Clinical & Experimental Pathology

Wang, et al., J Clin Exp Pathol 2014, 4:3
DOI: 10.4172/2161-0681.1000176

Letter to Editor Open Access

Why is Mycobacterium Tuberculosis Hard to Grow? The Principle of Biorelativity Explains

Rui-An Wang*, **Zhen-Yu Ke, Yuan Liang, Tong Yang, Jun-Hui Qin and Li Wang**

Department of Pathology, The Fourth Military Medical University, Xi'an, 710032, China

***Corresponding author:** Rui-An Wang, Department of Pathology and Pathobiology, The Fourth Military Medical University, Xi'an, 710032, People's Republic of China, Tel: 86-29-84779175; E-mail: wangra@fmmu.edu.cn

Rec date: Mar 27, 2014, **Acc date:** May 26, 2014, **Pub date:** May 28, 2014

A Long Time Puzzle in Bacteriology is Why does it Take so Long for Mycobacterium Tuberculosis (MTB) to Grow?

Mycobacteria are notorious for causing two major human diseases: tuberculosis and leprosy. Both are hard to cure, and TB alone causes more than a million deaths each year. Fortunately, they are very slowly growing bacteria.

MTB is difficult to grow *in vitro*. The mycobacterium leprae, which causes leprosy, is even more difficult to study because it has never been successfully grown *in vitro*.

When discussing the difficulties of cultivating MTB, we are accustomed to saying that it is simply picky of culturing conditions. Solid medium, strictly obligate aerobic and highly nutritious conditions are required; yet it still takes more than a month for MTBs colonies to form. If we continue questioning why, it will annoy every one. Yet, the answer may not be that difficult.

It is because MTB lives longer than most other bacteria. The principle of nature in the circle of life reveals that the longer the lifespan, the lower the fecundity. We deem it to be the principle of biorelativity. We have discussed this principle many times in classrooms and nobody had ever come up with an exception.

Comparing the lifespan and the proliferative potential of E. coli and MTB, we see a reverse relationship. E. coli live short, and grow fast. It just takes 18-20 minutes for them to duplicate. Conversely, MTBs live long, are quite tolerant to different environments, and grow so slowly that their duplication time exceeds 18 hrs. The duplication time of mycobacterium leprae is even longer, so that all the cultivation efforts have failed. Although nobody knows exactly how long these bacteria can live since they cannot be cultivated, it can be postulated that they live very long. That explains why leprosy is so difficult to cure.

There are many studies documented the inverse relationship between the lifespan and the fecundity [1], such as in the C. Elegans [2], drosophila [3,4], and mice [5]. Either by diet restriction or gene modification, when the lifespan is extended, fecundity inevitably decreased. This relationship also applies to single cell organisms. For example, the lifespan of yeast is classified as a chronological lifespan (of the mother yeast cell) and replicative lifespan, which is determined by how many daughter cells a mother yeast cell could give rise to. Sir2, a well-known lifespan regulating gene, was found to play a pivotal role in balancing the two types of lifespans of yeast. When Sir 2 was overexpressed, the chronological lifespan extended, while the replicative lifespan which equals the fecundity decreased [6]. In the cultured mammalian cells, when the anti-apoptotic proteins such as Bcl-2 and p202 were over expressed, cell growth was inhibited [7-11]. Reversely, overexpression of the cell death protein such as CD95, and Caspase-3, promoted tumor cell growth [12,13].

Most people agree with our viewpoint that the length of life is the major restriction of fecundity. Species with short lifespans tend to overpopulate to avoid extinction. This relationship holds true from tiny bacteria to human beings. In countries with long life expectancy, population maintains zero or even negative growth. In contrary, we see the most rapid population growth in Africa, where life expectancy is among the shortest in the world currently.

Based on this point of view, it is easy for us to understand why bacteria that have short lifespans tend to cause acute infections, while TB and leprosy cause chronic infections. In acute infections, so far as we can control the proliferation of bacteria, an infection will quickly go away since the bacteria will die very soon. But in chronic infections such as TB and leprosy, it could take many months or even years to get rid of the infections since the mycobacteria live very long and are tough for immune cells to eliminate.

A remarkable pathological feature of TB and leprosy is caseous necrosis. In the typical lesion, numerous epithelioid macrophages and multinucleated Langhans cells are often seen. This type of immune reaction reflects the toughness of these bacteria. Large amounts of macrophages have to be aggregated and then fused into giant cells to deal with the tough germs.

In short, the long lifespan of MTB limits its ability to duplicate and propagate.

Acknowledgement

This work was supported by The National Natural Science Foundation of China, Grant number: NSFC 30971535.

References

1. Partridge L, Gems D, Withers DJ (2005) Sex and death: what is the connection? Cell 120: 461-472.
2. Wu D, Tedesco PM, Phillips PC, Johnson TE (2012) Fertility/longevity trade-offs under limiting-male conditions in mating populations of Caenorhabditis elegans. Exp Gerontol 47: 759-763.
3. Zhan Z, Ding Y, Zhao R, Zhang Y, Yu H, et al. (2012) Rapid functional divergence of a newly evolved polyubiquitin gene in Drosophila and its role in the trade-off between male fecundity and lifespan. Mol Biol Evol 29: 1407-1416.
4. Metaxakis A, Partridge L (2013) Dietary restriction extends lifespan in wild-derived populations of Drosophila melanogaster. PLoS One 8: e74681.
5. Chen YF, Wu CY, Kao CH, Tsai TF (2010) Longevity and lifespan control in mammals: lessons from the mouse. Ageing Res Rev 9 Suppl 1: S28-35.

6. Fabrizio P, Gattazzo C, Battistella L, Wei M, Cheng C, et al. (2005) Sir2 blocks extreme life-span extension. Cell 123: 655-667.
7. Knowlton K, Mancini M, Creason S, Morales C, Hockenbery D, et al. (1998) Bcl-2 slows in vitro breast cancer growth despite its antiapoptotic effect. J Surg Res 76: 22-26.
8. Koul D, Lapushin R, Xu HJ, Mills GB, Gutterman JU, et al. (1998) p202 prevents apoptosis in murine AKR-2B fibroblasts. Biochem Biophys Res Commun 247: 379-382.
9. Yan DH, Wen Y, Spohn B, Choubey D, Gutterman JU, et al. (1999) Reduced growth rate and transformation phenotype of the prostate cancer cells by an interferon-inducible protein, p202. Oncogene 18: 807-811.
10. Choubey D (2000) P202: an interferon-inducible negative regulator of cell growth. J Biol Regul Homeost Agents 14: 187-192.
11. Yan DH, Abramian A, Li Z, Ding Y, Wen Y, et al. (2003) P202, an interferon-inducible protein, inhibits E2F1-mediated apoptosis in prostate cancer cells. Biochem Biophys Res Commun 303: 219-222.
12. Chen L, Park SM, Tumanov AV, Hau A, Sawada K, et al. (2010) CD95 promotes tumour growth. Nature 465: 492-496.
13. Huang Q, Li F, Liu X, Li W, Shi W, et al. (2011) Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. Nat Med 17: 860-866.