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The fascinating biology of bacteria: from gene regulation to their role in colorectal cancer

Detail

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Bio

Eric Massé received his PhD from the University of Montreal in 2000. He then completed his post-doctoral training at the National Institutes of Health (Bethesda, MD, USA). In 2004, Prof Massé opened his lab at University of Sherbrooke as an Associate Professor, focusing his research on small regulatory RNAs in bacteria. Since then, he supervised multiple postdocs, PhD, and MSc students and welcomed more than 30 undergraduate trainees.

Marie-Claude Carrier received her BSc in Microbiology from the University of Sherbrooke in 2013. During her BSc studies, she completed more than 12 months of training in Prof Eric Massé's lab. In 2014, Marie-Claude started her MSc-PhD cursus under Prof Massé's supervision, during which she participated in multiples studies on bacterial small regulatory RNAs. She plans to obtain her PhD degree in the spring of 2021.

Funding

- Natural Sciences and Engineering Research Council (NSERC)
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- Fonds de Recherche du Québec - Nature et Technologies (FRQNT)
- National Institutes of Health (NIH)

Collaborators

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- Cari Vanderpool (Department of Microbiology, University of Illinois at Urbana-Champaign, Urbana, Illinois, USA)
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- Isabelle Laforest-Lapointe (Department of Biology, Faculty of Science, University of Sherbrooke, Sherbrooke, Québec, Canada

Research Objectives

The Eric Massé laboratory is deciphering RNA-based regulations in bacteria.

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Personal Response

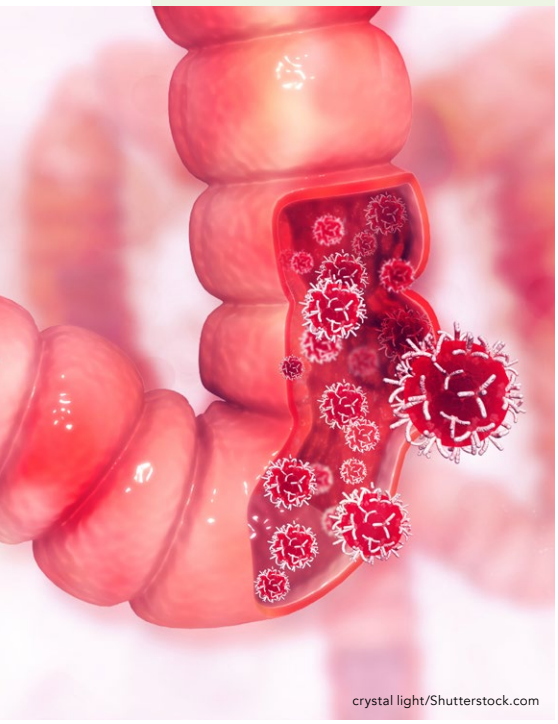
Do sRNA sponge mechanisms take place in higher-order mammals, including human and if so, would they be important from a drug development point of view?

"In eukaryotic organisms, RNA-based regulation is a major determinant of gene expression, just as it is in bacterial cells. The close relatives of bacterial sRNAs are termed microRNAs (miRNAs). The sponging mechanisms observed in bacteria is also observed in eukaryotes. Indeed, in these organisms of higher complexity, sponge RNAs, sometimes called competitive inhibitors, are usually circular RNA molecules and harbour multiple binding sites for a miRNA, efficiently sequestering them from their mRNA targets. Currently, synthetic RNA sponges are designed for loss-of-function miRNA studies. MicroRNAs are known to be involved in a plethora of human pathologies, such as cancer, viral diseases, immune-related diseases and neurodegenerative diseases. Accumulating evidence suggest that synthetic miRNA sponges could hold vital clues in the fight against these serious diseases."

The fascinating biology of bacteria

From gene regulation to their role in colorectal cancer

Small regulatory RNAs (sRNAs) are key molecules in gene regulation. The length of sRNAs can vary, from less than 50 nucleotides to more than 500. sRNAs typically bind to target mRNAs, promoting their degradation or interfering with translation. Prof Eric Massé and PhD student Marie-Claude Carrier from the University of Sherbrooke, Canada, aim to decipher the regulatory networks between bacterial sRNAs and their targets. Another aspect of the Massé Lab's research is understanding the role of the gut microbiome in colorectal cancer.



