Scientists discover a key protein regulator of inflammation and cell death

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Reporting in the journal *Nature*, researchers led by Emad Alnemri, Ph.D., professor of Biochemistry and Molecular Biology in the Kimmel Cancer Center at Jefferson, discovered a key protein component involved in inflammation.

The protein, AIM2 (absent in melanoma 2), is involved in the detection and reaction to dangerous cytoplasmic DNA that is produced by infection with viral or microbial pathogens, or by tissue damage. AIM2 also appears to be a tumor suppressor, and its inactivation may play a role in the development of cancer, according to Dr. Alnemri.

AIM2 belongs to a class of proteins called inflammasomes, which are multi-protein complexes that play major roles as guardians against both viral and bacterial infections. Inflammasomes also detect dangerous self-molecules associated with tissue damage.

According to Dr. Alnemri, when cells are infected with pathogens, AIM2 senses the presence of the pathogen's DNA in the cytoplasm. It then binds to the foreign DNA and causes a rapid inflammatory reaction that sends a danger signal alerting the body to the invading pathogen.

When AIM2 binds to the foreign DNA, it recruits a cytoplasmic protein called ASC. ASC and AIM2 then work together to activate caspase-1, a cysteine protease involved in the production of interleukin1beta and other inflammatory cytokines that cause inflammation.

"Researchers have long sought this elusive protein that senses the presence of DNA in the cytoplasm, which is associated with pathogenic infection or the escape of undigested self-DNA into the cytoplasm," Dr. Alnemri said. "We not only identified the key protein in this process, but also discovered how this protein reacts to DNA and causes inflammation. The inflammatory response triggered when AIM2 binds to foreign DNA in the cytoplasm is the body's way of alerting other systems that there is a danger present in the cell."

According to Dr. Alnemri, the activation of AIM2 also leads to death of the infected cells, which removes the damaged cells from the body. This prevents the pathogen from replicating in the cells and spreading to other parts of the body. The fact that AIM2 can induce cell death raises the possibility that AIM2 might function as a tumor suppressor, by killing cells with damaged DNA before they transform into cancers. Inactivation of AIM2 thus might confer a growth advantage to abnormal cells and lead to the development of cancer.

"The discovery and understanding of the AIM2 inflammasome should enable scientists to design novel therapeutics that modulate its activity," Dr. Alnemri said. "Such therapeutics may be useful for the treatment of nucleic acid-dependent pathogenic and autoimmune diseases, such as arthritis and systemic lupus erythematosus," Dr. Alnemri said.

Source: Thomas Jefferson University