Doubling Down on Rare Melanomas

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When someone says “melanoma,” they think skin. Indeed cutaneous (skin) melanoma is the most common type of melanoma, accounting for roughly 90% of cases and receiving the lion’s share of funding. But what about the remaining 10% of melanomas?

Acral, uveal, and mucosal melanoma — known collectively as “rare melanomas” — represent a type of black hole for the clinical community. We know far less about them — what causes them, how they progress, and how to effectively treat them. Rare melanomas frequently appear in parts of the body that are shielded from the sun (such as palms, under fingernails, in eyes, or nasal cavities), and so their development is not directly related to sun exposure. And because these areas of the body aren’t traditionally associated with melanoma, patients with rare melanomas are more likely to have late diagnoses and poorer prognoses.

Recognizing the importance of accelerating research and improving outcomes for people diagnosed with rare melanomas, MRA has invested more than $10.3 million through 22 awards specifically focused on these subtypes. This makes MRA the largest nonprofit funder of research focused on rare melanoma worldwide.

Titia de Lange, PhD, is hoping her research will help drive change in this rare melanoma space. de Lange is a recipient of The Black Family-MRA Team Science Award and is examining acral melanoma on the chromosome level to determine whether a process known as “telomere crisis,” which causes extensive damage to a cell’s genome, contributes to acral melanoma development and progression. de Lange, who is the director of the Anderson Center for Cancer Research, a Leon Hess professor, and the head of the Laboratory of Cell Biology and Genetics at Rockefeller University, has spent more than 25 years researching telomeres, the protective elements at the ends of chromosomes.

Telomeres look like broken DNA but are not broken DNA at all. Instead, they are, in fact, critical for the stability and maintenance of genetic information. Telomeres are shielded by a dynamic complex of six proteins, which de Lange has dubbed “shelterin,” which helps regulate the length of telomeres and shelters them from DNA repair processes—an incredibly important but complex and still somewhat mysterious process.

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Flawed telomere function, however, can generate genome instability and drive cancer progression. "Cells are programmed to go through regeneration but cells that go through too many divisions are likely associated with cancer," explains de Lange. "Eventually cells peel off and die; however, some cells break through this 'death order' and can create tumors and chaos." This telomere crisis is very frequent in early stage cancers and telomere dysfunction also contributes to genome rearrangements in tumors.

de Lange, who studies telomere function, became interested in acral melanoma because it occurs in parts of the body that receive little sun exposure (and correspondingly little UV damage) and as a result, acral tumor cells have fewer mutations. Instead, acral melanoma cells often have large-scale changes to their genomes — for instance, large sections of chromosomes are either deleted or increased in number — changes that may result because of alterations to telomeres, which regulate so-called 'genome stability'.

de Lange's 3-year research project is examining how acral melanomas arise and what causes these chromosomal changes. She is also hoping to identify molecules that can be targeted with future therapies. de Lange says it's critical to keep an open mind for hypothesis-driven, basic research of what happens inside cells.

"What I hope patients know is that we are working as hard as we can to better understand this disease," says de Lange. "Our highest hope is that we have greater insight into how melanoma chromosomes and tumors function so that we can develop biomarkers for disease staging and predictive information to help us with prognosis, diagnosis, and so on."

de Lange underscores the importance of organizations like MRA providing funding for preliminary research to let initial pilot projects mature: "I want everyone to know just how important it is that MRA is willing to take risks and fund research like this in its early stages. I don't think our project would have been funded by the NIH. This type of research is so important because if you only fund research on existing treatments then you will never find the next big breakthrough."

To learn more about rare melanomas and melanoma subtypes, visit curemelanoma.org/about-melanoma/types

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