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Researchers identify key enzyme in melanoma cell development

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Virginia Commonwealth University researchers have discovered a mechanism by which an enzyme regulates gene expression and growth in melanoma cells, a finding that could someday lead to more effective drugs to attack cancers and make them more treatable.

Melanoma, the most serious type of skin cancer, is highly resistant to current therapeutic strategies for reasons that are not well understood. New research at VCU suggests that an enzyme discovered in 2003 might be used to target a specific genetic component that helps to regulate gene expression and defends melanoma cells against treatment.

The findings are reported online this week in the Proceedings of the National Academy of Sciences.

"By selectively and specifically targeting molecules for degradation that serve as gatekeepers for cancer growth, progression and resistance to therapy, it may be possible to turn the cancer cells' defense into an offense that can be used as an effective approach to destroy the tumor," said Paul B. Fisher, Ph.D., professor and chair of the Department of Human and Molecular Genetics and director of the VCU Institute of Molecular Medicine in the VCU School of Medicine.

Several years ago, Fisher led a team of scientists at Columbia University in identifying an enzyme involved in halting the growth of human malignant melanoma and other cancer cells. The enzyme, called human polynucleotide phosphorylase or hPNPaseold-35, drives cancerous cells

to irreversibly lose their growth potential and acquire properties of more normal cells, a process called terminal cell differentiation. The enzyme also is important in cellular senescence, when a cell cannot divide anymore and dies. Additionally, the investigators developed new strategies for promoting cancer cell-specific expression of this enzyme, which reduced tumor growth in animal cancer models.

Fisher, now at VCU, and colleagues report that hPNPaseold-35 selectively targets and degrades a genetic component known as microRNA-221. MicroRNAs are short genetic components that act like a volume control knob to regulate the production of defined proteins in cells.

MicroRNAs regulate the expression of more than a third of human genes. In recent years, they have been recognized as causing over- or under-expression of genes linked to the majority of cancers and other diseases. Researchers are exploring microRNAs' roles to understand how they could be used as potential targets for therapies.

The work by Fisher's group indicates that showering the cell with the hPNPaseold-35 enzyme preferentially degrades microRNA-221, a microRNA that is elevated in multiple cancers including melanoma and which regulates gene expression that promotes the cancer cells' ability to thrive and spread. MicroRNA-221 also endows melanoma and other cancers with the capacity to resist chemotherapy.

"The present study provides the first observation that microRNAs may be regulated by selective degradation, providing an entry point for developing novel approaches for the therapy of melanoma and other cancers, Fisher said.

The VCU study also found that interferon-beta, a treatment for melanoma and other cancers, induces cells to produce the enzyme while

also interfering with the ability of microRNA-221 to perform. Fisher said this provides one possible explanation for how interferon-beta suppresses growth of melanoma cells.

Provided by Virginia Commonwealth University