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Immune molecule that plays a powerful role in avoiding organ rejection identified

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When a mouse's immune system is deciding whether to reject a skin graft, one powerful member of a molecular family designed to provoke such a response can effectively reduce the visibility of the mouse's own cells and help the graft survive, researchers say.

"This is a molecule with huge potential to regulate immune response," Dr. Anatolij Horuzsko, reproductive immunologist at the Medical College of Georgia Center for Molecular Chaperone/Radiobiology and Cancer Virology, says of HLA-G dimer.

Dimer appears to be the most powerful among several known forms of HLA-G at inhibiting the immune response, researchers have found. Fetuses use this natural mechanism to hide from the mother's immune system and it's at work in some transplant patients as well.

Now that the scientists know which HLA-G is best at down-regulating the immune response and how it works, they believe the molecule's action can be augmented in people with organ transplants and autoimmune disease and turned down to help fight a tumor. Measuring endogenous levels of HLA-G dimer may also help physicians identify which transplant patients require little, if any, immune suppression.

Research published online in *Proceedings of the National Academy of Sciences* details that when HLA-G dimer binds with its inhibitory receptor, ILT4, it triggers a signaling pathway in which immune molecules IL-6 and STAT3 play a major role. "Biologically this is an

interaction that requires several important suppressive molecules," says Dr. Horuzsko, the study's corresponding author and a faculty member in the MCG Schools of Medicine and Graduate Studies.

They looked at the resulting strong signaling in culture, then measured its impact on skin graft survival in mice and found it prolonged survival. Now Dr. Horuzsko is working with Dr. Laura Mulloy, chief of the Section of Nephrology, Hypertension and Transplantation Medicine in the MCG School of Medicine, to see if this dimer form is at work in kidney transplant patients who avoid rejection.

HLA-G dimer's target is another MHC molecule, which is essentially an individual's unique tissue signature; HLA-G itself is a type of MHC. In fact, HLA - human leukocyte antigen - matching is done for organ and bone marrow transplants to try minimize the recipient's reaction to the new organ. Transplant patients also take drugs that broadly dampen the immune response but can leave them more vulnerable to infections and disease.

Dr. Horuzsko notes that HLA-G can work through other cells, not just MHC molecules, and that not every HLA-G form is good at down-regulating MHC.

He plans to look at HLA-G dimer levels in tumor patients as well. "Tumors already down- regulate MHC molecules," he says, referencing how tumors turn down their tissue expression so they can fly below the radar of the immune system. "We need to see what form of HLA-G cancers - including leukemia, lymphoma, melanoma and breast cancer - use and see their level of expression." He notes that HLA-G isn't the only mechanism cancers use to escape the immune response but that being able to control a tumor's use of this molecule could offer a new way to target tumors for natural destruction.

A recent grant from the National Multiple Sclerosis Society is enabling studies of whether down-regulating MHC expression in multiple sclerosis patients can slow or arrest the immune system's attack of the nerve's protective covering. "The expression of the MHC molecule for some reason goes up - an infection might trigger the recognition of your own tissue - and the immune system attacks," says Dr. Horuzsko. "We can generate a mouse with MS-like disease and target the HLA-G inhibitory receptor to see if it effectively down-regulates the disease." He'll look to see which, if any, of the HLA-G forms are most powerful in this autoimmune scenario.

Source: Medical College of Georgia