

Study finds HIV protease inhibitor drugs may adversely affect the scaffolding of the cell nucleus

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UCLA scientists, along with collaborators from Purdue University, have demonstrated that HIV protease inhibitors — crucial drugs for HIV treatment — block a cellular enzyme important for generating the structural scaffolding for the cell nucleus.

Published in the July 16 early edition of Proceedings of the National Academy of Sciences, these biochemical findings may offer insights into the side effects of HIV protease inhibitors, including metabolic syndrome and regional losses of some of the body's fat tissue. These side effects occur in up to one-third of patients taking anti-HIV drug regimens.

"We show, for the first time, that certain HIV protease inhibitor drugs directly inhibit an enzyme called ZMPSTE24, which is important for generating the structural scaffolding supporting the cell nucleus," said Catherine Coffinier, Ph.D., study author and an assistant researcher at the David Geffen School of Medicine at UCLA.

UCLA researchers added HIV protease inhibitors to cultures of mouse and human fibroblast cells. They found that the inhibition of ZMPSTE24 by the HIV protease inhibitor drugs led to an accumulation of prelamin A, which is a precursor to mature lamin A — a key molecule in the structural scaffolding for the cell nucleus. ZMPSTE24 is a membrane-bound intracellular zinc metalloproteinase that is required for the conversion of prelamin A to mature lamin A.

Interestingly, researchers found that the accumulation of prelamin A was exaggerated in cells that contained half the normal amount of ZMPSTE24.

Genetic defects in ZMPSTE24 in humans lead to an accumulation of prelamin A and cause a host of

disease phenotypes, including partial loss of body fat depots and metabolic syndrome.

"The fact that HIV protease inhibitors block ZMPSTE24 and have been associated with side effects similar to those observed with a genetic deficiency in ZMPSTE24 is intriguing," said Loren Fong, Ph.D., study author and an associate professor of medicine at the David Geffen School of Medicine at UCLA.

The UCLA research team is known for its work on progeria, a precocious aging syndrome. Progeria syndromes can be caused by genetic defects that interfere with the conversion of prelamin A to lamin A.

"Since HIV protease inhibitors interfere with the conversion of prelamin A to lamin A, we believe — at least at a biochemical level — that there is a link between progeria syndromes and HIV treatment regimens," Fong said.

There are many HIV protease inhibitors on the market. One of the next steps, according to Coffinier, is to determine whether the blocking of ZMPSTE24 activity and the accumulation of prelamin A is caused by every HIV protease inhibitor or only some of them.

All of the current studies were performed in cultured cells, not tissues from HIV-treated patients. In future studies, the UCLA team would like to assess the biochemical and pathological side effects of the HIV protease inhibitors in humans taking these medications.

"Ultimately, we would like to further explore why some HIV protease inhibitor-treated patients develop side effects while others do not," said Dr. Stephen Young, study author and a professor of

medicine at the David Geffen School of Medicine at UCLA.

The UCLA team was assisted by the laboratory of Christine Hrycyna, an associate professor of chemistry at Purdue University. The collaboration was a natural fit, as Hrycyna and the UCLA team share a common interest in ZMPSTE24 processing.

Source: University of California - Los Angeles

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