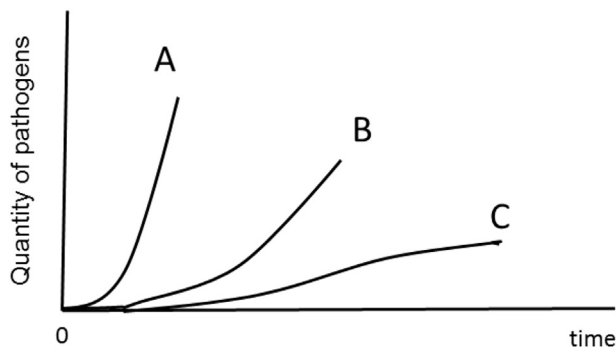
Figure 2 The growth curve of pathogens with different lifespan. A, short lifespan; B, mediate lifespan; C, long lifespan.

chronic infections caused by mycobacteria take years or even decades to be cured because of the longevity of the pathogens (Fig. 3).

The lifespan of viruses

Viruses are subcellular lives and they are strictly cell dependent, and thus designed as intracellular parasites. Unlike bacterium, they do not proliferate by division but by replication. Understanding the lifespan of viruses is not a problem like that of bacteria. However, because they are so tiny, their lifespans have been rarely considered previously. Even though virologists have begun to investigate the life history tradeoffs of viruses recently, they used the terms "persistence" or "survival",[9,10] which are somewhat vague in meaning. In the past two decades, cell biologists elegantly delineated the mechanisms of how cells die, but we do not have a slight idea of how viruses die and why some viruses have a long life while others have a short life.

Since the question has not been raised previously, there is neither experimental system to test, nor theory to calculate the longevity of the viruses. Three laboratory viruses, adenovirus (AV), lentivirus (LV), and adeno-associated virus (AAV), can be used as examples to illustrate the relationships between the lifespan and the replicative potential of the viruses.

Evidence from 3 laboratory virus vectors

Three laboratory viruses are commonly used expression vectors in the lab. They can only replicate in designed cells

with T antigen expression, such as 293T. In most of the experimental cells, the harvested vector viruses can only express specific proteins but they cannot replicate. Therefore, the duration of protein expression can be used as a surrogate marker for the lifespan of the viruses. The AV vector expression comes fast but it can only last 1 week. The LV vector expression comes slower but it can last about 1 month. AAV vector expression comes very slow but it can last 3 months. As for the commercial prices for the 3 virus vectors, the AV is the cheapest, the AAV is the most expensive, and the LV is in between. The AAV has the highest price because it is the most difficult virus vector to produce due to its weak replicative ability.

Evidence from phage studies

The study of lysogenic phage provides more evidence for the reverse relationship between the longevity of the virus and the replicative ability of the virus.[10] It has been shown that the burst potential of the lysogenic phages is inversely related to the survival ability of the phages outside the cells.[10]

The story of hepatitis viruses

Hepatitis viruses A, B and C are interesting cases for the illustration of longevity and replicative potential of the viruses. If a virus lives a short life, it will proliferate very quickly and produce huge amounts of pathogens in a short time. As a consequence, it produces a severe damage to the organ (Fig. 2, curve A). On the contrary, a long living virus will have much lower and limited replicative potential and produce little but lasting injury to the organ (Fig. 2, curve C). In the liver, we know the first case is hepatitis A virus (HAV), and the second case is the hepatitis C virus (HCV). The hepatitis B virus gives a more interesting example between the lifespan and the replicative potential.

