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Nodal alone does not produce anti-cancer effects

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Metastatic melanoma is the leading cause of skin cancer deaths in the United States; once melanoma has spread (metastasized), life expectancy for patients can be dramatically shortened. At present, the reference therapy for patients diagnosed with metastatic melanoma is Dacarbazine (DTIC), which is associated with poor patient outcomes.

In a study published in *Molecular Cancer Research*, March 12, 2015, the laboratory of Mary J.C. Hendrix, PhD, in collaboration with other scientists found that standard treatments for metastatic melanoma are not effective against a growth factor protein called Nodal. The study also showed that combination therapies incorporating anti-Nodal antibodies with DTIC are a promising alternative. Previous research in the Hendrix laboratory showed that Nodal, which is critical for human embryonic development, re-emerges in metastatic melanoma.

Katharine Hardy, PhD, a postdoctoral fellow in the Hendrix lab, led the effort by treating three different melanoma cell lines with DTIC. The group discovered that Nodal-expressing cells not only remained after the therapy, but their numbers actually increased. "Remarkably, the residual populations of tumor cells that were largely unaffected by DTIC were Nodal positive," Hendrix said.

The scientists' next step was to test whether a combination of anti-Nodal and DTIC therapy would be more successful combating the Nodal. "We found that using a lower concentration of the DTIC with a low concentration of an anti-Nodal antibody induced cell death and

decreased cell growth synergistically," Hendrix said. "Tumor cells are very dependent on this growth factor, and when you take it away, they die."

At any time, 20 to 30 percent of melanoma tumor cells express Nodal, according to the study. Their power to increase cell proliferation can even spread to nearby cells that don't produce the growth factor.

Hendrix and colleagues have begun to investigate whether other melanoma therapies on the market affect Nodal, and, if they don't, to determine if the therapies work in conjunction with anti-Nodal antibodies, in a similar manner to the DTIC study. In the same paper, they performed initial experiments testing a therapy that inhibits B-RAF, a mutation found in a portion of melanoma tumors. It did not work against Nodal, but the combination strategy did.

If the scientists can develop an anti-Nodal antibody that works in humans, the combination treatment could lead to better outcomes for patients with metastatic melanoma, a disease with an overall median survival of only six to nine months.

"Nodal is still a relatively new observation - made right here at Northwestern University and Stanley Manne Children's Research Institute, and it's a very powerful growth factor that represents a promising cancer stem cell target," Hendrix said.

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