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AIDS therapy: more harm than help?

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Researchers have shown that protease inhibitor drugs also inhibit protein processing in mitochondria. This might explain their metabolic side effects and could lead to improved therapies for treating patients with AIDS.

Gift of life at a price

Highly active antiretroviral therapy (HAART) has, at least in developed countries, transformed HIV disease from a fatal to a chronic, treatable condition. However, many patients using the HAART regimen develop metabolic side effects: lipodystrophy, hyperlipidemia, insulin resistance and even frank diabetes mellitus [1]. These side effects first appear after the advent of protease inhibitor therapy, and they result in some patients using other treatment regimens.

A new study shows *in vitro* and in organelles that HAART can inhibit mitochondria from processing proteins [2]. This is the first evidence directly linking protease inhibitors with mitochondrial dysfunction and could identify the cause of the metabolic side effects. Biochemistry professor Henry Weiner of Purdue University (http://www.purdue.edu) points out that much work remains to reproduce this result from yeast mitochondria in mammalian or human cells, and then to link it to the specific metabolic derangements observed in human patients.

Inhibition of mitochondrial proteases

Mitochondria, the central organelles for cellular energy metabolism, convert precursor proteins into the functional proteins that are responsible for metabolic processes. Mitochondrial proteases carry out this conversion by cleaving an N-terminal peptide group that translocation complexes use to transport the precursor proteins from the cytosol into

Mitochondria. Source micrograph courtesy of DOE Joint Genome Institute

the mitochondrial matrix. The Weiner team assayed the effect of HAART drugs on the production of these mitochondrial proteins. Their experiment involved exposing a protease involved in mitochondrial protein processing to increasing doses of the protease inhibitors indinavir, ritonavir, or saquinavir, and measuring the effects on the protease with autoradiography.

The sample preparation contained a precursor protein of rat liver aldehyde dehydrogenase, mitochondrial-processing protease, nutrients and increasing concentrations of protease inhibitors. The greater the concentration of the latter, the lower the conversion from precursor protein to protein. The results were similar when the team repeated the experiment using whole yeast mitochondria rather than mitochondrial processing protease.

Another, earlier, study by researchers at University of California, Berkeley (http://www.berkeley.edu) had shown that indinavir caused insulin resistance in HIV-seronegative men [3]. The two studies together are persuasive evidence that it is protease inhibitors, and not HIV itself that is causing the metabolic difficulties.

Prospects

Richard Dietrich, Professor of Pharmacology at the University of Colorado Health Sciences Center (http://www.uchsc.edu), considers these results provocative, and notes that other therapeutics are known to interfere with mitochondrial function. He suggests that it might be possible to use biopsied tissue taken (for whatever reason) from HIV-infected patients to correlate protease inhibitor therapy, mitochondrial dysfunction and specific metabolic derangements.

Judith Falloon, a researcher who specializes in HIV at the US National Institutes of Health (http://www.niaid.nih.gov) cautions that, although protease inhibitors (and indeed all antiretroviral medications now available) have side effects to a greater or lesser degree, it is undeniable that HAART has greatly reduced death rates from HIV [4]. She hopes that studies such as this, teasing out the details of toxicities and side effects, will lead to better results for all kinds of HIV drug.

References

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