Scientists identify interacting proteins key to melanoma development, treatment

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Researchers have discovered how a mole develops into melanoma by showing the interaction of two key proteins involved in 60-70 percent of tumors. The Penn State scientists also demonstrate that therapeutic targeting of these proteins is necessary for drugs to effectively treat this deadly form of cancer.

"We have shown that when two proteins – (V600E)B-Raf and Akt3 – communicate with one another in a mole, they cooperate leading to the development of melanoma," said Gavin Robertson, lead author and associate professor of pharmacology, pathology and dermatology, and director of the Foreman Foundation Melanoma Therapeutics Program at the Penn State College of Medicine Cancer Institute. "We have also shown that effective therapies for melanoma need to target both these proteins, which essentially eliminates the tumors."

Melanoma is the most deadly form of skin cancer because it metastasizes or moves around the body so quickly. In general, people with advanced-stage disease only have months to live. Currently, melanoma kills one person every hour in the U.S., and is predicted to affect one in 50 people by 2010. In recent years, researchers have zeroed in on two key genes – B-Raf and Akt3 – that cause this deadly cancer, and which could be important targets in the treatment of melanoma.

B-Raf is the most mutated gene in melanoma. The mutant protein, (V600E)B-Raf, produced by this gene is important in helping mole cells survive and grow but it is unable to form melanomas on its own. Nearly 90 percent of all moles have the mutant protein but it is not fully clear why only some of them turn into melanomas.

Robertson and his colleagues have found that a second protein – produced by Akt3 – regulates the activity of the mutated B-Raf, which aids the development of melanoma.

"What we have found is a second event that is necessary for melanomas to develop," added Robertson, whose findings are reported in the May 1 issue of the journal *Cancer Research*.

While comparing proteins within normal moles and human melanoma cells, the Penn State researchers noticed that the two proteins were communicating with one another only among melanoma cells but not among normal cells.

When the Akt3 protein was put into cells in conjunction with the mutant B-Raf gene, they were better able to form melanomas compared to cells just containing the mutant B-Raf gene.

"This tells us that you can have a mole but it cannot turn into melanoma without the presence of the Akt3 protein," explained Robertson.

While it is still unclear what brings the B-Raf and Akt3 proteins together, the Penn State researchers say they now have a better understanding of how these two proteins interact to cause melanoma.

The initial mutation of the B-Raf gene helps to create moles, but high levels of B-Raf activity due to the mutation prevents the cells from becoming a melanoma. It is only when the Akt3 protein is present in those cells and communicates with B-Raf that it lower its activity, thereby creating favorable conditions within the mole for cells to multiply, and allow them to turn into a melanoma.

Robertson said the discovery could pave the way for newer and more effective treatments for melanoma.

"We have shown that if we target the two proteins separately, it somewhat inhibits the development of tumors but if we target them together, the development of tumors gets inhibited significantly," he added. "It validates these proteins as key targets for effective melanoma therapy."

Robertson envisions that future physicians could look at blood samples from melanoma patients containing melanoma cells and determine whether the two proteins are in their cells. The patients could then receive drugs that target these proteins to more effectively treat their disease. It would be personalized cancer treatment that would be more effective and less toxic with fewer side effects, the Penn State researcher explained.

"In the search for a cure for melanoma, we are now closer because we know that we need to target these two proteins in order to have a dramatic impact on the development of melanoma," Robertson added.

For patients, this means that in the future, some new drug could target these proteins to treat advanced disease or be added to sunscreen lotion, for instance, that would prevent Akt3 functioning in the cell. It would not only help control a tumor, but also prevent one as well.

Source: Penn State