New strategies for an old problem – Oral vaccines research

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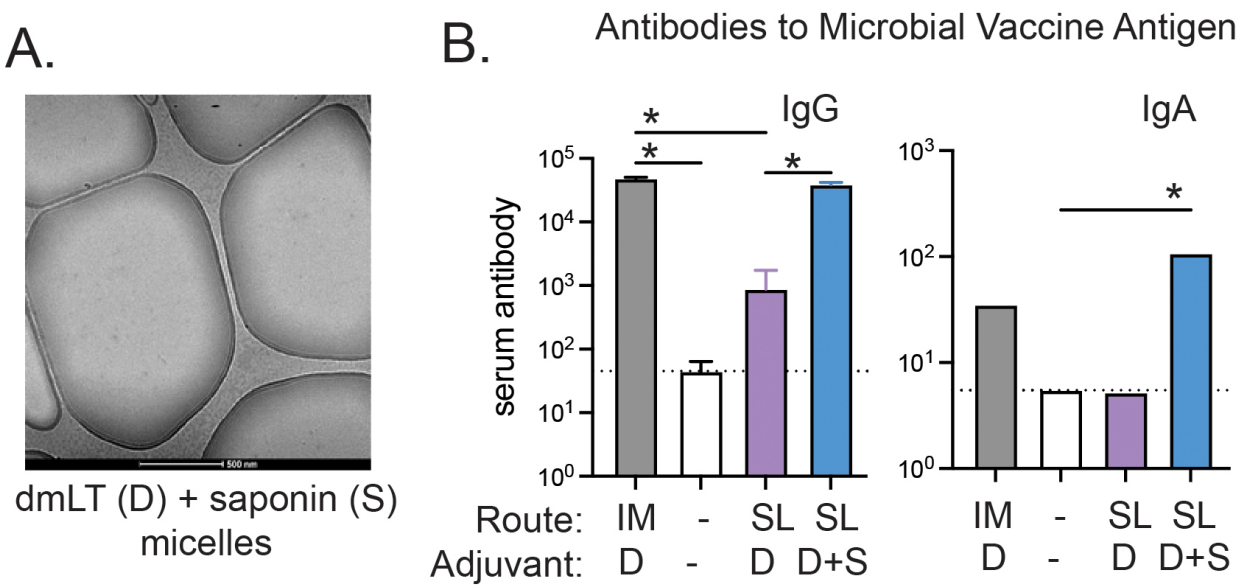

Figure 1. Systemic immune responses elicited by oral dmLT-saponin combinations compared to injected vaccines (A) Cryo-electron microscopy (cryo-EM) image of the dmLT and saponin formulation demonstrating the formation of acid-stable micelle particles upon the addition of saponin to dmLT. (B) Preclinical evaluation of systemic serum IgG and IgA antibody responses following prime/boost vaccination. Antibody levels against the microbial protein antigen included in the vaccination were assessed two weeks post-final vaccination in immunized mice. Groups were stratified by vaccination route (intramuscular [IM] or sublingual [SL]) and adjuvant formulation (dmLT [D] and/or saponin [S]). Comparisons with unvaccinated controls (white bars) are shown. Statistical significance between groups is indicated (*P < 0.05), with the SL D+S group achieving the best IgG and IgA responses to vaccine antigen.

Despite their advantages, oral vaccines encounter several challenges. Professor Elizabeth Norton from Tulane University discusses how her team is addressing these issues and their research on developing and testing dmLT and saponin combination adjuvants

The gut is home to a remarkable concentration of the body's immune cells, particularly antibody-secreting plasma cells. It serves as a critical site for interactions with microbes, exposure to pathogens, and maintaining overall health. Globally, several human vaccines leverage oral delivery routes due to their ability to stimulate mucosal immunity and suitability for mass immunization campaigns. [(1)] Notable licensed oral vaccines include live-attenuated vaccines for polio, rotavirus, Salmonella typhi, and adenovirus, as well as whole-inactivated vaccines for cholera. These vaccines offer additional benefits, such as eliminating the need for syringes and needles. This is particularly valuable in resource-

limited settings, where needle reuse can lead to accidental transmission of bloodborne infections like HIV and hepatitis, and it also mitigates needle-related aversion among individuals.

Challenges of oral vaccines

Despite these advantages, only a small fraction of the vaccines in use today employ oral delivery. Remarkably, none of these are subunit vaccines, which are generally safer and less reactogenic than live-attenuated or whole-killed formulations. Oral vaccines face several challenges, [1] including the physiology of the gastrointestinal tissue, difficulty inducing robust systemic immunity alongside mucosal responses, limited duration of immunity, and reduced efficacy in developing countries due to factors such as environmental enteropathy, malnutrition, and maternal antibody interference.

Alternative oral delivery strategies, such as buccal or sublingual delivery, are being explored to address these challenges. These routes, while still targeting the gastrointestinal system, are still in experimental stages but may offer advantages for antigens that degrade in the gastrointestinal tract or in cases where microbial dysbiosis hinders immune responses in the intestines. Another promising avenue lies in the use of adjuvants, which can enhance immune responses and improve vaccine efficacy.

dmLT (double-mutant heat-labile toxin)

Our group has been at the forefront of developing and testing dmLT (double- mutant heat-labile toxin), a genetically detoxified derivative of E. coli heat-labile toxin (LT). With two mutations (R192G and L211A) that reduce toxicity while preserving strong immunostimulatory properties, dmLT stimulates both mucosal and systemic immunity. [2-3] Notably, it is effective across multiple delivery routes, including oral, buccal, and sublingual. Preclinical studies have demonstrated its efficacy in vaccines targeting pathogens such as ETEC, Shigella, polio, and HIV, among others. Importantly, dmLT is versatile, pairing successfully with live-attenuated, whole-killed, and subunit antigens. In animal models, dmLT-adjuvanted vaccines have shown protective immunity, reducing microbial colonization and disease severity.

Clinical studies have also confirmed dmLT's safety and effectiveness across sublingual, oral, and injectable routes. However, its success with oral vaccines has so far been limited to two candidates, ETVAX and ACE527 (both targeting ETEC), [3] neither of which employs a subunit antigen approach.

dmLT-saponin adjuvant

To address the enduring challenge of developing effective subunit oral vaccines, we have begun exploring innovative combined adjuvant approaches. One of the most promising strategies involves combining dmLT with saponin adjuvants. [4] Derived from plant glycosides, particularly the bark of Quillaja saponaria, saponin adjuvants are amphiphilic molecules that can form micelles. Saponin-derived adjuvants are already included in licensed injectable vaccines, such as those for malaria and shingles. [5] In recent studies

using preclinical models, we find that sublingual formulations combining dmLT, saponin adjuvants, and protein antigens can induce systemic and mucosal immunity comparable to – or even surpassing – levels achieved by dmLT alone or by injectable routes (see Figure 1). This groundbreaking finding offers an exciting new platform for revitalizing oral vaccination strategies, particularly when combined with temperature-stable delivery formats like dissolvable tablets or swallowable pills.

References

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