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Unlike other more complex organisms, bacteria are in direct contact with their environment. Sudden variations in temperature, nutrient availability or pH can be fatal and bacteria have evolved mechanisms of adaptation that allow them to survive these ever-changing conditions. What allows bacteria to adapt to the selection pressures is their ability to very rapidly express proteins and enzymes that can quickly provide protection against the harsh external environment. Proteins are encoded by genes (DNA) in the chromosome. Genes are transcribed into messenger RNAs (mRNAs), which are then read and translated by the ribosomes, which are ribonucleoproteins decoding the RNA messages. Along with this multi-step process there are some genes that do not actually code for a protein. They rather produce functional non-coding RNA molecules that fulfil various essential roles in the cell. Some non-coding RNAs, for example, act as powerful regulators of gene expression.

Small RNAs (sRNAs) have the unique role of reprogramming gene expression and reroute metabolisms in response to the environment. The main mechanism by which sRNA regulate gene expression is by directly interacting with an mRNA, interfering with, or – in some instances – facilitating the process of protein synthesis. Negative regulation occurs when a sRNA induces degradation of the mRNA and/or interferes with the translational machinery. On the other hand, positive regulation occurs when an sRNA stabilises an mRNA and/or facilitates translation initiation. In doing so, sRNAs reprogram gene expression and reroute metabolisms in response to the environment.

Although sRNAs were previously believed to present common general characteristics such as their small length or their non-coding nature, new evidence suggest that sRNAs are more versatile than anticipated. Some sRNAs even encode short regulatory peptides and, contrary to what was previously thought, sRNAs do not always originate from independent genes.

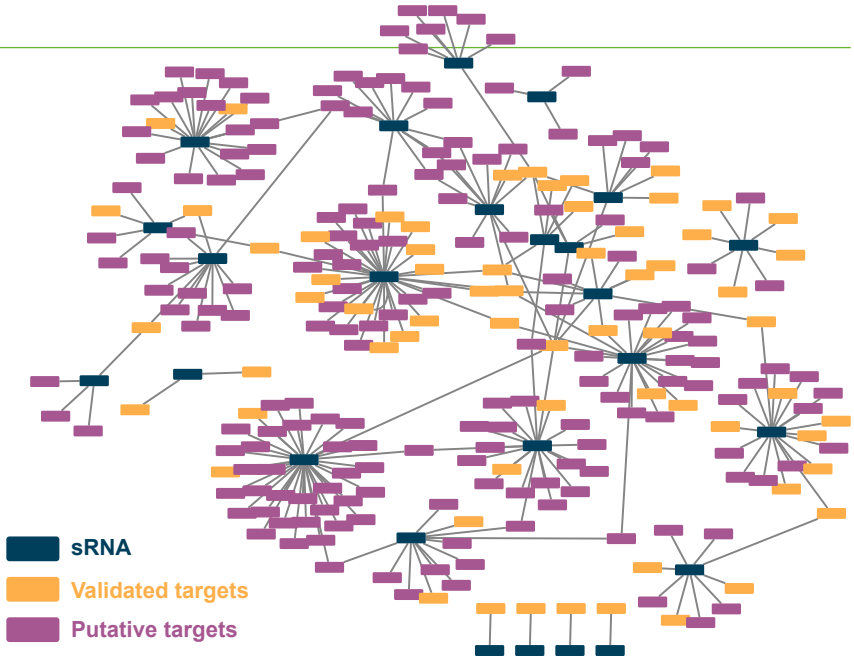
Prof Eric Massé and PhD student Marie-Claude Carrier from the University of Sherbrooke, Canada, aim to decipher the complex regulatory networks that exist between bacterial sRNAs and their targets. A better understanding of these networks will allow scientists to shed light on how bacteria survive the most challenging extracellular conditions.

WHEN THE PREDATOR BECOMES THE PREY: THE ROLE OF sRNA 'SPONGES'

A single sRNA can regulate a considerable number of target mRNAs, acting as a bridge between various cellular metabolisms. Almost a decade ago, in an effort to identify mRNA targets rapidly and reliably, the Massé Lab combined RNA affinity purification and RNA sequencing in a single technique called MAPS, an acronym for MS2 Affinity Purification (coupled to RNA) Sequencing. This allows the genome-wide identification of a sRNA interactome in bacterial cells.