China is a country with a high rate of hepatitis B virus infection, at about 10% before the widespread of hepatitis B immunization in 1990s. The past epidemiological data have shown that the HBV carrier rate of children at age 5 is at around 10%,[13] which means that most HBV infections occur in the childhood. It is also a well-known fact that childhood infections usually generate a condition termed immune-tolerance, which means that the immune system does not attack the infected pathogens. Then a paradoxical question occurs: why don't HBVs relentlessly replicate without the immune response at check? It is obvious that the classic
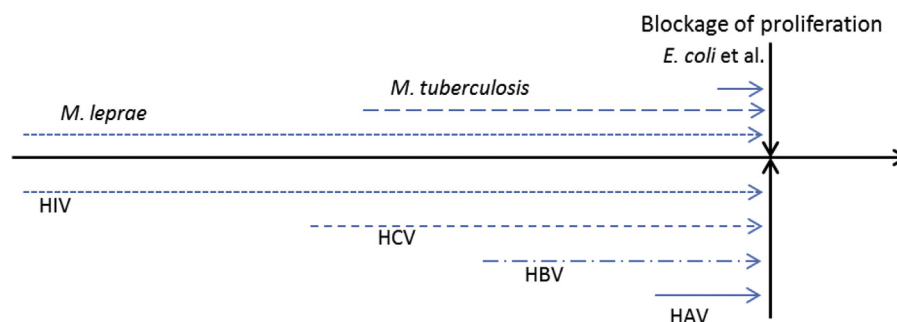

Figure 3 Schematic diagram depicting the principle of antibiogenesis in medical treatment. Long living pathogens take longer time of treatment.

paradigm of the balance between the viruses and the immune system of the host have failed to answer this question. However, the new paradigm of the balance between the lifespan and replicative ability can provide a clear answer to the question. Infection of HBV in childhood generates an immune-tolerance, i.e., the immune system of host are tolerant of the infected viruses. As a result, the viruses can live long in the host and their replicative potential decreases to a very low level. When the virus load is at a low level, it cannot be observed under the microscope, either electron or light microscope, even with immunocytochemical staining.

However, adult infection of HBV posits a very different situation. Liver damage at clinical level usually occurs since immune-tolerance at this stage is less possible. Interestingly, the stronger the immune response is to the HBV, the shorter life the virus will have. Consequently, the balance between the longevity and replicative potential tips to the side of replicative potential. As a result, increased amount of viruses are generated and severe damage to the liver occurs. Acute or even fulminant hepatitis might ensue. If the host response is mild, the viruses live longer and fewer viruses will be produced. Consequently, a mild and chronic hepatitis will happen to the patient. The outcomes of these infections are also in concord with these tradeoffs. In the more severe cases of acute hepatitis, the viruses live short and will die out with the increased resistance of the body. Consequently, more severe cases are less likely to turn into chronic hepatitis or a HBV carrier.

As evidence and mechanism of increased replicative ability of HBV, core promoter mutations are frequently seen in adult infections.[14] Point mutations at 1762/1764 sites could increase the DNA replicative ability at 2 fold,[15—18] while mutations at 1766/1768 sites could bolt the DNA replicative ability up to 20 fold,[17—19] and thus trigger a fulminant episode of infection. Interestingly, the fulminant infections usually are not transmitted from existing fulminant hepatitis patients, but rather from chronic infections. These implicate that the new infections of HBV in adults would drive mutations for higher replicative potential.

Moreover, the characteristics of various genotypes of HBV are also in line with the life history tradeoffs. HBeAg levels are generally inverse to the replicative ability of the HBV viruses.[15] Type A HBV infections usually have a high level of HBeAg, up to 20% type A HBV infections in adult transform to chronic infections in Japan.[20,21] In contrast, type B, C, and D HBV infections in adult cause acute hepatitis and only around 1% transform to chronic infections.[22,23]

Antibiogenesis — the treatment principle of bacteria and virus infections, and chemotherapy of cancer

There is an interesting question concerning the treatment of bacterial infections. Most antibiotics are not bactericidal. They simply inhibit the proliferation of the bacteria. When a bacterial infection gets controlled by application of antibiotics, where have those bacteria that produced before the application of antibiotics gone? I have asked the same question to senior medical students many times, and have gotten the same answer "they were taken care of by the immune system" every time. Medical students and doctors really have a high opinion of the immune system, and think that it is versatile. But if it can do the job of clearing huge amount of bacteria, why does the immune system fail to do it at the beginning of infection when there is much less amount of bacteria?

