Key epigenetic switch mechanism in gene regulation discovered

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A Purdue University study pinpointed an epigenetic mechanism that is a key factor in how genes are switched on and off.

Both genetic and epigenetic mechanisms regulate human gene expression. External or environmental factors, such as carcinogens from tobacco smoking, disrupt normal epigenetic regulation. This leads to changes in gene expression, which results in the production of cancerous cells.

Humaira Gowher, a Purdue assistant professor of biochemistry, is interested in the mechanisms that control gene expression by directing epigenetic regulators such as DNA methylation to specific portions of a gene.

Gene expression is controlled by its genetic regulatory elements called promoters and enhancers. When cells need to express a specific gene, its enhancer element interacts with its promoter to stimulate the activation process. When a gene needs to be turned off or repressed, its specific enhancer is disengaged from the promoter.

DNA methylation refers to the addition of a methyl group to one of the bases of the DNA, cytosine, converting it into a methylcytosine. Presence of methylcytosine at the promoters and enhancers of genes signals the associated gene to be inactive.

DNA methylation is catalyzed by the enzymes called DNA

methyltransferases or Dnmts.

Gowher and her team found that these Dnmts are important for releasing enhancers during gene repression and determined that a particular enzyme acts as a type of relay switch where the activity of one enzyme turns on the activity of the next, ultimately triggering an enzyme called Dnmt3a to methylate DNA in a specific location.

"The process we discovered provides a way for cells to control the activity of Dnmts at specific enhancers where DNA methylation must be deposited to ensure that genes are turned off when required," said Gowher, whose findings were published in the journal *Nucleic Acids Research*.

Gowher and her team studied this mechanism for a class of genes named pluripotency genes, which are expressed in stem cells. Stem cells replicate rapidly and stay in an undifferentiated state until they get an assignment and become a particular type of cell. During the process of cell differentiation, the pluripotent genes are turned off and DNA methylation occurs.

When external or environmental factors act on differentiated cells, DNA methylation can be disrupted, triggering a pluripotent state that leads to rapid proliferation of now damaged and cancerous cells.

"Understanding the way that cells regulate these mechanisms of repression may be able to help us understand what is being damaged and what we can watch for that can turn these genes back on," Gowher said.

Gowher said future research will involve looking further upstream in the process, particularly at the signals that can modulate the activity of these enzymes.

More information: Christopher J. Petell et al. An epigenetic switch regulatesDNA methylation at a subset of pluripotency gene enhancers during embryonic stem cell differentiation, *Nucleic Acids Research* (2016). DOI: 10.1093/nar/gkw426

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