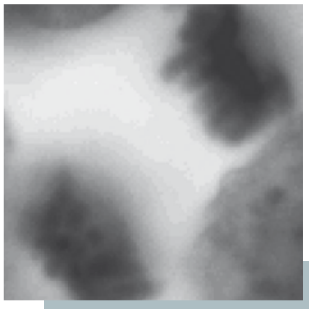

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Where cures begin.

Diana Hargreaves

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The Problem

Our bodies are comprised of several hundred different cell types, yet each cell possesses the same genetic material. This diversity arises from selectively activating genes that are particular to each cell type, whether it is skin, liver or brain. This activation is achieved by proteins called epigenetic regulators, which work to make specific regions of our genome more or less accessible to transcription. Unlike our fixed genome, epigenetic regulation is dynamic and reversible, allowing cells to respond to developmental and environmental cues. In the past few years, researchers have found that these regulators are often mutated in cancer, suggesting the exciting possibility that the features driving such cancers can be reversed.

The Approach

Diana Hargreaves studies a particular epigenetic regulator, the SWI/SNF complex, which uses energy to unpack and unwind DNA from structural proteins to alter DNA accessibility and in turn, gene transcription. The SWI/SNF complex is polymorphic, meaning that the complex can assume different forms through various combinations of individual subunits. These particular complex assemblies have been shown to be essential in stem cells and development.

Hargreaves brings her knowledge of biochemistry and epigenetic regulation to investigate a subunit of the SWI/SNF complex called ARID1A, which is mutated in many solid tumors, such as in ovarian, bladder and colorectal cancers. In the absence of ARID1A, the essential activity of the SWI/SNF complex is provided by a similar protein, ARID1B. Hargreaves is exploring the different activities of these complexes in normal and cancer settings, with an eye toward targeting the essential activities of the SWI/SNF complex in ARID1A mutant cancers.

The Innovations and Discoveries

- Hargreaves has demonstrated that ARID1A is indeed frequently mutated at rates comparable to other known tumor suppressors, the findings of which could have a translational impact for ovarian and other cancers. She has also shown that ARID1A mutations often co-occur with oncogenic mutations in the PI3K signaling pathway, suggesting a connection between these mutations.
- Hargreaves has uncovered an interaction between SWI/SNF and topoisomerase II alpha, a protein involved in DNA maintenance during replication, which underlies the essential activity of the complex in stem cells.
- By examining cells that lack ARID1A, Hargreaves is beginning to pinpoint changes in packaged DNA to better explain the role of ARID1A and ARID1B in driving cancer.

For more information, please visit:
http://www.salk.edu/faculty/hargreaves.html

Cancer, Developmental Disease, Epigenetics, Genetics, Neuroscience, Neurologic Disease