A recurring theme in the Massé Lab is the understanding of the role of a sRNA, called RyhB, in the response to iron starvation. MAPS was performed on the RyhB sRNA and lead to one of the most interesting discoveries of the Massé Lab: a new type of regulatory RNAs in *Escherichia coli*. The team was

able to identify the role of a fragment deriving from a transfer RNA molecule. The tRNA fragment (tRF) acts as a sRNA sponge: it interacts with the RyhB sRNA and sequesters it to prevent its action. In a surprising twist, the predator becomes the prey as RyhB is degraded following its interaction with the tRF. In this case, the tRF sets a concentration threshold that RyhB needs to overcome before regulatory events can be detected. The necessity of the tRF is explained by the fact that even if RyhB is essential during iron starvation, its expression is never totally shut down, even when plenty of iron is available. If the resulting RyhB molecules were not sponged, they would regulate their targets even when iron is available, decreasing bacterial fitness. For example, unwanted RyhB increases bacterial sensitivity to a type of natural antibiotics called colicines.



The researchers aim to decipher the complex regulatory networks that exist between bacterial sRNAs and their targets.

NAVIGATING THE sRNA WEB: ONGOING STUDIES

Early research on sRNA showed that most interactions with their targets led to very strong regulatory effects. However, sRNA regulation is not exclusively of the 'all-or-nothing' type. The Massé Lab team members are currently working on identifying subtle regulatory events that are at the base of bacterial adaptation.

As mentioned, a group of people is directing their efforts in understanding the extended network surrounding RyhB, expressed in the response to iron starvation. Other lab members are studying how sRNAs are involved in the survival to oxidative stress and how sRNAs coordinate cellular division. PhD student Marie-Claude Carrier is specifically interested in how *E. coli* adapts to different growth phases, particularly by studying novel regulatory mechanisms by which sRNAs modulate expression of membrane transporters.

FUTURE DIRECTIONS IN THE STUDY OF sRNAs

Prof Massé and the other members of the lab are currently carrying out studies on the model non-pathogenic bacterium *Escherichia coli* K-12. In the future, and with the help of Prof Massé's collaborators, the team aims to investigate the importance of sRNA subtle regulatory events in pathogenic bacteria. The team hopes to unravel the intricate molecular mechanisms behind sRNA-dependent modulation of pathogenicity and to understand how sRNAs interact with metabolic processes to coordinate the cellular responses to changes in the environmental conditions.

One of the most interesting discoveries of the Massé Lab is the identification of a new type of regulatory RNAs in E. coli.

TOWARDS NEW FRONTIERS IN CANCER SCREENING: RESEARCHING THE MICROBIOME

Colorectal cancer (CRC) is the third most common cause of cancer mortality in the world. While CRC is largely preventable by removal of intestinal polyps, there is a dramatic decline in survival following tumour establishment. This is why early detection and removal of polyps at the precancerous stage is critical for patient survival. A common screening test for polyps and tumours is the immunochemical-based faecal occult blood test (iFOBT), which consists in the detection of blood in patient's stool. However, this test is nonspecific and leads to many invasive nonessential procedures. Recent studies demonstrated that the microbiome, bacteria living in the human gut, has emerged as an important risk factor for colon cancer. Bacteria can directly foster tumorigenesis by interacting with the immune system.

The team at the Massé Lab observed significant differences in the intestinal bacterial composition that could be solely caused by the presence of blood in stools. More precisely, they identified 4 bacterial species whose abundance increased in the presence of blood and 8 species that showed decreased abundance in patients with blood in their stools.

The team published these findings in a recent paper (2020) where it is concluded that in the absence of disease, blood in the stools has a major influence on the composition of the microbiome. This suggests that blood itself should be taken into consideration when investigating the microbiome signatures of intestinal diseases.

Taking this into consideration, the team will conduct further studies with the aim of establishing the microbiome as a biomarker for colorectal cancer, including the precancerous polyp stage. The study will involve the use of hospital screenings for CRC combined with bioinformatic tools to improve prediction of most at risk patients. The Massé Lab hopes to offer a robust methodology for the diagnosis of CRC and aims to dramatically increase the quality of CRC prevention for patients participating in the early stage pilot studies.

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