Pushmi-pullyu of B-Cell Development Discovered

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DENVER — Although every cell in the body carries the genes necessary to function as an antibody-producing B cell, only a small proportion of stem cells mature into those important immune-system cells. James Hagman, PhD, Professor of Immunology at National Jewish Health and his colleagues have identified two "molecular motors" that work in opposing directions to control the development of B cells. They published their findings June 19 in the online version of *The Proceedings of the National Academy of Sciences USA.*

"We found that these two 'chromatin remodeling complexes' work in a sort of pushmi-pullyu manner to induce or retard epigenetic changes that allow for the development of a B cell," said Hagman. The pushmi-pullyu was a fictional animal in the Dr. Doolittle stories that had a head at opposite ends of its body, each pulling in a different direction. "The complexes help control both the unspooling of DNA to make genes accessible and the demethylation of DNA that removes silencing markers."

Although DNA in every cell contains the genes necessary to become B cells, two factors help keep them silent. One is the fact that the two meters of DNA inside a tiny cell nucleus is wrapped around millions of tiny spools, linked together like a string of pearls, which help keep the hereditary molecule from becoming irretrievably tangled. When wrapped tightly around these spools, individual genes are inaccessible to the molecules that bind and activate them. Second, many of the genes have small methyl groups, a carbon and three hydrogen atoms (CH_3), on their DNA in specific places, which also prevent them from being activated. These factors are considered epigenetic states, modifications to existing DNA that control their activation or silencing.

Dr. Hagman and his colleagues previously identified a protein, known as Early B-cell Factor or EBF, which they dubbed a 'pioneer factor.' By altering the epigenetic state of several genes, it is estimated that EBF can turn on hundreds of genes necessary for B-cell development. The researchers did not know, however, how EBF controlled those epigenetic factors.

They suspected that two chromatin remodeling complexes, conglomerations of several different proteins known to burn energy and physically move the tiny spools holding DNA, played a role. In a series of cell-culture experiments they showed that the two chromatin remodeling complexes, SWI-SNF and Mi2/NuRD, had opposing effects.

Transcription of a B-cell gene increased 70-fold when a cell contained both EBF and the two chromatin remodeling complexes. When the researchers inactivated the SWI/SNF complex, that activation fell to 8-fold, suggesting that SWI/SNF helped promote B-cell development. When they inactivated Mi-2/NuRD instead, expression of the B-cell gene increased 1,727-fold. Mi-2/NuRD was apparently acting as a brake, and its removal vastly increased expression of the B-cell gene.

Additional experiments showed that these two CRCs influenced the arrangement of DNA on the tiny histone spools inside the cell nucleus *and* the methylation of the B-cell gene.

"We knew that the two complexes were capable of influencing the arrangement of histone spools and accessibility of different genes, but were pleasantly surprised that they also affected the methylation state of the genes," said Dr. Hagman.

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