The key to the answer is that the lifespan of the pathogens in acute infections are very short, from minutes to hours. When antibiotics are applied, the bacteria cannot divide. They come to the end of their life and finally die. But in those infections involving long living microbes, such as *M. tuberculosis*, the treatment requires a long process. We cannot easily kill the microbes inside the body as we can outside the body. What we can do is to block their reproduction, i.e., division of the bacteria and replication of the viruses. I here propose a new term to define the principle of this treatment, "antibiogenesis", which is coined from "anti-" and "biogenesis", indicating the blocking of the production of new lives.

Antibiogenesis can be applied to the treatment of infections of viruses, bacteria, fungi, etc., but not parasites. This principle also extends to the chemotherapy of cancer. We used to think chemotherapy works by killing cancer cells, but in fact chemotherapy works by blocking the proliferation of cancer cells, just as antibiotics do to the bacteria. It hardly does anything to those cells at G0 stage except pushing some of them into proliferation status. Take breast cancer for example, chemotherapy can make the cancer tissue smaller, but it cannot make the breast smaller.

Understanding diseases with the two new concepts

With these two concepts in mind, many clinical and biological phenomena can be connected and easily explained. Short living pathogens can be highly virulent due to their robust fecundity, such *Y. pestis*, *B. perfringens*, viruses of SARS, variola, hepatitis A, etc (Fig. 2, curve A). However, once the body generates resistance such as antibodies and interferons, or when effective antibiotics or antiviral drugs are applied, the infected pathogens soon die out, and the patient will get cured (Fig. 3). This type of pathogen will rarely cause a chronic infection, if it ever could.

Long living microorganisms often have much less amount of pathogens in infection. Many tuberculosis infections are hard to diagnose even in pathological sections. Although the amount of bacteria is so small that it cannot be stained with the common acid-fast staining, it can be detected with the more powerful polymerase-chain reaction technique. For viruses, similar cases can be found in hepatitis C virus and HIV infections. The virus loading is generally very low for both of the infections (Fig. 2, curve C).

The evolution of HIV is a very interesting case of life history tradeoffs. When AIDS was discovered in early days, the death rate it caused was very high. But very soon more people were found to be HIV positive without suffering from the disease. More than 3 decades have passed, and with several rounds of large-scale mutations, HIV becomes more fitted to their new host — the human. Fitting refers to the increased survival and longevity. As a tradeoff,

however, the virus loses in their fecundity. So the virus loading is gradually getting smaller and HIV infection becomes a chronic disease. There exists a possibility that HIV would become more fitted to humans in another few decades or hundreds of years and live harmoniously inside the human body without causing disease, just as it does in monkeys.

Since antibiogenesis is the principle of the treatment of viral and bacterial infections, a long duration of treatment is needed in chronic infections by the long living microorganisms. For example, it takes a few years for the treatment of tuberculosis and decades for the treatment of leprosy. In addition, the same principle also applies to virus infections. It takes a long duration for the anti-virus treatment of HBV, HCV, and HIV infections because of the extreme longevity of their lifespan. After blocking the production of new microbes, we have to wait for the existing microbes to die out naturally. The trick is, the efficiency of antibiogenesis cannot get 100%, so it usually takes many rounds of the pathogen life cycles to gradually eliminate them (Fig. 3).

Summary

As that of large life forms, the lives of microorganisms are also limited by time, the so-called lifespan. It is paramount to be noted that the lifespan is inversely related with the reproductivity, be it large or small the life is. Pathogens with long lifespan proliferate in a slow speed and the caused infections doomed to be a slow process—long latent period, mild symptoms, and a long time for recovery. Reversely, pathogens with short lifespan proliferate explosively and consequently cause acute, severe infections, which could be highly contagious, and may cause pandemics such as influenza, plague, and SARS. Interestingly, when the proliferation of these short-lived pathogens is blocked, which is designed as anti-biogenesis here, all the pathogens soon die out. Therefore, there is hardly a chronic case of plague, influenza or SARS.

Conflicts of interest

The author has none to declare.

