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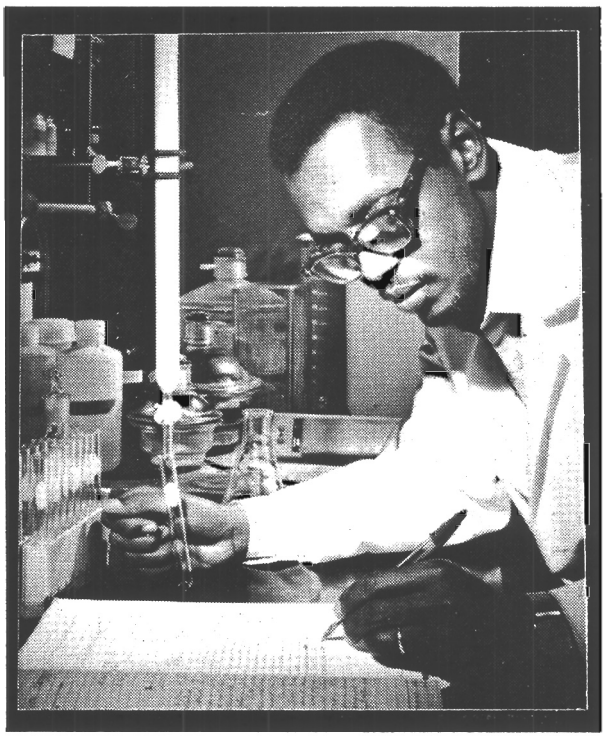
EXPLORING THE WILDERNESS OF BIOCHEMICAL REACTIONS: CONTROLLING THE ACTIVITY OF ENZYMES RELEASED BY DISEASE-FIGHTING CELLS

If biochemistry were represented as a land mass on a map, many expanses of it would be marked "uncharted." Researchers at Georgia Institute of Technology are making inroads into one such biochemical wilderness -- identifying and characterizing serine proteases, enzymes released by disease-fighting blood cells called lymphocytes. The researchers are using a certain type of enzyme inhibitors to identify the serine proteases.

Presented August 23 at the American Chemical Society's national meeting in Washington, D.C., this research could lead to medical applications, said Dr. Chih-Min Kam, senior research scientist.

"If we find out how the serine proteases work, maybe we can use the inhibitors of these enzymes as therapeutic agents against disease," she said of the research.

The study might also provide new information about the family of serine proteases that attacks proteins in the body, sometimes causing illnesses such as emphysema, Kam added. Other problems that can result from uninhibited enzyme activity include organ transplant rejection and skin blistering.



The research is led by Dr. Jim Powers, Regent's Professor in the School of Chemistry and Biochemistry, and is sponsored by the National Institutes of Health and the University of Nevada in Reno. The proteases being studied are found in granules housed in lymphocytes, which are white blood cells formed in lymphoid tissue such as the tonsils and lymph nodes.

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FOR MORE INFORMATION:

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Lymphocytes make up between 22 and 28 percent of all the disease- and virus-fighting white blood cells in an adult human body.

Scientists know that many and varied serine proteases are released from lymphocyte granules in the process of fighting a disease or virus, along with a protein called perforin. They know that the perforin's function is to break down the walls or coatings of infected cells. However, the exact functions and characteristics of the lymphocyte serine proteases are not so well-known, Kam said.

To capture the serine proteases released by rat natural killer cells used in the study, Ph.D. graduate student Ahmed Abuelyaman synthesized substances called biotinylated isocoumarins.

These substances combined isocoumarins, inhibitors that capture enzymes and keep them from functioning, with the H vitamin biotin. The biotinylated isocoumarins are dubbed "suicide inhibitors" because they self-destruct after reacting with an enzyme. Each isocoumarin was given a slightly different composition by linking it with a different alkoxy group. That made each inhibitor specific to certain kinds of serine proteases, Abuelyaman said.

Once the biotin-laced isocoumarins captured serine proteases, the entire combination was exposed to immobilized avidin, a protein found in egg white. Avidin holds on to biotin -- thus, the biotin/inhibitor/enzyme combination was trapped on the immobilized avidin. A spacer compound linking the biotin and the isocoumarin kept the bulky avidin from interacting with the serine proteases at the other end of the string. The enzymes could be reactivated with hydroxyamine, or a change of pH, then extracted for identification and study.

The researchers found that isocoumarin combined with a small methoxy group inhibited porcine pancreatic elastase, or PPE. That enzyme found in pigs is quite similar to a human neutrophile elastase enzyme that can destroy lung linings and cause emphysema if it is not controlled by a natural inhibitor. Isocoumarin combined with a phenethoxy group was a useful inhibitor of chymotrypsin, a digestive enzyme also found in humans that is linked with pancreatitis, or inflammation of the pancreas.

The researchers are applying their findings in efforts to make various types of inhibitors for granule serine proteases. They want to use these inhibitors to determine which serine proteases are essential for cell-mediated killing processes.

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