Vaccination against periodontitis

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Prevention of disease, in this case chronic periodontitis, is always better than cure. Developing a vaccine for periodontal infections is the hot subject for periodontal researchers. The old dogma was that the role of vaccination is to induce a humoral immune response, meaning protection by the production of memory B cells and antibodies against the pathogen. This dogma however is too simple. Recent evidence suggests that immunization can modulate the host response and shift the response, a key element in successful protection. The nature of the cellular response and which molecules are secreted by the site of these cells are critical to disease processes, as well as protection.

What is the process of developing a vaccine? First, we have to identify the key pathogens, and then identify and isolate virulence factors from the pathogens as candidate antigens. The candidate vaccine should be tested first in preclinical models followed by safety and efficacy tests in humans.

Eighteen years ago, a research group headed by Roy Page from Seattle was the leader in periodontal vaccination research. They vaccinated primates with whole-cell P. gingivalis, and demonstrated partial protection against experimental periodontitis. Interestingly, they found that the levels of specific antibodies against P. gingivalis were high in all animals that were exposed to the bacteria, immunized and non-immunized, and antibody production was not able to explain the protection achieved.

From then on, significant efforts were made in identifying molecules that are virulence factors and may serve as good candidates for vaccine development, with most researchers concentrating on molecules derived from P. gingivalis. Some of these proteins were isolated and used for immunization studies. Many investigators focused on a specific group of important enzymes – cysteine proteases, which are considered to be essential for P. gingivalis survival and for disease pathogenesis.

Modern molecular biology offers new approaches in making vaccines by cloning genes from bacteria, expressing the protein antigen in other bacteria in culture and isolating the pure protein in the laboratory. This makes the preparation safer and easier to prepare. Professor Mike Curtis from the Queens Mary University of London has cloned a gene containing the code for the adhesive part of an important cysteine protease of P. gingivalis, rgpA. The vector in bacteria was expressed by our own Dr. Asaf Wiznisky, who produced a recombinant peptide and used it in vaccination experiments with mice, in which periodontitis was induced by inoculation of P. gingivalis, and bone loss was assessed using micro-CT.

A recent hypothesis is that targeting P. gingivalis may have a community-wide impact on the flora, and may be important for preventing chronic periodontitis.

“...we still lack data from clinical trials in animals...”

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Modern molecular analyses and in particular next-generation sequencing (NGS) techniques have revolutionized oral microbiology. Being able to analyze all oral bacteria, the oral microbiome, is of particular relevance and importance because it is well known that micro-organisms cooperate collectively in a polymicrobial ecosystem, causing chronic oral infections, such as periodontitis.

Studies of cultivable sub-gingival micro-organisms had already shown that the predominant bacteria in periodontal lesions are Gram-positive facultative rods and cocci. In periodontitis, there is a decrease in the number of these “healthy” organisms and an increase in the number of “pathogenic” Gram-negative rods and spirochetes.

Indeed, culturing sub-gingival micro-organisms has provided considerable knowledge on the pathogenic bacteria associated with periodontitis, but unfortunately this has been limited by the fact that it focuses (by definition) on cultivable micro-organisms. As has been underlined frequently in the past, many oral bacteria cannot be cultivated and therefore conclusions are drawn on an incomplete picture. With this in mind, and because scientists started to realize that the polymicrobial ecosystem actively sustains oral health, even before NGS, molecular microbial analyses had been developed, which give a better, more complete overview of the oral microbial ecology in health and during disease.

Many molecular microbial analyses have been targeted at a selection of (pathogenic) micro-organisms, but only open-ended approaches, where there is no selection for specific species to be detected, can be used for oral microtome studies.

The open-ended approach that has been most widely used for oral microbial communities and oral infections in clinical trials is through a culture-clone-library approach. Indeed, by using this technique, several uncultivated bacteria have been identified and have been associated with periodontitis, but after the first NGS study in which several orders of magnitude (i.e. millions) bacterial 16S DNA codes were analyzed, it became clear that so far we had only explored the tip of the iceberg.