New discovery could lead to new way to screen drugs for adverse reactions

May 29 2012

Adverse drug reactions are a major issue that cause harm, are costly and restrict treatment options for patients and the development of new drugs. A groundbreaking finding by researchers from the La Jolla Institute for Allergy & Immunology could lead to a new way to dramatically improve drug safety by identifying drugs at risk to cause potentially fatal genetic-linked hypersensitivity reactions before their use in man.

Hypersensitivity reactions are similar to allergic reactions, whereby the immune system responds too strongly to something foreign that is not infectious or dangerous. This response produces symptoms ranging from mild, such as rashes, to severe including anaphylactic shock, organ failure and even death.

La Jolla Institute scientist Bjoern Peters, Ph.D., led the study which illuminated, for the first time, the specific mechanism leading to HLA gene-linked hypersensitivity to the drug abacavir, a finding that will have widespread importance and applicability to the study of drug hypersensitivity in association with other drugs.

HLA is a gene that helps the immune system to identify if the body's own cells have been infected by foreign invaders such as viruses and bacteria. Individuals have many different variations of HLA. In the case of abacavir, a drug used to treat HIV, the majority of people who carry a particular HLA variant, known as HLA-B*57:01, may experience serious, and in some cases, life-threatening hypersensitivity reactions.

"Many drug hypersensitivity reactions are HLA-linked, meaning that they will occur much more often or even exclusively in individuals who have certain variants of the HLA gene," said Dr. Peters, adding that some gene variants appear to be more commonly associated with drug hypersensitivity. "The present system of clinical trials is very powerful in identifying side effects that occur in many people. However, HLA-linked hypersensitivity has been a really big problem that often doesn't surface until after the drug is approved and taken by thousands of people."

To use the example of abacavir, Dr. Peters said there is now a genetic test, which is routinely used to exclude patients carrying the HLA-B*57:01 variant from receiving abacavir and hence preventing the hypersensitivity reaction. However, during the development of abacavir thousands of patients carrying HLA-B*5701 experienced hypersensitive reactions. "We are hopeful that our enhanced mechanistic understanding of HLA-linked hypersensitivities will contribute to the identification of drugs at risk to cause these syndromes before use in man and also to the development of safer drugs," he said.

Dr. Peters and his team have established assays (tests) that can be applied to test drug compounds to determine if a specific HLA variant reaction occurs. "You wouldn't have to wait until after the drug is introduced and thousands of people are potentially affected," he said, explaining the testing could be done in human blood samples. "This type of testing could be done before human subjects are exposed to the drug, and could lead to the design of drug types that do not have this effect, or - if this is not possible - to ensure that only individuals who do not have this HLA variant are given the drug, as is now done for abacavir."

Previous scientific studies have shown a strong linkage between hypersensitivity reactions to several drugs and specific HLA variants. However, the mechanism of action leading to this hypersensitivity was

not previously known and so testing for its presence was extremely difficult.

Mitchell Kronenberg, Ph.D., La Jolla Institute president & chief scientific officer, said the finding has the potential to significantly improve the efficiency and safety of the drug development process. "Some drugs are never released because of drug hypersensitivity that turns up in clinical trials," he said. "By using this mechanism for pre-screening, drug makers could identify and work to address the problem before it is tested in human clinical trials. This could enable important therapies to move forward that might otherwise have been scrapped."

The finding is discussed in a paper entitled "Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire," and was published online today in the scientific journal *Proceedings of the National Academy of Sciences.*

In conducting the study, Dr. Peters said they used the antiviral drug abacavir because it had previously been shown to cause hypersensitivity reactions in patients expressing the HLA molecular variant B*57:01. "In our study, we asked, 'how does that version of the HLA gene (variant B*57:01) cause those side effects?" he said.

The scientific team found a novel explanation that boils down to a case of mistaken identity. "We found that certain drugs can alter which peptides specific HLA molecules show to the immune system," said Dr. Peters. Peptides are pieces of proteins that make up the body. "Abacavir causes a self-peptide, derived from a human protein, to be shown to the immune system by the HLA variant B*57:01. This peptide would otherwise never be seen by the immune system." Having not previously recognized the peptide, Dr. Peters said the immune system mistakes it for being derived from an invader and launches an attack. This immune attack results in drug hypersensitivity.

Dr. Peters likened the occurrence to the immune system's reaction to an organ transplant. "The immune system perceives the organ as "non-self" and so rejects it. That's why you cannot transplant organs from one person into another unless the individuals have closely related HLA variants. Even then, people who receive transplanted organs have to take anti-rejection drugs, so the immune system doesn't launch an attack."

The study was done in collaboration with an international team which included clinical drug hypersensitivity experts Professors Simon Mallal and Elizabeth Phillips who discovered and championed the use of HLA-B*5701 testing to prevent abacavir hypersensitivity since 2002. They commented, " We are thrilled to see that the connection between HLA-B*5701 and abacavir hypersensitivity has provided us a roadmap for the use of personalized genetic medicine in everyday clinical practice around the world and is now also providing us a roadmap for safer drug development."

Provided by La Jolla Institute for Allergy and Immunology