Research team uncovers mechanism behind drugs that cause altered immunity

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(Medical Xpress) -- An Australian research team has opened the door to understanding why certain drugs cause a so called altered immunity response when offered as treatment for certain specific ailments. In their paper published in the journal *Nature*, the team explains how they've uncovered the mechanism that causes an HIV treatment drug to lead to hypersensitivity syndrome.

In order to protect us from pathogens, the human body has developed an immune system that works by making use of a paired set of systems. On one side are cells that display fragments of their inner proteins on their surface so that those on the other side, T cells (agents of the immune system), can recognize them as either "self" or "not self" cells. "Self" is any protein that is supposed to be where it is, while "not self" indicates that a pathogen has attached itself to the cell, in which case the T cells attack. This system works great when everything is as it should be. Unfortunately, that is not always the case. Sometimes something goes wrong with the process, most specifically with human leukocyte antigens (HLAs); proteins whose purpose is to hold the inner protein pieces in place on the surface of their cells. If these holder proteins go awry the immune system can become confused and fail to attack when it's supposed to, or more commonly, attack when it's not supposed to.

In this new study, the Australian team has found that the drug abacavir, which is used to treat HIV patients, causes changes to occur with the HLAs. Their research shows that when abacavir is administered it tends to bind to the cleft formed by HLAs that are used to hold the inner cell

fragments in place. When this happens, the inner protein bits that normally bind to the outer parts of their cells can't fit properly, so the body tries to compensate by allowing the HLAs to hold on to other similar bits. This tends to confuse the T cells which take the "when in doubt, attack" approach, which in turn leads to a state of altered immunity. It's this state that leads to hypersensitivity syndrome, which is where the immune system tends to overreact to perceived threats.

The team also found that abacavir is not the only drug that leads to such a situation, the mood stabilizer carbamazepine was also found to settle in the HLA clefts causing changes to the types of protein bits that can be presented to T cells, thus setting off the same sort of reaction.

More information: Immune self-reactivity triggered by drug-modified HLA-peptide repertoire, *Nature* (2012) doi:10.1038/nature11147

Abstract
Human leukocyte antigens (HLAs) are highly polymorphic proteins that initiate immunity by presenting pathogen-derived peptides to T cells. HLA polymorphisms mostly map to the antigen-binding cleft, thereby diversifying the repertoire of self-derived and pathogen-derived peptide antigens selected by different HLA allotypes. A growing number of immunologically based drug reactions, including abacavir hypersensitivity syndrome (AHS) and carbamazepine-induced Stevens–Johnson syndrome (SJS), are associated with specific HLA alleles. However, little is known about the underlying mechanisms of these associations, including AHS, a prototypical HLA-associated drug reaction occurring exclusively in individuals with the common histocompatibility allele HLA-B*57:01, and with a relative risk of more than 1,000. We show that unmodified abacavir binds non-covalently to HLA-B*57:01, lying across the bottom of the antigen-binding cleft and reaching into the F-pocket, where a carboxy-terminal tryptophan typically anchors peptides bound to HLA-B*57:01. Abacavir binds with

exquisite specificity to HLA-B*57:01, changing the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides that can bind HLA-B*57:01. In this way, abacavir guides the selection of new endogenous peptides, inducing a marked alteration in 'immunological self'. The resultant peptide-centric 'altered self' activates abacavir-specific T-cells, thereby driving polyclonal CD8 T-cell activation and a systemic reaction manifesting as AHS. We also show that carbamazepine, a widely used anti-epileptic drug associated with hypersensitivity reactions in HLA-B*15:02 individuals, binds to this allotype, producing alterations in the repertoire of presented self peptides. Our findings simultaneously highlight the importance of HLA polymorphism in the evolution of pharmacogenomics and provide a general mechanism for some of the growing number of HLA-linked hypersensitivities that involve small-molecule drugs.

Press release