Acknowledgement

References

1. SC S. *The Evolution of Life Histories.* London: Oxford University Press; 1992.
2. Fabian D, Flatt T. Life history evolution. *Nat Educ Knowl.* 2012; 3(10):24.
3. Fabrizio P, Gattazzo C, Battistella L, et al. Sir2 blocks extreme life-span extension. *Cell.* 2005;123(4):655—667.
4. Partridge L, Gems D, Withers DJ. Sex and death: what is the connection? *Cell.* 2005;120(4):461—472.
5. Kaeberlein TL, Smith ED, Tsuchiya M, et al. Lifespan extension in *Caenorhabditis elegans* by complete removal of food. *Aging Cell.* 2006;5(6):487—494.
6. Westendorp RG, Kirkwood TB. Human longevity at the cost of reproductive success. *Nature.* 1998;396(6713):743—746.
7. Flatt T, Heyland A. *Mechanisms of Life History Evolution.* Oxford university Press; 2011.
8. Holmes DJ, Fluckiger R, Austad SN. Comparative biology of aging in birds: an update. *Exp Gerontol.* 2001;36(4-6): 869—883.
9. Goldhill DH, Turner PE. The evolution of life history trade-offs in viruses. *Curr Opin Virol.* 2014;8:79—84.
10. Keen EC. Tradeoffs in bacteriophage life histories. *Bacteriophage.* 2014;4(1):e28365.
11. Aktipis CA, Boddy AM, Gatenby RA, Brown JS, Maley CC. Life history trade-offs in cancer evolution. *Nat Rev Canc.* 2013; 13(12):883—892.
12. Wang RA, Ke ZY, Liang Y, Yang T, Qin JH, Wang L. Why is mycobacterium tuberculosis hard to grow? the principle of biorelativity explains. *J Clin Exp Pathol.* 2014;4(3):176.
13. Kane MA, Hadler SC, Lee L, et al. The inception, achievements, and implications of the China GAVI alliance ppoject on hepatitis B immunization. *Vaccine.* 2013;31(Suppl 9):J15—J20.
14. Tong SP. Hepatitis B virus: sequence variability and evolution. *Chin Bull Life Sci.* 2016;28(3):344—356.
15. Buckwold VE, Xu Z, Chen M, Yen TS, Ou JH. Effects of a naturally occurring mutation in the hepatitis B virus basal core promoter on precore gene expression and viral replication. *J Virol.* 1996;70(9):5845—5851.
16. Moriyama K, Okamoto H, Tsuda F, Mayumi M. Reduced precore transcription and enhanced core-pregenome transcription of hepatitis B virus DNA after replacement of the precore-core promoter with sequences associated with e antigen-seronegative persistent infections. *Virology.* 1996;226(2): 269—280.
17. Parekh S, Zoulim F, Ahn SH, et al. Genome replication, virion secretion, and e antigen expression of naturally occurring hepatitis B virus core promoter mutants. *J Virol.* 2003;77(12): 6601—6612.
18. Tsai A, Kawai S, Kwei K, et al. Chimeric constructs between two hepatitis B virus genomes confirm transcriptional impact of core promoter mutations and reveal multiple effects of core gene mutations. *Virology.* 2009;387(2):364—372.
19. Baumert TF, Rogers SA, Hasegawa K, Liang TJ. Two core promotor mutations identified in a hepatitis B virus strain associated with fulminant hepatitis result in enhanced viral replication. *J Clin Invest.* 1996;98(10):2268—2276.
20. Ito K, Yotsuyanagi H, Yatsuhashi H, et al. Risk factors for long-term persistence of serum hepatitis B surface antigen following acute hepatitis B virus infection in Japanese adults. *Hepatology.* 2014;59(1):89—97.
21. Kobayashi M, Suzuki F, Arase Y, et al. Infection with hepatitis B virus genotype A in Tokyo, Japan during 1976 through 2001. *J Gastroenterol.* 2004;39(9):844—850.
22. Imamura T, Yokosuka O, Kurihara T, et al. Distribution of hepatitis B viral genotypes and mutations in the core promoter and precore regions in acute forms of liver disease in patients from Chiba, Japan. *Gut.* 2003;52(11):1630—1637.
23. Zhang HW, Yin JH, Li YT, et al. Risk factors for acute hepatitis B and its progression to chronic hepatitis in Shanghai, China. *Gut.* 2008;57(12):1713—1720.