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Dr. Holger Sondermann featured on Cornell Research

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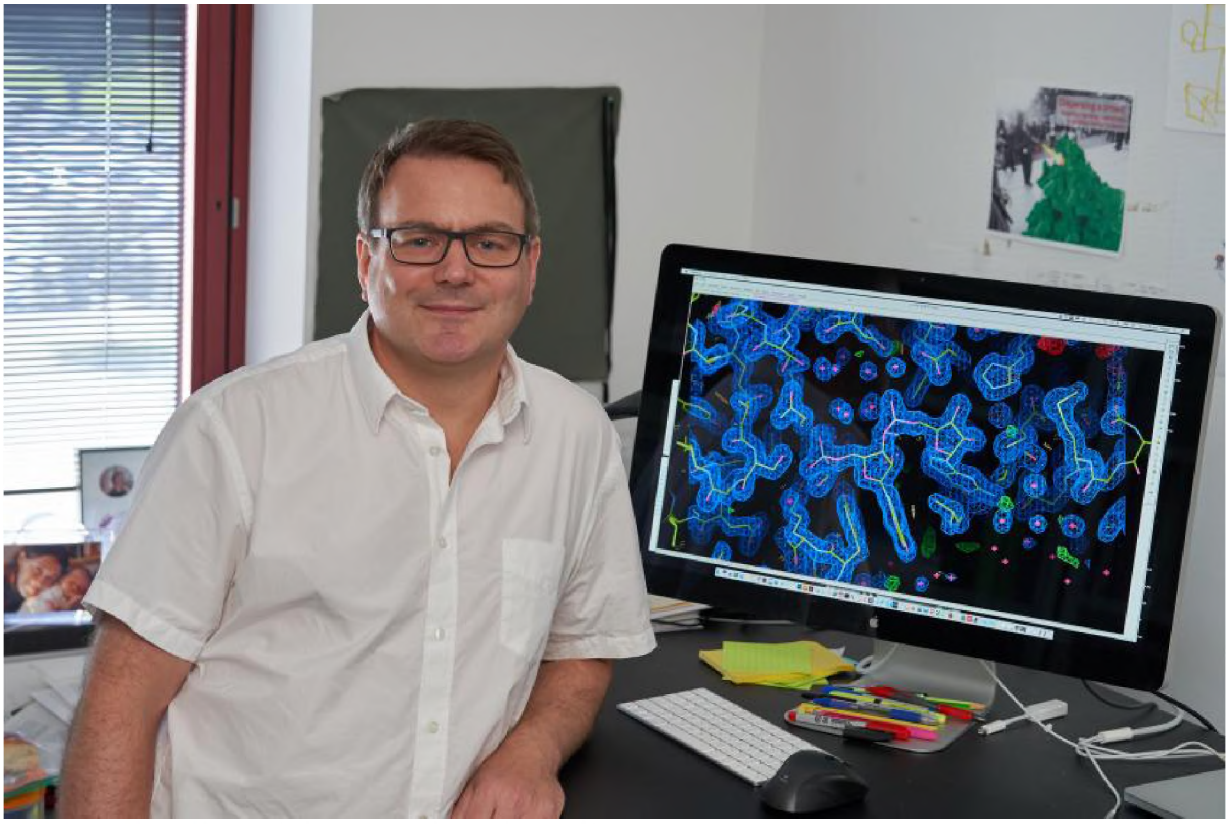

Holger Sondermann, Molecular Medicine, College of Veterinary Medicine
Credit: Dave Burbank, Cornell Research

If you think bacteria are unsophisticated, single-celled organisms passively floating around in their environment, you might want to think again. Over the past few decades, scientists have discovered bacteria are not the knuckleheads we once thought they were (at least in comparison to their eukaryotic counterparts). “It turns out they have a pretty complex lifestyle,” says Holger Sondermann, Molecular Medicine. “They can be either free floating, or they can be part of a larger, coordinated community, called a biofilm. They’re able to switch their lifestyle depending on what is happening in their environment.”

Sondermann and his lab are interested in bacterial physiology and signaling, especially as they relate to biofilm formation and pathogenicity. Biofilm, which looks like an oily slime, is often referred to as the social lifestyle of bacteria. “It’s implicated in the majority of chronic infectious diseases,” Sondermann says. “It’s one of the reasons why many antibiotics don’t work efficiently because bacteria living in a biofilm are protected from antibiotics.”

Bacteria, Floating in and out of Colonies, Seeking Nutrients

Sondermann aims to understand how free-floating bacteria are stimulated to form into biofilm colonies and the processes that make that formation possible, as well as why and how the bacteria dissolve the biofilm and go back to their mobile lifestyle. Supported by funding from the National Institutes of Health, the Sondermann lab has focused specifically on a small nucleotide called cyclic diguanylate, or c-di-GMP, found uniquely within bacteria. This nucleotide is known as a second messenger, an intracellular signaling molecule produced by enzymes within the cell, which forms part of a signal transduction pathway. Its function is to instruct the bacterium on how to change its lifestyle, based on external environmental factors.

