Study shows how inflammation can lead to cancer

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A new study shows how inflammation can help cause cancer. Chronic inflammation due to infection or to conditions such as chronic inflammatory bowel disease is associated with up to 25 percent of all cancers.

This study by researchers at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) found that inflammation stimulates a rise in levels of a molecule called microRNA-155 (miR-155).

This, in turn, causes a drop in levels of proteins involved in DNA repair, resulting in a higher rate of spontaneous gene mutations, which can lead to cancer.

"Our study shows that miR-155 is upregulated by inflammatory stimuli and that overexpression of miR-155 increases the spontaneous mutation rate, which can contribute to tumorigenesis," says first author and post-doctoral researcher Dr. Esmerina Tili. "People have suspected for some time that inflammation plays an important role in cancer, and our study presents a molecular mechanism that explains how it happens."

"Our findings also suggest that drugs designed to reduce miR-155 levels might improve the treatment of inflammation-related cancers," Tili says.

The findings were published recently in the *Proceedings of the National*

Academy of Sciences.

MicroRNAs form a large family of non-coding genes involved in many important cell processes. They carry out this function by suppressing the amount of particular proteins in cells, with each type of microRNA often affecting many different proteins.

MiR-155 is known to influence blood-cell maturation, immune responses and autoimmune disorders, and high levels of this molecule have been directly linked to the development of leukemias, and breast, lung and gastric cancers.

For this study, Tili and her colleagues examined the effects of inflammation-promoting substances such as tumor necrosis factor or lipopolysaccharide (found in the outer walls of bacteria) on miR-155 expression and on the frequency of spontaneous mutations in several breast-cancer cell lines.

When the researchers exposed breast-cancer cells to the two inflammatory factors the levels of miR-155 rose abnormally high, and the mutation rate increased two- to three-fold. To understand why, the investigators focused on the WEE1 gene, which stops the process of cell division to allow damaged DNA to be repaired.

The investigators learned that miR-155 also targets WEE1 and showed that high levels of miR-155 lead to low levels of WEE1. They reasoned that low levels of WEE1 allowed cell division to continue even when DNA damage is present, leading to a growing number of mutations.

"It is believed that cancer is caused by an accumulation of mutations in cells of the body," says principal investigator Dr. Carlo M. Croce, professor and chair of molecular virology, immunology and medical genetics, and director of the Human Cancer Genetics program the

OSUCCC – James. "Our study suggests that miR-155, which is associated with inflammation, increases the mutation rate and might be a key player in inflammation-induced cancers generally. This could make it an important therapeutic target."

Provided by Ohio State University Medical Center