Enzyme necessary for development of healthy immune system

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Mice without the deoxycytidine kinase (dCK) enzyme have defects in their adaptive immune system, producing very low levels of both T and B lymphocytes, the major players involved in immune response, according to a study by researchers with UCLA's Jonsson Comprehensive Cancer Center.

The finding could have ramifications in treating auto-immune disorders, in which the body attacks itself, and possibly certain cancers of the immune system. A drug could be developed to create lower levels of dCK in the body, thereby tamping down immune response. Such a drug might also be effective in transplant patients to decrease risk for rejection, said Dr. Caius Radu, an assistant professor of Molecular and Medical Pharmacology, a Jonsson Cancer Center researcher and senior author of the study.

The study, part of a long-term research project that has resulted in the development of a new probe for Positron Emission Tomography (PET) scanning and the creation of a non-invasive approach to observe chemotherapy at work in the body, appears this week in the early online edition of the *Proceedings of the National Academy of Sciences*.

"It would be desirable to have drugs that can inhibit immune response when that response is detrimental and increase response when needed," said Radu, who also is a scientist with the Broad Stem Cell Research Center. "We are now trying to identify drugs that inhibit or activate dCK in the hopes of testing them on certain diseases."

The dCK enzyme helps recycle the products of DNA degradation, allowing cells to efficiently replicate their DNA during cell division. Until now, the enzyme was thought to play a relatively minor role in providing cells the material for DNA replication. However, this finding challenges that view and indicates the enzyme plays a profound role in normal lymphocyte development.

Wayne Austin, a graduate study in Molecular and Medical Pharmacology and first author of the study, said the research team expected to find widespread defects in development when they knocked out the dCK enzyme in the mice.

"Surprisingly, we found that the gene had a highly specific role in the development of organs crucial to a normally-functioning immune system," Austin said. "Mice lacking the dCK enzyme have thymuses that are reduced in size by 90-fold. That defect in thymus size resulted in mice having 5 to 13-times fewer lymphocytes circulating throughout the body."

This finding is part of research that was launched several years ago and represents the third significant discovery. The first was the development of a new probe for PET scanning created by modifying a common chemotherapy drug, an advance that allowed UCLA researchers to model and measure the immune system in action and monitor response to new therapies.

Researchers created the molecule, called FAC, by slightly altering the molecular structure of gemcitabine, a chemotherapy drug that is activated by dCK activity. They added a radiolabel so the cells that take in the probe can be seen during PET scanning.

The probe was based on a fundamental cell biochemical pathway called the DNA Salvage Pathway, which includes dCK. All cells use this

biochemical pathway to different degrees. But in lymphocytes, which are the active players in the adaptive immune system, the pathway is activated at very high levels. Because of that, the probe accumulates at high levels in those cells, said Dr. Owen Witte, director of the Broad Stem Cell Research Center and a Howard Hughes Medical Institute investigator.

That work was published June 8, 2008 in the journal *Nature Medicine*.

The second significant finding was the development of a non-invasive approach that may allow doctors to evaluate a tumor's response to a drug before prescribing the treatment, enabling physicians to personalize therapy to the patient's unique biochemistry.

In this study, the UCLA team injected the FAC probe into mice that had developed leukemias that either had or did not have active dCK enzyme. After an hour, the researchers imaged the animals' bodies with a PET scan, which operates like a molecular camera, enabling the researchers to watch biological processes inside animals and people.

The PET scan offered a preview for how the tumor will react to a specific therapy because tumor cells that retained the probe also will be sensitive to chemotherapy drugs that also are activated by dCK. If the cells didn't absorb the probe, the tumor might respond more favorably to the drugs that don't need interaction with dCK to be effective.

That work appeared Feb. 2, 2009 in the Proceedings of the National Academy of Sciences.

The next step, outlined in this study, was to determine what would happen without any dCK in the body at all, and what ramifications that might have on certain diseases and their treatment.