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Enzyme revealed as promising target to treat asthma and cancer

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In experiments with mice, Johns Hopkins Kimmel Cancer Center scientists have identified an enzyme involved in the regulation of immune system T cells that could be a useful target in treating asthma and boosting the effects of certain cancer therapies.

In research described online April 6 in *Nature Immunology*, the investigators show that mice without the enzyme SKG1 were resistant to dust mite-induced asthma. And mice with melanoma and missing the enzyme, developed far fewer lung tumors—less than half as many—than mice with SKG1.

"If we can develop a drug that blocks the enzyme in a way that mimics what happens when the enzyme is missing, we would not only have a treatment to inhibit asthma, but also a drug that could be used in conjunction with other experimental therapies aimed at helping the immune system fight cancer," said Jonathan D. Powell, M.D., professor of oncology at the Johns Hopkins Kimmel Cancer Center.

The unusual dual potential of an SKG1-blocking compound stems from the enzyme's role in a key pathway linked to T cells, which act as either "generals" of the immune system by directing how the system works, or "soldiers" that seek and destroy foreign cells.

Powell and his colleagues decided to look at SKG1 because it works along the same pathway of a protein called mTOR, a focus of their previous research. The mTOR pathway helps T cells decipher signals

from their environment, and prompts the cells to transform into specific T cell types.

As part of this pathway, SKG1 dials down production of a signaling protein called interferon-gamma. When SKG1 is inactive, T cells produce increased amounts of interferon-gamma that appear to be useful in fighting tumor cells.

Powell said that a SKG1-blocking drug might be used in conjunction with other cancer immunotherapies as a sort of booster medication to enhance their effects. Experimental cancer immunotherapies, including vaccines and so-called checkpoint blockade inhibitors, are the focus of intense research within the past few years, he added.

The researchers also discovered that SKG1 promotes the production of T helper 2 cells, which become overactive in asthma and other allergies in a sort of runaway case of inflammation. Finding a drug that could shut down SKG1 could help block the inflammation that causes asthma and other allergic reactions.

By untangling the different effects of SKG1, Powell said, his team has advanced efforts to fine-tune immune responses in patients. "We're not suppressing or exacerbating the immune system, we're regulating it," he noted. "We're regulating it to do exactly what we want it to do."

More information: The AGC kinase SGK1 regulates TH1 and TH2 differentiation downstream of the mTORC2 complex, www.nature.com/ni/journal/vaop … nt/full/ni.2867.html

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