Molecular 'movies' may accelerate anti-cancer drug discovery

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Using advanced computer simulations, University of Utah College of Pharmacy researchers have produced moving images of a protein complex that is an important target for anti-cancer drugs. This advancement has significant implications for discovering new therapies that could attack cancer without damaging the DNA of healthy cells, according to an article published July 31, 2012 in the *Proceedings of the National Academy of Sciences.*

The researchers used high-performance computing technology to demonstrate that a protein complex called LSD1/CoREST undergoes major changes in shape, which are regulated by binding to a DNA-packaging protein known as histone H3. LSD1 gene expression is increased in many cancers and insight into the changes in the LSD1/CoREST complex may help to accelerate development of epigenetic drugs that reprogram cancer cells to behave more normally.

Epigenetics is the study of changes in gene expression that are not caused by alterations in the DNA itself. Instead, these changes are caused by chemical modifications that switch parts of the genome on and off to regulate gene activity. These chemical modifications occur within the epigenome, a layer of chemical labels that covers the genome, and help to determine whether specific genes are active or inactive. Epigenetic drug discovery is based on the knowledge that the epigenome is flexible and could potentially be altered by therapeutic drugs.

Lysine-specific demethylase-1 (LSD1)/CoREST is a protein complex

involved in epigenetic changes. Recent studies have shown that LSD1-CoREST is a binding partner for various proteins involved in regulating genes and modifying chromatin, the combination of DNA and DNA-packaging proteins called histones that make up the nucleus of a cell. Previous research also revealed that LSD1-CoREST binds to histone H3.

"In our earlier work, we discovered that LSD1/CoREST functions as a tiny clamp that can reversibly open and close to adjust the size of its binding partners," says Riccardo Baron, Ph.D., assistant professor of medicinal chemistry at the University of Utah and lead author on the study. "The goal of this study was to learn more about the conformational changes that occur when LSD1/CoREST binds to H3."

Baron and Nadeem A. Vellore, Ph.D., postdoctoral researcher in the Baron lab, performed molecular dynamics computer simulation on existing x-ray crystal structures of LSD1/CoREST, effectively transforming a static photo of the protein complex into a molecular movie. They discovered that, in an unbound state, the arms of the LSD1/CoREST clamp exhibit remarkable rotation, shifting back and forth among open or closed configurations. They also found that binding to H3 reduces the overall flexibility of the clamp and triggers a major loss of rotation. These dynamic changes in shape help to explain the ability of LSD1/CoREST to bind to such a wide variety of partners and may also be relevant to how LSD1/CoREST performs chromatin remodeling.

Epigenetics is an active topic in cancer research because an epigenetic mechanism known as DNA or histone methylation is commonly disrupted in cancer cells. In cancer, methylation turns off critical genes, and previous research has suggested that the use of drugs to inhibit the alteration mechanism may lead to re-expression of the affected genes. Unlike traditional chemotherapy drugs, epigenetic drugs would not

affect the DNA of healthy cells. This makes epigenetic drug discovery extremely promising for reducing the side effects of chemotherapy.

"Epigenetic drug discovery hinges upon identifying the right protein targets and drug molecules, which is challenging because both are highly dynamic," says Vellore. "It would be extremely difficult to hit a dynamic target using only a static photo. Increasing our understanding of the molecular dynamics of LSD1 has allowed us to screen large compound libraries effectively and to identify the molecules that are most likely to inhibit epigenetic targets."

This research is currently fueling international collaborations with leading experimentalists in enzymology and epigenetics, including the group of Andrea Mattevi at the University of Pavia in Italy.

In the past decades, computing power has steadily risen, increasing by more than one order of magnitude every six years or less. High performance computing using graphic processing units and special-purpose hardware is currently pushing scientific boundaries even further. By taking advantage of such technological advancements, the development and application of chemical theory and computational approaches are becoming increasingly relevant for addressing important biomedical problems.

"My group's long-term goal is to significantly advance the use of computer chemistry in pharmacological applications," says Baron. "I believe in the extremely fascinating idea that physics-based approaches and computers can drive the discovery of new molecules and their practical use."

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