

Researchers explore new driver of transplant rejection: Platelets

February 17 2009

Platelets, tiny and relatively uncharted tenants of the bloodstream known mostly for their role in blood clotting, turn out to also rally sustained immune system inflammatory responses that play a critical role in organ transplant rejection, according to a new report from Johns Hopkins scientists.

"Platelets potentially hold sway over many aspects of transplant biology," says Craig Morrell, D.V.M., Ph.D., an assistant professor of molecular and comparative pathobiology at the Johns Hopkins University School of Medicine. "Our data, as well as others', show a surprising interplay of platelets and the immune system, so it's time for the transplant world at large to have platelets on its radar."

A self-described "platelet guy" transfixed by the unexplored biology of these circulating bodies, Morrell collaborated with clinicians in the fields of transplant to write a comprehensive review of platelets and transplant biology, published in the January issue of the *American Journal of Transplantation*.

"It all began with the observation that when transplant tissue is rejected, platelets line up in the interior of blood vessels feeding the tissue," Morrell says. "It turns out they are not just bystanders, but have a role in driving that rejection."

As one of the most abundant cell types in the blood — second only to the oxygen-carrying red variety — platelets are ubiquitous but relatively



unexplored, Morrell says. "It's crazy how many potentially active molecules are jam-packed in these small cells and that we're only just beginning to appreciate their pro-inflammatory qualities."

In fact, mounting evidence from Morrell and others shows that platelets are part of a sustained and general immune response that can trigger or exacerbate organ rejection. Not only do they rush to the scene of a wound and adhere to local blood vessels, preventing fatal bleeding, they also dump out granules that "talk to" immune system white blood cells, Morrell says, recruiting them from far and wide to stave off potential infections.

These are on the whole very good things for platelets to do, Morrell says, but in the context of organ transplants, their pro-inflammatory function gets out of control, and they do more bad than good after contributing to initial wound healing.

Strategies using drugs or other means to keep platelets quiet and noninflammatory might benefit transplant patients in the long run because chronic rejection — as contrasted with acute or immediate organ rejection — is a major complication for which there is little current treatment, according to Hamid Rabb, M.D., medical director of kidney transplantation and a professor of medicine at the Johns Hopkins University School of Medicine.

In prior research using mice with skin transplants, Morrell and his team noted that increased platelet interactions led to increased and prolonged white cell interactions with the inner lining of the blood vessels and worsened transplant vessel damage.

"We watched platelets flowing through the blood vessels of transplanted skin in mice with and without platelets and determined tissue-platelet interactions by comparing the speeds of those flows," says Morrell,



whose team ultimately demonstrated that antibodies made in reaction to the transplanted tissue sparked platelet activation and white cell recruitment.

Studies on tissue from platelet-depleted mice helped confirm the importance of platelets in white cell activation and recruitment, strongly suggesting that limiting the inflammatory response might improve transplanted tissue survival.

Mounting evidence suggesting that platelets are activated not only posttransplant, but also during organ harvest, presents new opportunities for attacking organ injury and rejection head-on, says Rabb. The traditional target of current anti-rejection medicine is the so-called T lymphocyte — a white blood cell believed to be the major orchestrator of the immune response against any foreign tissues, including transplants.

"The thought was that if we hit the general that initiates acute rejection, it would put the troops in disarray," says Rabb. "Traditional therapies therefore inhibit or deplete T lymphocytes and other white blood cell components of the immune system. The newest kid on the block is the platelet and it represents an opportunity to target the effectors of organ injury rather than only the general."

Source: Johns Hopkins Medical Institutions

Citation: Researchers explore new driver of transplant rejection: Platelets (2009, February 17) retrieved 6 May 2024 from <u>https://medicalxpress.com/news/2009-02-explore-driver-transplant-platelets.html</u>

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