The Complex Web of Colorectal Cancer

The causes of colorectal cancer, scientist believe, emanate from nutritional and genetic factors, along with many other uncertain contributors.

Dave Burbank

by Pooja Patel ’20

Jonathan W. Villanueva’s path toward his calling has been untraditional. A second-year PhD student in biomedical sciences, he studied developmental biology and worked in an evolutionary and ecology lab as an undergraduate student at the University of North Carolina (UNC), Chapel Hill. When it came time to apply for graduate school, he originally applied to evolutionary ecology programs. Upon rejection, Villanueva took two years off. He spent the first year working in industry for a company that develops tools to diagnose people with bacterial infections. He spent the second year at UNC Chapel Hill, working on a cancer biology project with Praveen Sethupathy, who is now one of his advisers at Cornell University.

Having found his way to cancer biology and Cornell, Villanueva studies with Praveen Sethupathy and Charles G. Danko, Biomedical Sciences, looking at mechanisms of gene regulation in colorectal cancer. As a result of his winding path, Villanueva gained a wide variety of perspectives, which contributed to his interest in colorectal cancer.

Colorectal cancer is believed to stem from a multitude of different factors, including nutritional and genetic components. All of these factors together create a complex web, and this web has peaked Villanueva’s interest.

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Jonathan W. Villanueva
Graduate Researcher

Highlights

MicroRNA 375 and Colorectal Cancer

Tumor Heterogeneity

MicroRNA 375 and Potential Therapeutics

Research, a Lifelong Learning and Mentoring Endeavor

“Part of the fun of the problem is untangling one thread from another, slowly getting to the center,” says Villanueva.

MicroRNA 375 and Colorectal Cancer

Villanueva approaches colorectal cancer from two angles: transcriptional and post-transcriptional regulation. The Human Genome Project resulted in the realization that a very small portion of the genome is actually translated into protein. This means that most of the genome consists of noncoding RNA that doesn’t code for protein. MicroRNAs, a kind of noncoding RNA, are negative regulators of transcription. They downregulate certain genes. They look for RNAs with a complementary sequence. Once this sequence is found, the microRNA binds and localizes the RNA-induced silencing complex (RISC), targeting RNA in order to inhibit its function. There is evidence that certain microRNAs are differentially expressed in colorectal cancer, compared to non-tumor tissue, which can play a role in the production of certain cancerous phenotypes.

> “It isn’t that microRNA 375 by itself will be a therapy for individuals with a particular type of colorectal cancer, but we are trying to investigate that and see if it can be a viable option.”

Villanueva is looking specially at microRNA 375, because previous work suggests that abnormal levels of microRNA 375 can have an effect on proliferation, tumor invasion, and apoptosis (cell death). MicroRNA 375 is also one of the most significantly downregulated microRNAs in colorectal cancer. Villanueva wants to identify the mechanism behind how microRNA 375 functions. The research includes identifying binding partners of microRNA 375 since it can interact with a variety of RNAs.

To identify the binding partners of microRNA 375, Villanueva tags microRNA 375 mimics with a biotin label. Afterward, he pulls down the labeled microRNA 375 mimic and sequences the RNAs bound to the mimic in order to identify binding partners.

“MicroRNA 375 is loaded onto Argonaute. Argonaute is one of a series of proteins that makes up the RISC. It ends up binding to a complementary messenger RNA sequence, and what we want to do is have this marker that can then pull down microRNA 375, which will also bring down anything that is bound to it,” says Villanueva.

Tumor Heterogeneity

Villanueva’s research also entails investigating tumor heterogeneity in colorectal cancer. In the field of cancer biology, there is the idea that a cancer tumor varies in composition from person to person. Villanueva took the microRNA data from the cancer genome atlas and used a series of statistical methods, including principal component analysis (PCA), to identify groups of tumors that share similar microRNA profiles. He is analyzing the data to study individual microRNAs and identify which microRNAs are uniquely expressed in conjunction with samples that show the lowest levels of microRNA 375.

From his analysis, Villanueva will set up a screen where the expression of microRNA 375 will be altered along with the identified microRNAs of interest in colorectal cancer cells. Then he will assess how the different permutations of microRNA alterations lead to changes in cancer phenotypes.

MicroRNA 375 and Potential Therapeutics

The application of Villanueva's work is very promising. Currently, there are four different subtypes of colorectal cancer, although many other subtypes have been proposed. Villanueva wants to dig deeper to better understand the context in which microRNA 375 promotes cancerous phenotypes. If microRNA 375 is found to be highly downregulated in a particular context, then a therapeutic that targets the pathways affected by microRNA 375 might be more effective in that particular tumor.

"Characterizing that and identifying the role of microRNA 375 is super important. It isn't that microRNA 375 by itself will be a therapy for individuals with a particular type of colorectal cancer, but we are trying to investigate that and see if it can be a viable option in a future that is moving toward personalized medicine," says Villanueva.

Research, a Lifelong Learning and Mentoring Endeavor

Villanueva describes conducting research as a lifelong process of learning, and it is exactly what he sees himself doing. When asked what's his favorite part of the research, he replies, "You have those things where, when you talk about them you smile. You just get this grin on your face. For me I think if I had to boil all of that down into two things, it would be that I am excited about the opportunity to do something that can help people and that I love the challenge of solving a puzzle."

Mentorship and teaching also have a special place in Villanueva's approach to research. "I want to help encourage people to become young scientists. It [research] is difficult. You'll have moments where you'll be frustrated because something isn't working; or you'll feel like you're running behind everybody in your program. So being supportive to the students in your lab is very important," says Villanueva. Sethupathy and Danko provide this support for Villanueva, and he wants to carry this kind of encouragement forward as he becomes the principal investigator of his own lab someday.

Villanueva participates in the Expanding Your Horizons program, in which middle school girls are given the opportunity to participate in science workshops at Cornell. Villanueva has also found another way to channel his love for science and discovery into science outreach. He is creating his own YouTube channel—dedicated to showcasing the life of a PhD student, as well as making the knowledge surrounding basic science topics more accessible.

"A couple of people have told me that their kids watch it, and they really enjoy it. For me even if only one or two kids watch it, but it gets them interested in the sciences, then I think that it is incredibly worth it," says Villanueva.

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