Invertible Promoters Mediate Bacterial Phase Variation, Antibiotic Resistance, and Host Adaptation in the Gut (Jiang, et.al.)

A Summary by Katie E Golden, MD

The gut microbiome, and its impact on human health and disease, is gaining traction in the research and medical community as an exciting potential for future therapeutics. Disease prevention and advanced therapies will rely on a fundamental understanding of the bacterial mechanisms that guide gut colonization. In a newly published study by Jiang et.al. in *Science,* researchers examine bacterial and host interactions with a fresh lens, and take a closer look at how a mechanism called phase variation guides bacterial adaptation and colonization in the human gut.

Phase variation is a process by which bacteria alter their genetic transcription, introducing diversity into bacterial populations to promote fitness and survival in a dynamic environment. This mechanism is possible because of regions of DNA, called invertons, that can switch between two different transcriptional states in a reversible fashion. This is a poorly understood, but evolved mechanism that allows for successful pathogenic infection and commensal colonization alike. In this study, researchers sought to understand both the prevalence and functionality of phase variation. They first developed an algorithm (PhaseFinder) to identify these invertons across a variety of bacterial species, and then subsequently investigated how these specific regions of DNA regulated genetic function to promote colonization.

The investigators detail several important observations in their published study. First, their novel approach to systematically identifying invertons with PhaseFinder definitively established the prevalence of these DNA regions across varied bacterial phyla, and furthermore, they noted an enrichment specifically in host-associated species. Second, when these regions are turned 'on' and actively transcribed, they are functionally engaged in biosynthesis of proteins expressed on outer surface membranes. These cellular components are responsible for the bacteria's interaction with host immune cells, which confers bacterial fitness in the setting of, for example, host immunity or antibacterial treatment.

One of the most important findings from their research was a characterization of how invertons regulate antibiotic resistance genes. From *in vivo* investigations in humans, they found that treatment with antibiotics increased expression of inverton-associated antibiotic resistance genes. The transcription of these genes was subsequently 'turned off' after completion of antibiotic treatment, presumably to conserve the fitness cost from continuous expression of these genes. As explained by the researchers, the invertons function as 'catastrophic insurance', preserving a portion of the bacterial population that is ready to resist antibiotic treatment and promote phenotypic heterogeneity for population survival. Their study lends important insight into the adaptive mechanisms employed by gut microbiota in response to host and environmental changes.