"The specific pathway we're interested in is controlled by environmental cues, in this case, nutrient availability," says Sondermann. "The bacterium senses the presence of a certain nutrient, which means conditions are good in that area. The bacterium wants to stay there, so it forms a biofilm. If the nutrient becomes limited, that's not a good environment for the bacterium. It disperses the biofilm and becomes free floating again so it can colonize other niches. It is the cellular levels of the second messenger c-di-GMP and the factors that react to this messenger, which control physiological changes—in the case of our system of interest, whether the cells are dispersed or reside in a biofilm."

The Duel between Antibiotics and Biofilm Colonies

Sondermann's most current research focuses on one particular protein that is at the heart of this signaling pathway in many bacteria, including several human pathogens. The protein and its associated factors control cell adhesion, which is one of the early steps in the formation of a biofilm. "This protein seems to be the regulatory hub, which kicks in when c-di-GMP levels in the bacteria rise," he explains. "It's the relay that controls the adhesion process that is happening outside the cell. If you could break the interaction outside the cell between these enzymes and this receptor protein, you would be able to control biofilm dispersal."

Controlling biofilm dispersal could lead to better treatment of chronic infectious diseases, according to Sondermann because the biofilm protects bacteria against standard antibiotics and our immune system. Once the biofilm is dispersed, bacteria would become more susceptible to antibiotic treatment and host responses.

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"Antibiotic tolerance and resistance is a major issue in bacterial infections," Sondermann says. "The idea is that it could be a combination therapy to enhance standard treatments, but we haven't explored this angle fully yet. At this point we're on the basic science side, seeking proof of concept about whether we can actually tinker with that signaling system to willfully induce biofilm dispersal."

Collaborating to Figure out Biofilm Formation

Sondermann collaborates with George O'Toole at Dartmouth University, who works with *Pseudomonas fluorescens*, a soil-dwelling bacterium, and *Pseudomonas aeruginosa,* a pathogen associated with cystic fibrosis and burn wound infections, and with Fitnat Yildiz at the University of California Santa Cruz, who is an expert in *Vibrio cholerae,* the causing agent of cholera. The researchers are currently exploring how the enzymes that make and break the second messenger c-di-GMP interface with receptors that control cell adhesion and biofilm formation in these and other bacteria.

"This is one of the most complex signal transduction pathways in bacteria," Sondermann says. "If you look at a pathogen like *Vibrio cholerae,* these bacteria have dozens of enzymes potentially involved in making or breaking c-di-GMP. While many share a basic mechanism, either they produce or breakdown the second messenger, signaling specificity is apparent. That is, not every enzyme that makes that same second messenger triggers the same biological response. Understanding the signaling pathways and molecular events that ensure their fidelity is key to unraveling this layer of complexity. We think the specificity is set up through protein-protein interactions between the enzymes that control the pool of c-di-GMP and the receptors that translate this signal into a physiological response. Looking forward, one has to consider the entire signaling network if one wants to understand how bacteria compute their responses to a multitude of environmental inputs."

From Biofilm to Cell Membrane Dynamics

Protein structure and function is the common denominator between the research into biofilms and the Sondermann Lab's other main focus: membrane dynamics in eukaryotic cells that have a membrane-enclosed nucleus, endoplasmic reticulum, mitochondria, and other organelles. This organization compartmentalizes various biochemical reactions and biological functions. The researchers investigate how cell organelles are shaped and how membrane trafficking is controlled via enzymatic activities in the cell.

For all cells—particularly neurons—membrane dynamics, fission, and fusion are important events. They provide transport mechanisms for biological information and nutrients within the cell. Membrane fission and fusion do not happen spontaneously. Enzymes and other proteins are needed to facilitate these processes. The Sondermann Lab focuses on a protein known as atlastin, which has a very basic function helping maintain the structure of a particular cellular organelle, the endoplasmic reticulum. It's also the genetic hotspot, especially in children, where mutations occur that result in an inherited neurodegenerative disease, hereditary spastic paraplegia.

"Early on, we were interested in the structure and regulation of atlastin, and how disease-associated mutations effect the protein and its function," Sondermann says. "If we can understand this, perhaps there are ways to correct the defects that mutant proteins exert on the cell and on an organism. We're moving from the specific outward, asking what aspects of this system are conserved in other, related, proteins and how they may differ. That is the driving force behind all my research. I'm motivated by basic principles and the exploratory nature of science."

by Jackie Swift
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