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Structure of Fat-Depleting Protein Reveals Important Functional Clues



Image Title: In the Groove: Finding a molecule that binds in ZAG's (red) groove may yield the template for a new class of obesity drugs. - Pamela Bjorkman

Following a mysterious crevice in a molecule that causes severe weight loss in some cancer patients may turn up a new generation of drugs to treat clinical obesity, say researchers from the Howard Hughes Medical Institute (HHMI) at the California Institute of Technology.

Zn- α_2 -glycoprotein, otherwise known as ZAG, occurs naturally in most body fluids, including blood, sweat, saliva, and urine. Researchers first isolated ZAG from blood samples more than 30 years ago, "but its been a molecule in search of a function for a long time," said Pamela Bjorkman, an HHMI investigator at the California Institute of Technology in Pasadena. Bjorkman, Luis Sánchez and HHMI associate Arthur Chirino published ZAGs structure in the March 19, 1999, issue of the journal *Science*.

"In the Groove: Finding a molecule that binds in ZAG's (red) groove may yield the template for

a new class of obesity drugs."

One of the mysteries surrounding ZAG is that it seems to be related to a large family of proteins known as class I major histocompatibility complex (MHC) molecules. These molecules bind to small pieces of other proteins, known as antigenic peptides, and in so doing trigger an immune response to invading microorganisms and viruses. Yet despite ZAG's similarity to MHC proteins, it apparently does not have a role in the immune system, Bjorkman said.

Last year, however, researchers at Aston University in Birmingham, U.K., discovered that ZAG is involved in cachexia, a wasting syndrome that can affect people with cancer, AIDS and other terminal illnesses. Cachexia can result in rapid, life-threatening weight loss and lead to shedding of both fat and muscle.

ZAG appears to drive the fat-loss in cancer patients. When the British investigators added ZAG to fat cells, the cells rapidly metabolized lipids, a major component of fat. Further evidence of ZAG's role in fat breakdown came when researchers, who fed the protein to genetically obese mice, noticed that the mice lost body fat even though they maintained normal eating habits. If ZAG produces the same effect in humans and is deemed safe, Bjorkman adds, it could provide a long-sought treatment for clinical obesity.

Understanding how ZAG boosts fat breakdown is a necessary precursor to any plans to develop ZAG-based obesity drugs. Knowing that structure often reveals details about function, Bjorkman's group created a molecular map of ZAG's structure using x-ray crystallography, which provides a three-dimensional picture revealing the location of each of the molecule's atoms. Surprisingly, this image showed that ZAG's structure is even more like that of its MHC relatives than researchers had previously thought.

One distinguishing feature of MHC proteins is a large groove that the molecules use to bind antigenic peptides. Bjorkman's group discovered that ZAG also has this groove, but unlike MHC molecules, ZAG's groove doesn't bind peptides. "We found that the ZAG groove contains some sort of compound. We know that it's not a peptide, but we haven't identified it yet," Bjorkman said. A search of small molecule databases for molecules capable of fitting in the groove failed to find any good candidates among known compounds.

Bjorkman's top priority is to find the molecule that binds in ZAG's groove, since this unknown partner may hold the key to understanding how ZAG promotes fat breakdown. "There's a big hint there," said Bjorkman, "we just don't know what the answer is yet. But once we identify this compound, it's possible you could inhibit the binding of this molecule to ZAG as a treatment for cachexia." She added that such a strategy might be particularly helpful for breast cancer patients since ZAG accumulates in 40 percent of cancerous breast tissue.

The information about ZAG's structure also provides important clues about the evolution of the MHC protein family. Bjorkman explained that prior to this and other structural work on MHC-related proteins, researchers believed that the MHC molecule groove evolved to bind antigenic peptides. Given the fact that ZAG shares this structure yet is not involved in the immune system suggests that the groove may have evolved for a different reason, she says.

"Perhaps the groove first evolved for a purpose other than antigen binding and MHC molecules have just capitalized on its existence," said Bjorkman. "But there's still a lot we don't understand." Determining ZAG's structure, she added, is simply the first step towards understanding how the molecule does its job.