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Developing a Lactobacillus-Based Vaccine for Tuberculosis

Tuberculosis (TB), the human disease caused by Mycobacterium tuberculosis that has killed many millions of people during at least the last 200 years, is still with us. Researchers at NMBU are making progress on a TB-vaccine based on surface antigen presentation on cells of Lactobacillus plantarum (1).

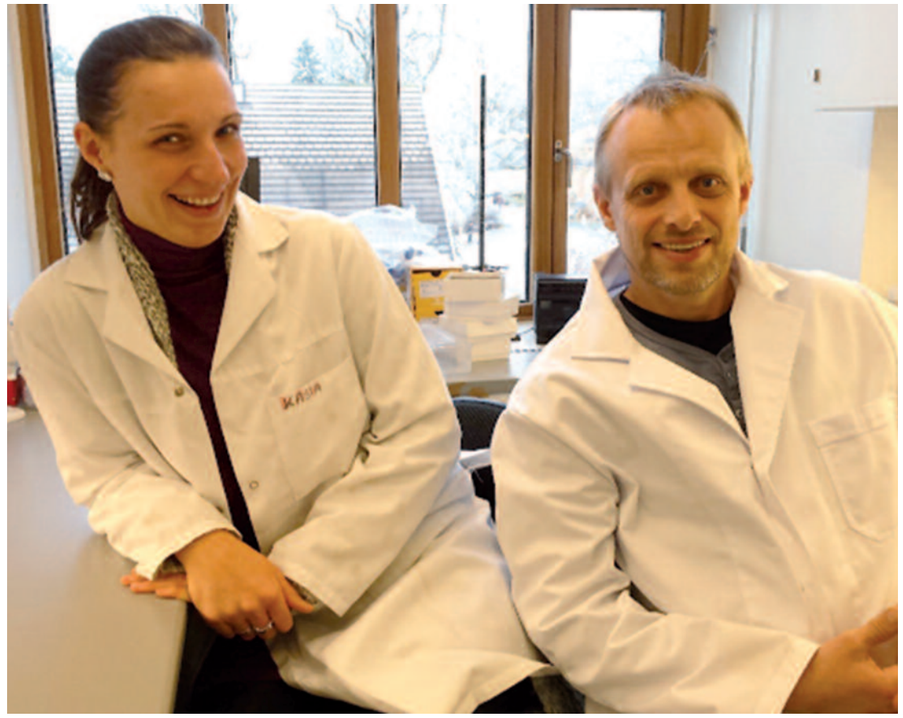
According to the World Health Organization (WHO), over 10 million people become ill with TB every year, resulting in about 2 million deaths. TB is one of the top 10 causes of death worldwide, ahead of both malaria and AIDS. An international project coordinated by WHO has as its goal a 90% reduction in world TB deaths by the year 2030. To accomplish this, new antibiotics are being screened for TB treatment and at least 13 different projects for TB vaccine development are ongoing worldwide (2). The so-called bacille Calmette-Guerin vaccine (BCG) for TB, based on an attenuated form of Mycobacterium bovis, was developed over 100 years ago but it is only effective against TB in children, not in adults.

At NMBU, researchers are developing a vaccine based on ingesting modified Lactobacillus plantarum that display M. tuberculosis antigens on its cell surface. Using Lactobacillus spp. as bioagents is interesting for several reasons: 1) they are considered to be safe for oral consumption, 2) they are natural inhabitants of the human gastrointestinal tract and 3) they can interact with immune cells.

The first step in this research involved constructing expression casettes to display Mycobacterium tuberculosis antigens (a fusion protein referred to as AgE6 which is composed of sequences from 2 different immunogenic proteins) on the surface of Lactobacillus plantarum cells. This was accomplished in two different ways using strategies similar to those used in earlier research at NMBU (3, 4) to produce Lactobacillus plantarum with cell-surface invasin or oncofetal antigen; namely, 1) by fusing AgE6 with a lipoprotein anchor sequence that directs AgE6 to the outside of the cell membrane or 2) by fusing AgE6 to a cell wall anchor sequence that directs AgE6 the cell wall peptidoglycan. Surface localization of AgE6 was then confirmed using immunofluorescence.

Figure 1 shows one of several experiments, demonstrating the immunogenic activity of AgE6-producing Lactobacillus plantarum. In this case, mice were immunized orally with different treatments, after which time the frequencies of AgE6-specific IFN-γ-secreting spleen cells were scored. Lactobacillus with cell membrane-directed AgE6 gave significantly higher frequencies compared to controls.

The immunogenic results with AgE6 directed to the cell-surface of Lactobacillus plantarum are small but they are significant and, therefore, are promising. Quoting from their paper, 'This study suggests that L. plantarum may have potential as a vector for delivering M. tuberculosis antigens to mucosal sites, which may be an approach in future TB vaccine development.'



Katarzyna Kuczkowska and Geir Mathiesen.

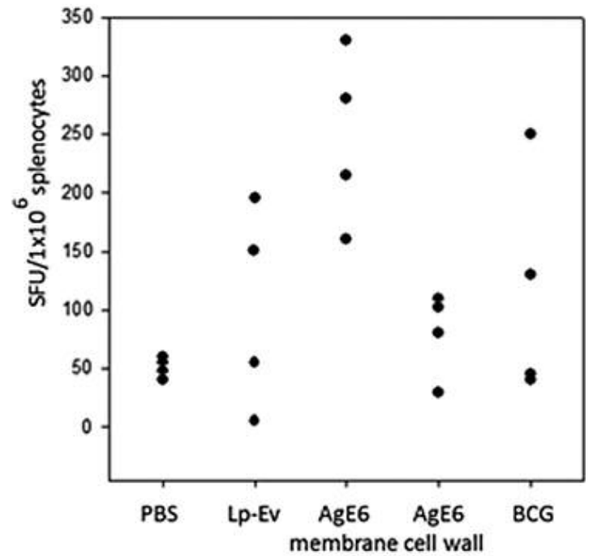


Fig. 1. Immunogenic potential of Lactobacillus-based TB vaccines, measured as frequency of AgE6-specific IFN-γ-secreting splenocytes (expressed as SFU/1 x 106 splenocytes, cf. reference 1 Methods) isolated from mice immunized orally with the following vaccine candidates: PBS, phosphate saline buffer negative control; Lp-EV, negative control, unmodified Lactobacillus plantarum; AgE6 membrane, antigen displayed on cell membrane; AgE6 cell wall, antigen displayed on cell wall; BCG, bacille Calmette-Guerin vaccine. Each point represents one mouse (N=4 mice per treatment). Figure is redrawn from data in ref. 1.

References

1. Kuczkowska, K et al.: Immunogenic properties of Lactobacillus plantarum producing surface-displayed Mycobacterium tuberculosis antigens. Appl Environ Microbiol 83 (2017) e02782-16

2. WHO: Global tuberculosis report. World Health Organization, Geneva, Switzerland. (2016) 201 pp.

3. Fredriksen L, et al.: Appl Environ Microbiol 76 (2010) 7359

4. Fredriksen L, et al.: Appl Environ Microbiol 78 (2012) 5864