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Scientists uncover key pathway, potential drug targets in autoinflammatory disease

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Molecular biologists at Jefferson's Kimmel Cancer Center in Philadelphia have detailed the cascade of cellular events behind some potentially dangerous autoinflammatory diseases. In doing so, they not only have gained a greater understanding of the disease process, but have also identified new potential drug targets for diseases ranging from arthritis to cancer.

Reporting in the journal Molecular Cell, Emad Alnemri, Ph.D., professor of Biochemistry and Molecular Biology at Jefferson Medical College of Thomas Jefferson University, and his co-workers describe how two proteins called PSTPIP1 and pyrin interact to cause autoinflammatory diseases, inherited diseases characterized by seemingly unprovoked and recurrent attacks of fever and inflammation. Such diseases have been found largely to be caused by defects in proteins that regulate inflammation.

According to Dr. Alnemri, defects in pyrin, for example, have been linked to familial Mediterranean fever, a sometimes fatal disease found in the Mediterranean, Middle East and Europe. Defects in PSTPIP1 have been linked to a rare, autoinflammatory disease called PAPA syndrome. The two proteins apparently worked together in the same inflammatory pathway, but no one understood how these proteins could lead to disease.

Dr. Alnemri explains, "Because mutant PSTPIP1 proteins interact with pyrin much more strongly than normal PSTPIP1, they cause uncontrolled or exaggerated activation of pyrin and consequently more

secretion of IL-1 beta in these patients."

These proteins now become potential therapeutic targets, Dr. Alnemri says. For example, there is a synthetic analog of the IL-1 receptor "antagonist" called Anakinra that has been successfully used in clinical trials to treat autoinflammatory diseases, including PAPA syndrome and familial Mediterranean fever, in addition to other chronic inflammatory diseases such as rheumatoid arthritis.

He explains that IL-1 beta binds to a receptor on the cell membrane that "induces the inflammatory phenotype." Anakinra mimics IL-1 beta and binds to the same receptor, preventing IL-1 beta from binding and consequently blocking its effects on cells. "Detailing these mechanisms is not only important for autoinflammatory disease, but for most inflammatory disease in general."

Chronic inflammation has been linked to the development of cancer, Dr. Alnemri points out. "IL-1 beta appears to play a major role in tumor growth. Elevated concentrations of IL-1 beta have been found in aggressive forms of colon, breast and lung cancers. It's not clear how IL-1 beta promotes cancer growth, but the data suggest that in addition to its ability to stimulate production of inflammatory factors, it also stimulates cells to produce angiogenic factors to enhance angiogenesis, or the development of tumor-growth promoting blood vessels."

Dr. Alnemri adds that "IL-1 beta antagonists are being tested against cancer in animal models with notable success, so you might actually be able to treat some forms of cancer by targeting proteins upstream in the inflammatory pathways, such as caspase-1, pyrin or PSTPIP1 to stop the generation of IL-1 beta."

The team plans next to investigate the role of inflammation in cancer. The researchers would like to study the potential involvement of the

inflammatory pathways that they have identified, and whether anti-inflammatory agents that could affect such pathways can also affect cancer.

Source: Thomas Jefferson University