VACCINATION

Oral vaccine induces genitorectal immunity

Genitorectal mucosal surfaces are key transmission sites for viruses, and the presence of antigen-specific $CD8^+$ cytotoxic T cells in the mucosa can protect against HIV and other sexually transmitted virus infections via this route in humans. Although protective immunity has been induced in animal models by intracolorectal vaccination, this route is clinically impractical. Reporting in *Nature Medicine*, Zhu *et al.* now show that a new oral vaccine can control genitorectal viral infection.

Previous attempts at oral delivery of vaccines to protect genitorectal mucosa have failed because of destruction of the vaccine in the upper gastrointestinal tract and probably also inadequate antigen uptake in the large intestine. To circumvent these problems, the researchers encapsulated their protein or peptide antigens, as well as Toll-like receptor ligands as vaccine adjuvants, in PLGA (poly(D,L-lactic-co-glycolic acid)) nanoparticles. The PLGA nanoparticles were then coated with either the anionic tripolymer Eudragit FS30D or Eudragit L100-55, which differentially protect the nanoparticles from the denaturing conditions of the upper gastrointestinal tract.

Having shown that these nanoparticle vaccines induced an antigen-specific T cell response when delivered directly to the colon of mice, the authors explored the efficacy of their oral administration. Uncoated and L100-55-coated PLGA nanoparticles were mostly delivered to the small intestine, whereas FS30D-coated PLGA nanoparticles were predominantly taken up by cells in the large intestine. Two oral immunizations, 2 weeks apart, of the FS30D-coated PLGA nanoparticles led to the induction of antigen-specific $CD8^+$ T cells in the colorectum. By contrast, uncoated and L100-55-coated PLGA nanoparticles primarily induced a T cell response in the small intestine. Therefore, these vaccines can induce immune responses in specific compartments of the gut mucosa.

So, can the large intestine-targeting vaccine provide protection against genitorectally transmitted viruses? To test this, Zhu *et al.* immunized mice orally with FS30D-coated PLGA nanoparticles containing an HIV envelope peptide and then challenged the mice rectally or intravaginally with a recombinant vaccinia virus expressing the HIV envelope protein. In both scenarios the oral vaccine induced a T cell response and reduced viral loads almost as well as when the animals were vaccinated via the intracolorectal route.

Next, the researchers immunized mice with whole vaccinia proteins encapsulated in FS30D-coated PLGA nanoparticles before challenging them with a pathogenic vaccinia strain, to see whether they could induce protective antibody responses. Indeed, this vaccine given orally induced vaccinia-specific IgA and IgG antibody responses in both the large intestine and vaginal tract and protected the animals from lethal vaccinia virus infection.

These data show that oral vaccination targeted to the large intestine can be as effective a strategy against viral infection of rectal and vagina mucosal sites as intracolorectal vaccination, with the advantage of being clinically applicable. In addition, the researchers' novel nanoparticle-releasing system has other potential applications, such as in vaccines against non-viral pathogens or possibly in cancer vaccines for mucosal malignancies. Their system is also likely to be a useful tool for further study of how immune responses are compartmentalized along the gastrointestinal tract.

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ORIGINAL RESEARCH PAPER Zhu, Q. *et al.* Large intestine-targeted, nanoparticle-releasing oral vaccine to control genitorectal viral infection. *Nature Med.* **18**, 1291–1296 (2012)
FURTHER READING Lycke, N. Recent progress in mucosal vaccine development: potential and limitations. *Nature Rev. Immunol.* **12**, 592–605 (2012)