



Editorial

The *Lactobacillus* and herpes simplex virus type 2 infection

The presence of *Lactobacillus* species has been thought to be the *sine qua non* of healthy vaginal microbial communities in women during the reproductive age,^{1–3} and much evidence supported the benefits of restoring vaginal microbiomes by application of oral or vaginal probiotic formulations of *Lactobacillus* species might be advantageous in vastly improving women's health and disease prevention, such as bacterial vaginosis, sexually transmitted disease (STD) and possible neoplasms, including cervical intraepithelial neoplasm (CIN) or cervical caners.^{4–7} In March issue of the *Journal of the Chinese Medical Association*, Dr. Mousavi and colleagues published an article addressing the anti-viral effects of *Lactobacillus crispatus* against herpes simplex virus type 2 (HSV-2) in Vero (African green monkey kidney cells) and HeLa cells (human cervical cancer cell line), and the authors found that *L. crispatus* could efficiently inhibit the entry of HSV-2 into both cell lines, and its mechanism might be mediated by formation of *L. crispatus* microcolonies in the cell surface which could block HSV-2 receptors and prevent viral entry to cells in initial infection steps and entrapment of viral particles by direct interaction of *L. crispatus* with HSV-2 envelop.⁸ This study suggested that a physical contact between *L. crispatus* and HSV-2 envelop might be a promising finding, which needs further investigation to provide much evidence for the prophylactic properties of *L. crispatus*. This study is very interesting and worthy of discussion.

First, since the authors supposed that the possible mechanism of the inhibition of HSV-2 infection to mammalian cell lines might be the formation of “barriers” between the virus and targeted cells, it is wondering why the authors used *L. crispatus* as agents for the current study? HSV has been previously considered as one of the possible factors inducing the development of cervical cancer for long time, although the final pathogen was proved as a causative factor—human papillomavirus (HPV).⁹ In the pathophysiology of virus infection, all are initiated from the attachment of the virus to the target cells. Therefore, it is reasonable to believe that the more powerful and “tight” or “ready” attachment ability of these *Lactobacillus* microbiota to the target cells is one of the most important factors to compete with the attachment ability of virus to the target cells. It should be considered to evaluate the anti-HSV-2 effects of the *Lactobacillus* species on the target

cells. Based on this reason, the tight and ready attachment ability of the *Lactobacillus* is important. Since there are so numerous *Lactobacillus* species in nature, the selection of *Lactobacillus rhamnosus* might be a good candidate, because *L. rhamnosus* attached more readily to the HeLa cells than did the other *Lactobacillus* species.¹⁰ However, the authors did not explain the reason.

We supposed the possible reasons, as shown below. In terms of considering to be successful in the selection of strategies to prevent the occurrence of diseases, “popularity” and “easy-to-use” might be a key factor. The authors' previous study provided a good rationale for this. At first, the authors have identified *L. crispatus* as the most common *Lactobacillus* species in the vaginal of Iranian healthy women.¹⁰ In addition, some studies showed *L. crispatus* is good for women's health, and *L. crispatus*-dominated cervicovaginal microbiota formula treatment can provide a better healthy environment of the lower genital tract in women.¹¹ Furthermore, the *L. crispatus*-dominated formula do not disturb the normal balance of vaginal microbiomes. That is to say that it will not result in dysbiosis.¹¹ Moreover, the study showed that the *L. crispatus*-dominated formula was associated with lower prevalence of STD.¹¹ Furthermore, the HPV study showed that *L. crispatus* supernatants could decrease expression of autophagy related 14 and beclin 1 and inhibit the HPV early 6 oncogene activation on the cell lines.¹¹ Based on the above finding, the similar thinking process can be applicable for the anti-HSV-2 study. All supported the use of *L. crispatus* as agent to study anti-HSV-2 infection of mammalian cells in the current study.

Besides above, the other consideration is how much (amount) of these microbiota is enough for the healthy women. Much more “covering areas” for the surface of target cells (for example, epithelial cells of the lower female genital tract, such as vagina and cervix) by these microbiota are believed to produce much more effective “blockage” of the virus (HSV-2) to attach these target cells. A decreasing relative abundant of *Lactobacillus* species is positively correlated with a severity of CIN.¹¹ An elevated proportion of *L. crispatus* is often found in samples from women with normal Papanicolaou cytological examination, especially for those women without HPV infection.¹²

Taken together, although the current study is promising and interesting, there is a still big gap in the development of

effective preventive approaches to improved women's health. The normal distribution of *Lactobacillus* species within the healthy women is still uncertain. A scientific level understanding how the microbiota is associated with global health remains problematic and deficient.¹³ It is still unknown what species of *Lactobacillus* species are of most importance, which should be included in the probiotic formulations.¹⁴ One study favored the multiple strains probiotics, because these combinations of multiple strains appear to be the most feasible and effective strategy for the prevention of necrotizing enterocolitis (NEC) and reduction of mortality in these preterm very low birth weight infants.¹⁵ Multiple strains probiotics were associated with a marked reduction in the incidence of NEC, with a pooled odd ratio (OR) of 0.36 (95% confidence interval (CI) 0.24–0.53).¹⁵ By contrast, single strain probiotic using *Lactobacillus* species had shown a marginal effect in reducing NEC (OR 0.60; 95% CI 0.36–1.0).¹⁵ In terms of studying the effect in mortality reduction, multiple strains probiotics also showed a greater effectiveness in reducing mortality (OR 0.58, 95% CI 0.43–0.79).¹⁵ All suggested that more studies focusing on human microbiomes and searching for the best probiotic combination formula are encouraged and microbiomes may be an important research area in the future.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Acknowledgments

This article was supported by grants from the Ministry of Science and Technology, Executive Yuan (MOST 106-2314-B-075-061-MY3), and Taipei Veterans General Hospital (V106C-129; V106D23-001-MY2-1; and V107C-136).

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