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Small gene, big problem: Wistar researcher working to better understand how small protein affects melanoma growth

In the past 15 years, the worldwide melanoma research community has made tremendous strides unlocking the biology of the disease and devising nearly 15 approved treatments for the fastest-growing, most aggressive form of skin cancer. Despite significant progress, nearly half of all melanoma tumors evade pharmacological therapies completely or respond initially, but soon become resistant. Researchers at The Wistar Institute are working to understand how certain melanoma tumors bypass treatment. By learning more about these tumors, they hope to discover a strategy that blocks melanoma's critical pathways and contributes to the development of treatments for patients who have few therapeutic options.

In Wistar's Melanoma Research Center, Jessie Villanueva, Ph.D., and her lab are researching a tumor mutation in a gene called NRAS (neuroblastoma ras viral oncogene homolog). It's a small protein, she says, but it plays a big role in regulating cell division. All humans have NRAS – a normal gene that signals to cells when to grow, and when to stop growing. But when it mutates, the gene stays persistently on and tells cancer cells to keep growing. According to Dr. Villanueva, scientists have not been able to develop a drug that directly targets the mutated NRAS proteins yet leaves proteins in healthy cells alone. That's where Wistar science steps in.

"We are hopeful with new technologies and research, we might be able to find a way to directly target these NRAS proteins," says Dr. Villanueva. "We're trying to understand how tumors carrying mutant NRAS survive. If we can find their Achilles' heel, we can work on developing new drugs to stop them."

Multiplying, migrating

Exposure to ultraviolet radiation from the sun—or tanning beds and lights—leads to changes in DNA molecules that contain our bodies' genetic information. When those genes become damaged, they contribute to cancer.

Melanoma originates in skin cells called melanocytes that produce melanin pigment, which gives skin its color. Melanocytes normally grow in a slow, controlled manner. But with certain environmental cues, such as excessive UV exposure, they accumulate genetic alterations, start proliferating at incredible rates, and lead to melanoma.

A family history of melanoma—especially in a first-degree relative such as a parent or sibling—increases one's risk of developing the disease. About 10% of those with a family history tend to develop melanoma. Dr. Villanueva explains that this could be attributed to family habits, such as spending considerable time outdoors, or to shared genetic traits, such as fair skin, freckling, light eyes or hair. But she is quick to caution that these "typical" risk factors don't mean that people with dark skin cannot develop skin cancer.

"It's a complete misconception that people with dark skin don't need to protect their skin from UV rays," she says. "We can all develop melanoma."

Melanoma most commonly develops in skin exposed to the sun – the trunk, chest or back in men, and the legs, neck and face for women. But it can also develop in the eyes (known as ocular or uveal melanoma), ears and vagina.

For those with darker skin, melanoma tends to present on the palms of the hands, soles of the feet or nails – areas not typically exposed to the sun. These are acral melanomas, and Dr. Villanueva describes them as "rare, but super aggressive, and in urgent need of effective therapies."

As the melanocytes acquire additional genetic mutations, they multiply uncontrollably and migrate beyond the skin to other organs, a process known as metastasis. This is where most serious problems begin.

Interestingly, men older than 50 are at higher risk for developing melanoma, while for women, it's the other way around.

Great hope

"We're seeing a high increase in melanoma among young women," Dr. Villanueva says. "We think it could be related to younger women going to the beach or using tanning beds, but likely it is related to UV exposure."

Bolstered by Wistar's state-of-the-science technology and one of the largest human-derived melanoma cell lines in the world outside of the National Institutes of Health, Wistar scientists hold great hope for advances that will allow them to pharmacologically inhibit melanoma.

"We are extremely optimistic about the search for combination therapies that are more effective, more durable, less toxic and that, hopefully, prevent or delay a melanoma tumor's ability to resist treatment," Dr. Villanueva says. "Our focus is on identifying molecular markers that will help us determine which patients are likely to respond to certain treatments."

For more information, visit wistar.org.

Dr. Jessie Villanueva

Dr. Jessie Villanueva is Associate Professor, Molecular & Cellular Oncogenesis Program, and Associate Director for Diversity, Equity and Inclusion at The Wistar Institute's Ellen and Ronald Caplan Cancer Center.

Dr. Villanueva focuses on understanding the molecular paths that are disrupted by melanoma to uncover targets for therapy, particularly for patients who have NRAS mutant melanoma, an aggressive and difficult-to-treat form of the disease.