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Taming intolerance in bone marrow transplantation

RIKEN researchers unveil a novel advance in drug-free, cell-based immunotherapy for combating complications of bone marrow transplantation.

Scientists from the RIKEN Research Center for Allergy and Immunology, Yokohama, led by Katsuaki Satoh, and from the University of Tokyo have improved a new therapy directed against a common cause of disease and death arising from bone marrow transplantation (BMT) in mice. The researchers report in the latest issue of the journal *Blood*, that their non-pharmacological approach, using specially manipulated immune cells, suppresses a common and deadly complication - graft-versus-host disease (GVHD) - of BMT.

BMT has now become a common therapy for various types of cancers, immune deficiency disorders and genetic diseases. In allogeneic BMT (alloBMT), unhealthy or damaged bone marrow cells are replaced with healthy tissue from a genetically-matched donor. Genetic matching involves an array of specific proteins - antigens - on the surface of white blood cells called leukocytes. The genetic identity of an individual's immune system is determined largely by this human leukocyte antigen (HLA) array. A transplantation is more likely to be successful when a subset of all the HLA proteins - the major HLA antigens - is carefully matched between donor and recipient.

Host rejection of donor tissues is not the only major concern in transplantation medicine; alloBMT is often accompanied by GVHD. This disease amounts to a form of donor tissue intolerance - ranging from mild to deadly - whereby specific donor immune cells, T-cells, do not recognize the HLA identity of recipient cells and so attack host tissues. Current methods to reduce GVHD involve using immunosuppressive drugs and/or removing as many of the specific donor T-cells as possible prior to transplantation. These treatments have their own problems, however, since along with the reduced incidence of GVHD there are often increases in transplant rejection rates, severe immunosuppression, lethal infections and other serious side-effects.

The researchers worked beyond these therapies within the still largely experimental field of 'cell-based tolerogenic immunotherapy,' which, as the term 'tolerogenic' implies, involves 'pacifying' pivotal warring players of the recipient and donor immune systems. The group focused specifically on the key modulators and stimulators of cell-mediated immune responses, dendritic cells (DCs). Before T-cells can be activated to drive GVHD, they must first sample the HLA antigens, in a DC-mediated antigen presenting process. T-cell activation is extremely complicated and can only occur when the antigen presenting process works in concert with proper co-stimulatory signals. The RIKEN researchers exploited this inherent complexity to suppress GVHD.

The team subjected isolated mouse recipient DCs to a regimen of immunosuppressive chemicals to yield 'tolerogenic DCs' with a compromised capacity for T-cell stimulation. Because these modified DCs demonstrate a greater capacity for modulating T-cell-mediated immune responses in recipient mice than do other tolerogenic DCs, the researchers describe these cells as 'regulatory DCs,' with the designation DC_{reg}. These researchers had previously shown that DC_{reg} protect mice from an acute form of GVHD with an early onset after alloBMT.

The current study demonstrates that DC_{reg} also protect alloBMT-treated mice from a less understood and more intractable form of late onset GVHD - chronic GVHD - by specifically modulating, and essentially calming, the T-cell response of transplanted tissues. Importantly, some recipient DC_{reg} which were first exposed to fragments of various donor proteins before being reintroduced to the alloBMT-treated recipient mice, reduced the anti-host reactivity of the donor T-cells in an antigen-specific way. Crucially, human DC_{reg} also demonstrate similar T-cell pacifying profiles. These findings are all the more exciting since the mice used here share critical physical and functional features with human chronic GVHD.

This approach is also attractive because it may spare patients from a life-long regimen of debilitating immunosuppressive drugs. Since small animal studies are not always easily extrapolated to clinical settings, the RIKEN team will next strive to demonstrate that this approach can be used to promote transplant tolerance in humans.

Original work:

Fujita, S., Sato, Y., Sato, k., Eizumi, K., Fukaya, T., Kubo, M., Yamashita, N., Sato, K.
Regulatory dendritic cells protect against cutaneous chronic graft-versus-host disease

mediated through CD4+CD25+Foxp3+ regulatory T cells. *Blood*, online Aug. 8, 2007.

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