Homing toward tolerance

By Lev Osherovich, Senior Writer

A Portuguese team has uncovered how invariant NK T cells, which are primarily thought of as having an immunostimulatory function, can become immunosuppressive and help keep autoimmunity in check.

Although the question remains whether the cells will prove therapeutically tractable, the team's leader has already cofounded a startup, **Acellera Therapeutics Ltd.**, to develop the cells to combat liver transplant rejection and autoimmunity.

Conventional T_{reg} cells dampen immune response, so increasing their activity has been a goal in fighting autoimmunity and transplant rejection. Now, a **University of Lisbon** team led by Luis Graça has found that treating invariant NK T (iNKT) cells with α-galactosylceramide, a lipid antigen, results in the development of lipid-sensing T_{reg} cells and that these so-called T_{reg} cell–like iNKT cells home preferentially to the liver.[1]

Graça, who is assistant professor of immunology, and his team began by fractionating immune cells from a murine model of autoimmunity in which iNKT cells had previously been shown to play a suppressive role.[2] The team found that treatment with α-galactosylceramide led to greater numbers of iNKT cells bearing T_{reg} cell–associated markers than no treatment.

The team then figured out how to induce the appearance of such $iNKT_{reg}$ cells in cell culture using a cocktail of cytokines that included transforming growth factor-β (TGFB; TGFβ).

Graça's group went on to show that $iNKT_{reg}$ cells are in most respects like conventional protein-sensing T_{reg} cells, displaying the same markers and immunosuppressive properties *in vitro*. However, when cultured $iNKT_{reg}$ cells were introduced into mice, they migrated to the liver, whereas conventional T_{reg} cells gravitated toward peripheral lymphoid organs.

Results were reported in *The Journal of Immunology*.

According to Elizabeth Leadbetter, assistant member at the **Trudeau Institute**, the specific mechanism of immune suppression by iNKT cells was unknown until now. Graça's study "really gives these regulatory cells an identity," she said.

Antonin de Fougerolles, CSO of **Tolerx Inc.**, added that the Lisbon team has "uncovered a new cell type that's centrally important to regulation."

Tolerx is developing T_{reg} cell–directed immunomodulatory therapies for cancer and autoimmune disease. The company's lead product is otelixizumab, an anti-CD3 mAb in Phase III testing for type 1 diabetes and Phase II testing for rheumatoid arthritis (RA).

Many livers to cross

The next challenge is to produce proof of therapeutic efficacy in a mouse model of transplant rejection.

According to Graça, the liver tropism gives $iNKT_{reg}$ cells a therapeutic edge over conventional T_{reg} cells or systemic pharmaceutical immunomodulators.

"So far, most immunosuppressive strategies have been global," said Graça. $iNKT_{reg}$ cells "offer a prospect for immune suppression that is specific to a particular location."

Graça hopes to develop an autologous cell therapy that uses the liver-homing immunosuppressive cells to tone down liver transplant rejection, which is currently treated with systemic immunosuppressants.

He noted that a long-lasting, cell-based immunomodulatory therapy could allow patients to get away with a lower dosage of systemic immunosuppressants.

The procedure he envisions would involve "collecting a blood sample, then expanding and converting the iNKT cells isolated from the blood into these $iNKT_{reg}$ cells," said Graça. The cells would then be injected into the patient.

> **"For a chronic disease, you might want to activate these cells multiple times or infuse multiple rounds of antigen,"**
> ***—Elizabeth Leadbetter, Trudeau Institute***

Another outstanding question is whether a lipid antigen will be needed to stimulate $iNKT_{reg}$ cell development *in vivo*.

"For a chronic disease, you might want to activate these cells multiple times or infuse multiple rounds of antigen," said Leadbetter.

Although Graça's team used a synthetic lipid to initially kick off $iNKT_{reg}$ cell production, it's unclear what effect endogenous or bacterial lipid antigens might have on these cells.

Understanding how lipids in the body or from bacterial pathogens affect $iNKT_{reg}$ cells may help to shape the course of therapy.

To answer this question, de Fougerolles suggested that the Lisbon team could "take some of the other known experimental antigens and test if they can activate these cells *in vivo*."

Graça told *SciBX* that, at least *in vitro*, the TGFβ-containing cytokine cocktail is as effective as lipid antigen at inducing $iNKT_{reg}$ cells, potentially bypassing the need for a lipid adjuvant.

Going forward

Graça has filed patents on his discoveries and has licensed them to Acellera, which he cofounded earlier this year.

Acellera CEO and cofounder David Cristina told *SciBX* the company had secured seed financing to produce proof of therapeutic relevance for the $iNKT_{reg}$ cells. The company is also developing a protocol for scaling up *in vitro* production of the cells.

Besides the autologous transplant approach, Cristina said the company is exploring an oral therapy based on Graça's $iNKT_{reg}$ cell–inducing cytokine cocktail.

Cristina said Acellera has found evidence that "gavage of a cytokine cocktail can induce high populations of $iNKT_{reg}$ cells in the gut," which could be useful for treating Crohn's disease.

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COMPANIES AND INSTITUTIONS MENTIONED

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