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Scientists discover genetic 'shut down' trigger in healthy immune cells

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A fundamental genetic mechanism that shuts down an important gene in healthy immune system cells has been discovered that could one day lead to new therapies against infections, leukemia and other cancers. Results of a University of Pittsburgh School of Medicine study on the mechanism, called a somatic stop-codon mutation, are being reported today in the online journal PLoS ONE, published by the Public Library of Science.

"This kind of loss-of-function mutation can be very dangerous, and it is the first such mutation that has been identified in normal immune cells in blood," said Bora E. Baysal, M.D., Ph.D., assistant professor of obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine. "We did control experiments for two years to make sure it was real and not a technical error."

Dr. Baysal and his colleagues tested 180 samples, including blood from healthy individuals and other material from those with childhood leukemia, looking at specific portions of DNA in immune cells known as monocytes, natural killer cells and lymphocytes. These cells are key to the body’s immune response against infection and disease. The investigators found somatic stop-codon mutations in an average of 5.8 percent of crucial portions of genetic material that deliver instructions from DNA, called messenger RNA, in normal blood samples and in a quarter of leukemia samples.

"DNA is the blueprint for all living cells. It carries the genetic code for

most biological functions and is passed virtually unchanged from generation to generation," said Dr. Baysal, who also is an associate investigator at the university-affiliated Magee-Womens Research Institute. "Harmful alterations in the code – mutations – can produce genetic disorders and play an important role in the development of cancer. Normal cells such as monocytes, lymphocytes and natural killer cells have many mechanisms to recognize and repair mutations, but a stop-codon mutation is a kind of permanent "off" switch that has escaped DNA repair," he added.

"We believe there is a good biological reason for this. It may allow the cells to survive in a low-oxygen environment, such as where there is cancer or infection," said Dr. Baysal. "It is part of the process for immune cells to ‘armor up’ for battle against cancer cells and other diseases."

Earlier research on the mutated gene suggests the stop-codon mutation might be part of the programmed adaptive response to oxygen deprivation. This mutation and its location is "unusual because it predicts loss-of-function, it targets a classical tumor-suppressor gene, and it occurs in (peripheral blood mononuclear cells)," Dr. Baysal wrote, adding that the mutation is present at much higher levels in messenger RNA compared to DNA.

"This may give us a tool to modify the immune cells’ survival in a low oxygen environment, which could help the cells to survive and fight infections and tumors," said Dr. Baysal, calling the mutated gene a potential "therapeutic target."

Source: University of Pittsburgh Schools of the Health Sciences