New Clues to Help Reduce Transplant Rejection

By Lila Abassi — December 16, 2015

transplant rejection via shutterstock [1]

Everyday in the United States an average of 22 people die waiting for life-saving organ transplants [2]. And in 2014, of the 121,272 in need, just 29,532 people actually received one. Securing a transplant is the first hurdle of many for graft recipients. Often they are subject to life-long immunosuppressive medications to prevent rejection [3] of donated tissue one of the many fears of transplantation.

In a study published in *Science Translational Medicine*, researchers have been able to identify a discrete mechanism using mice that may provide some hope in reducing the risk of transplant rejection. They have found (building on previous research) that *pre*-transplant individuals with failing organs have circulating autoantibodies (immune proteins that react with one s own tissue) thought to be triggered by dying cells.

As cells die, they are normally cleared by the immune system. They decompose into fragments known as apoptotic bodies and apoptotic exosome-like vesicles. Because this process happens within an individual, the process is not supposed to trigger an immune response it happens within the self. The immune system, under normal circumstances, has the ability to distinguish between self and non-self, otherwise everyone would have autoimmune disorders.

Some of the dying cells, specifically endothelial cells, have vesicles that are pinched off the cell membrane called apoptotic exosome-like vesicles. These vesicles were previously thought to be nothing more than cellular debris, but now researchers from the University of Montreal have elucidated that they play an integral role in transplant rejection.

They contain a protein known as LG-3 and antibodies to LG-3, which have been associated with transplant rejection in animal models and transplant patients. Extracellular vesicles have been increasingly scrutinized in the past decade, as they are now known to be involved in many

different processes in our bodies. They are comparable to ferries that shuttle cargo around, and how they choose what cargo to carry is what is under strenuous investigation.

The Montreal scientists injected mice with these vesicles and observed a concomitant increase in LG-3 antibodies and elevated levels of other autoimmune markers such as anti-nuclear antibodies (ANA). By injecting mice with these vesicles they also observed a heightened severity of rejection that was independent of the presence of donor tissue. The vesicles can trigger an immune response that subsequently causes inflammation (which increases the risk of rejection) of a donated graft.

These extracellular vesicles contain machinery known as a proteasome core that is similar to a garbage disposal unit for proteins. This system is sine qua non, or indispensable, for the production of antibodies that produce graft inflammation. In turn, the more damage incurred by the graft, the greater the activity of the proteasome core. This proteasome core is highly conserved between species, meaning it is similar in almost all cells**.** In humans, extracellular proteasome concentration has been correlated to the severity of inflammatory, autoimmune and neoplastic processes.

The degree of proteasome activity within these extracellular vesicles is a key determinant of their capacity to trigger the immune system to react. When scientists in this study injected mice with exosome-like vesicles that had inactive proteasomes there was significantly *less* antibody production and lower levels of other immune responses involved in transplant rejections.

Targeting this proteasome and blocking its activity is a potential target for future therapeutic interventions in preventing transplant rejections.

Research using the roundworm [4], *Caenorhabtitis elegans*, is being spearheaded by Maureen Barr, PhD, professor of genetics at Rutgers. She had this to say to say about extracellular vesicles, When we know exactly how they work, scientists will be able to use EVs for our advantage. This means that pathological EVs that cause disease could be blocked and therapeutic EVs than can help heal can be designed to carry beneficial cargo.

This is an area of research that has great potential for many scientific applications and surely one where we will hear much more about in the future.
