Research News

Research Team Discovers Quorum-Sensing Signal in *Pseudomonas aeruginosa*

Prior to joining the faculty of the Department of Surgery and his appointment as Instructor in Surgery at HMS, Arunava Bandyopadhaya, Ph.D., was a postdoctoral fellow in Dr. Laurence G. Rahme's Molecular Surgery Lab. One key area of ongoing investigation Dr. Bandyopadhaya has been studying is understanding how bacterial quorum sensing helps pathogens evade elimination by host innate immune responses.

Bacterial cells communicate and synchronize themselves by excreting chemicals (signaling molecules) that permit bacterial populations to function as a group. Through a process called quorum-sensing (QS), the bacteria are able to respond in unison and to control the expression of specific genes when the population reaches critical mass, leading to phenotypes that are beneficial for pathogen survival. Although immune-driven resistance is the host's prevailing defense strategy against infection, organisms (plants and animals, including humans) can also defend themselves by establishing "tolerance" to invading pathogens, thereby limiting pathogen damage without affecting host fitness or controlling pathogen burden. Drs. Bandyopadhaya, Tsurumi and Rahme (first, second and senior authors, respectively) have recently identified a QS signaling molecule secreted by *P. aeruginosa* that promotes host "tolerance" training. Their paper received advanced online publication in *Nature Microbiology* (Bandyopadhaya et al., A quorum-sensing signal promotes host tolerance training through HDAC1-mediated epigenetic programming. Nature Microbiol. 2016 Oct 3;1:16174. doi: 10.1038/nmicrobiol.2016.174).

The paper describes the first demonstration of a bacterial QS molecule that acts as a critical mediator (training agent) of host-tolerance/resilience against bacterial pathogens. It is the first published work to show that QS molecules, such as 2-aminoacetophenone (2-AA), train the host to tolerate high bacterial burdens via epigenetic reprogramming, thereby increasing host survival. The novel mechanistic insights described in this publication may prove to be enormously valuable for developing preventive treatments that allow hosts to become resilient to some types of pathogen-elicited damage. Moreover, the findings have the potential to revolutionize our view of host defense and immunologic memory and may lead to new classes of vaccines and immunotherapies which could a have broad impact on human

Arunava Bandyopadhaya Ph.D.
Instructor in Surgery, Harvard Medical School

health. Since QS molecules are shared widely across various bacterial species, and microbes are commonly found in polymicrobial settings, it is likely that 2-AA or 2-AA-like bacterial molecules promote similar effects in mono- and polymicrobial settings. Indeed, the Rahme laboratory has shown that 2-AA affects other gram-negative bacteria as well. Additional published and unpublished works have linked the epigenetic reprogramming Dr. Rahme and her research team have identified with metabolic changes that also involve mitochondrial dysfunction. Such links may open avenues for new areas of research and provide a solid understanding of pathogen-elicited epigenetic changes. This knowledge may aid the understanding of host resilience and immunologic memory at large, including resilience to commensals (i.e., one organism living on or within another organism and deriving benefit without harming or benefiting the host).

The Molecular Surgical Lab is bridging basic and clinical sciences to address the current antibiotic resistance epidemic. *P. aeruginosa* is a common, difficult-to-treat, human opportunistic pathogen and is resistant to most antibiotics. Dr. Rahme has been recognized internationally for her pioneering use of this pathogen to develop anti-virulence drugs that block pathogenesis but not cell viability. Discovering the mechanism by which 2-AA essentially "trains" the immune system to allow the continued presence of the bacteria without initiating a damaging uncontrolled inflammatory response is a significant finding that could lead to new treatments and minimize the effects of antibiotic resistance. According to Dr. Rahme, the findings are "unprecedented in that we have identified a specific bacteria-excreted molecule that acts as a host-tolerance/

Laurence G. Rahme, Ph.D.
Associate Professor of Surgery, HMS

resilience training agent. These new insights may prove useful for developing preventive strategies to train host immune systems to become safely tolerant to pathogens and could provide avenues for novel therapeutic interventions against bacterial infection."

The publication of this research represents the fruits of a winning mentor/mentee relationship. Lead author, Dr. Bandyopadhaya, is a host-pathogen biologist with a comprehensive background in microbiology, molecular biology, biochemistry, genetics, small-molecule biology, and immunology. He sought out Dr. Rahme as a mentor because of her groundbreaking research in bacterial regulatory systems that govern virulence, including the *P. aeruginosa* QS transcription factor MvfR, which she identified in 2001 (Rahme et al., *Proc. Natl. Acad. Sci. USA*). Dr. Bandyopadhaya is working to obtain knowledge that can be applied towards the development of host-protective interventions that target critical cell signaling pathways. In 2015, while he was a postdoctoral fellow, Dr. Bandyopadhaya won the Scientific Advisory Committee (SAC) Distinction Award, under Dr. Rahme's mentorship, for his research paper "A quorum sensing signal promotes host tolerance training through chromatin modifications." According to Dr. Bandyopadhaya "host tolerance training" mechanisms might be as important as those conferring immune-driven resistance. His work has already earned substantial national recognition.

As Dr. Lillemoe expresses, "It is difficult to understate the benefit the Department of Surgery, and ultimately our patients, derive from the scientific output produced by a strong mentoring relationship, and the work that Drs. Rahme and Bandyopadhaya are doing is a stellar example."

Research Resident Awarded Two-Year NIH/NCI NRSA Fellowship

Over the next two years, Dr. Zhi Ven Fong (principal investigator) will study the impact of volume-based regionalization on access to care in patients undergoing pancreatectomy. It is long established that hospital volume is inversely correlated with surgical mortality rates for complex surgeries. Since the popularization of this concept, a strong case has been made for volume-based regionalization of care. However, while limitations on complex procedures, like pancreatectomy, may improve patient outcomes, they may also produce unforeseen consequences detrimental to patient care. In the past year, three major health systems (Johns Hopkins Medicine, University of Michigan, and Dartmouth-Hitchcock Medical Center) have imposed minimum volume standards that will bar hospitals and surgeons from performing pancreatectomy unless they meet threshold requirements (20 cases/year for pancreatectomy). These institutions are pushing other health systems to follow suit.

The potential impact of this strategy on patient preferences and access to care is unclear. Although pancreatectomy exhibits the highest association between volume and mortality rates, and as such, stands most likely to gain from this policy, up to 70% of patients already do not receive surgical intervention for resectable pancreatic cancer (Bilimoria KY, Bentrem DJ, Ko CY, Stewart AK, Winchester DP, Talamonti MS. National failure to operate on early stage pancreatic cancer. Ann Surg. 2007 Aug;246(2):173-80.). The size of this cohort can be hypothesized to be attributed to two factors: the nihilism that has developed toward this disease and the complexity of the operation one needs even to hope for a favorable long-term outcome. Moreover, the bulk of this cohort is disproportionately comprised of racial minorities, patients on Medicaid, and the uninsured. Preliminary data (accepted for publication, *Surgery* 2017) show that this vulnerable cohort tends to travel shorter distances for pancreatectomy and to undergo surgery at hospitals of poorer quality. While the focus on quality is important, there is a legitimate concern that patients in lower income groups will be further disadvantaged by this policy.

During his NRSA fellowship, Dr. Fong will assess the potential impact of the proposed low-volume mandate on access to care in patients undergoing pancreatectomy. Specifically, the study will quantitatively assess the impact of "distance traveled by patients" on overall mortality rates in a setting where all patients are redirected to high-volume centers, in comparison with a simulated setting where patients with lower likelihood of traveling do not receive care. Dr.