Team discovers dual purpose of cancer drug in regulating expression of genes

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Keck Medicine of USC scientists have discovered new clues about a drug instrumental in treating a certain blood cancer that may provide important targets for researchers searching for cures.

The team investigated whether demethylation of gene bodies induced by the drug 5-Aza-CdR (decitabine), which is used to treat pre-leukemia, could alter gene expression and possibly be a therapeutic target in cancer.

"When we put the drug in cancer cells, we found it not only reactivated some tumor suppressor genes , but it down-regulated the overexpressed oncogene (cancer gene)," said Gangning Liang, Ph.D., associate professor of research, Keck School of Medicine of USC Department of Urology, who is corresponding author on the research. "Overexpression is what turns cancer 'on.' The mechanism by which the drug accomplishes this dual action is by removing DNA methylation in the gene body, which we didn't expect."

DNA methylation is an epigenetic signaling tool used by cells use to turn genes off. DNA methylation is an important component in many cellular processes, including embryonic development. Mistakes in methylation are linked to several human diseases, including cancer.

The research builds upon past research by Peter Jones, Ph.D., D.Sc., former director of the USC Norris Comprehensive Cancer Center, Distinguished Professor of Urology and Biochemistry & Molecular Biology, and now director of research at the Van Andel Institute.

"The beginnings of epigenetic therapy, which is now the standard of care for myelodysplastic syndrome, can be traced back to the discovery of the DNA demethylating effects of 5-Azacytidine at Children's Hospital Los Angeles in 1980," Jones said. "Since that time we have always assumed that the drugs act by switching genes on, thus reapplying the 'brakes' to cancer cells. In this paper we show that they may also work by turning down the levels of genes, which have become overexpressed in cancer. In other words, they may also decrease the 'gasoline' and this two pronged mechanism, which was entirely unexpected, may help explain why patients respond to epigenetic therapy."

The research, "Gene body methylation can alter gene expression and is a therapeutic target in cancer," was published online Sept. 25, 2014 in *Cancer Cell*.

More information: Yang, X., Han, H., DeCarvalho, D.D., Lay, F.D., Jones, P.A., & Liang, G. (2014). Gene body methylation can alter gene expression and is a therapeutic target in cancer. *Cancer Cell*, Published online Sept. 25, 2014 dx.doi.org/10.1016/j.ccr.2014.07.028

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