

RESEARCH SPOTLIGHT

TRANSLATING SCIENCE TO PRACTICE



Looking Beyond Periodontitis

SOME PEOPLE MIGHT think that the idea of studying gum disease for insights into diseases such as multiple sclerosis is rather odd. To George Hajishengallis, it's a springboard into entirely new realms of cutting-edge research with implications far beyond dental science.

"Basically I'm interested in understanding the inflammatory mechanisms that drive periodontitis," says Dr. Hajishengallis, Penn Dental Medicine's Thomas W. Evans Centennial Professor in the Department of Microbiology. But as he explains, those mechanisms are actually a gateway into a much broader range of questions. For years, the conventional wisdom held that the main culprit in periodontal disease was the bacterium *Porphyromonas gingivalis*. But matters are far more complicated — and interesting — than that.

Dr. Hajishengallis found that *P. gingivalis* is a "keystone pathogen," meaning that its presence is key to setting the stage for other pathogens to act. To survive and feed, the bacterium exploits the functioning of complement, the oldest part of the innate immune system, by hijacking certain receptors on white blood cells. That subversion of the immune system benefits not just *P. gingivalis* but a wide range of other bacteria

living in the mouth, since the inflammatory responses mediated by the immune system also create food for them. When *P. gingivalis* disrupts those processes, inflammation goes wildly out of control.

The result is a dysbiotic "vicious cycle" in which greater inflammation leads to larger numbers of bacteria, which produce still more inflammation, creating fertile ground for periodontitis to attack the tooth-supporting tissues. "One may consider periodontitis as the side effect of the effort of the bacteria to get their food," explains Dr. Hajishengallis. "And the tissue damage, the disease we see from our perspective, is the collateral damage."

To stop *P. gingivalis* from derailing the body's normal defenses, Dr. Hajishengallis and his research team have taken several approaches. One involves targeting the C3 component of complement, which is a main player in cell signaling pathways that trigger inflammation and activate the immune system. By blocking C3 with the complement inhibitor drug compstatin, Dr. Hajishengallis, in collaboration with Dr. John Lambris of Penn Medicine, has been able to stop or prevent inflammatory periodontal bone loss in their two study models, and has

achieved similar success in mice by targeting two protein receptors, C5aR and TLR-2. By blocking these receptors on white blood cells, their effectiveness to defend against *P. gingivalis* was restored.

Another effective strategy evolved from Dr. Hajishengallis' prior work at the University of Louisville studying the relationship between aging and periodontitis. He found a particular gene called Del-1 showed significant downregulation in gingival tissues of older animals. "But unfortunately, we knew nothing about Del-1 and there was very little literature about it," he remembers.

He would get a break several months later at a scientific conference. Dr. Triantafyllos Chavakis, then at the National Cancer Institute of the NIH, presented work on Del-1 showing it as a key regulator of white blood cell recruitment from the bloodstream. "After I saw that, I realized this is the answer," says Hajishengallis. "Perhaps decreased levels of Del-1 with old age explained their greater tendency to develop inflammation and periodontitis."

He soon confirmed that Del-1 knockout in mice indeed resulted in periodontitis, not only in older but even in younger animals. He and Dr. Chavakis, now at the University of Dresden, Germany, "recently showed that Del-1 is important not only in periodontal disease but also in multiple sclerosis, with a very similar mechanism." With Del-1 also implicated in other diseases associated with inflammatory processes, Dr. Hajishengallis is presently investigating therapeutic possibilities.

For a dentist turned researcher such as Dr. George Hajishengallis, such an outcome represents the best of both worlds. After all, he notes, "we are awarded grants by the NIH not only to satisfy our scientific curiosity and discover new mechanisms — which is very important — but mainly to serve patients. So once we have something that seems to be promising from a translational point of view, we want to see whether we can have a therapeutic approach." ■