Plan B for diabetes

By Lev Osherovich, Senior Writer

Evidence has emerged in recent years that inflammation and abnormal T cell activity in adipose tissue contribute to type 2 diabetes. Now, North American researchers have evidence of another immune player in inflamed adipose tissue—B cells that secrete autoreactive antibodies.¹

The findings help build a case for treating metabolic syndrome and type 2 diabetes with immunomodulators originally developed for B cell-driven autoimmune indications.

“There has been plenty of work to document that there is significant inflammation in the adipose tissue in type 2 diabetes, but this has been mostly around macrophages,” said team leader Edgar Engleman, professor of pathology and medicine, immunology and rheumatology at **Stanford University School of Medicine**. “That data led us to hypothesize that it’s not just a matter of the innate immune system, and that there might be a role for T cells and B cells.” Engleman is also a cofounder of **Dendreon Corp.** and a founder and managing partner at **Vivo Ventures**.

Previous reports by Engleman’s team and others have shown autoimmunity-associated changes in T cell populations in diabetic adipose tissue.^{2–4} In the new study, Engleman’s team looked at B cell activity, which is downstream of the T cell involvement his team previously identified.

The researchers captured and analyzed immune cells in the adipose tissue of overfed, diabetic mice and found evidence of B cell infiltration and autoantibody accumulation compared with those in normally fed controls.

To test whether these B cells and antibodies contributed to disease, the team overfed mice genetically engineered to lack B cells and tested them for signs of type 2 diabetes. Although B cell-deficient mice became obese, the animals did not develop signs of type 2 diabetes, including increased insulin and decreased glucose tolerance.

To resolve whether B cells themselves or the antibodies they produce are to blame for type 2 diabetes, the team transfused serum from overfed, diabetic mice into nondiabetic mice lacking B cells. Recipient mice developed high insulin and low glucose tolerance compared with controls receiving serum from overfed, normal mice. Thus, Engleman suspects the B cell-produced autoantibodies are the cause of insulin resistance.

The team also provided proof of concept for treating type 2 diabetes with an antibody that eliminates B cells. An antibody against CD20, a B cell surface protein, improved glucose tolerance and insulin levels compared a control antibody.

Results were reported in *Nature Medicine*.

“A lot of work has been done on the role of innate immunity in type 2 diabetes, but this paper really puts things back to the adaptive immune system,” said Scott Koenig, president and CEO of **MacroGenics Inc.**

“In addition to macrophages, CD8⁺ T cells and T helper type 1 cells, it now looks like B cells are probably involved” in adipose tissue inflammation and type 2 diabetes, said Diane Mathis, professor of pathology at **Harvard Medical School**. “Every piece that you add to the puzzle is interesting. What will be important is working out how this orchestra plays together, which is going to be pretty complex.”

Anti-antibody strategy

Based on the new findings, Engleman has formed a hypothesis about how autoantibodies fit into the immunological train wreck taking place in diabetic adipose tissue.

Type 2 diabetes “is a multistep process that starts with a bad diet,” Engleman told *SciBX*. “Perhaps in the fatty tissue there’s too much growth of adipocytes. They outgrow their blood supply and die, which leads to apoptosis. This brings scavengers like macrophages, which leads to inflammation. This in turn brings in T cells and B cells,” the latter of which are the source of the pathogenic autoantibodies.

Mathis thinks this model is plausible.

“If the macrophages and T cells are killing fat cells, this could be promoting the production of antibodies,” said Mathis. In support of this idea, she cited evidence that some diabetic patients have antibodies against insulin receptors, “which could exacerbate insulin resistance.”

The outstanding questions are what exactly the antibodies recognize and whether blocking the production or activity of autoantibodies will slow disease progression in patients.

Engleman’s study “shows the potential effects of B cells and antibody response in the pathogenesis of type 2 diabetes in mice, but where this fits in with patients is not clear,” said Koenig.

Last year, MacroGenics and partner **Eli Lilly and Co.** reported that the biotech’s teplizumab, a mAb against the T cell protein CD3, failed in a Phase II/III trial to prevent type 1 diabetes. Teplizumab is in an ongoing Phase II trial to prevent progression of type 1 diabetes in patients who have already developed the disease.

Koenig said Engleman’s findings suggest that companies in the type 1 diabetes space should be watching for opportunities in type 2 diabetes, but that it’s too soon to tell which targets to pursue.

“It’s intriguing that there are similarities in the mechanisms” of the two forms of diabetes, said Koenig. “The ultimate question is whether similar therapies could be used for both indications.”

Immunomodulatory strategies for type 2 diabetes have not yet borne fruit. For example, **Xoma Ltd.**’s XOMA 052, a mAb that targets the inflammatory cytokine IL-1 β , failed in a Phase II trial for type 2 diabetes in March.

XOMA 052, which is partnered with **Servier**, is in Phase II testing for Behcet’s uveitis and rheumatoid arthritis (RA).

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— Scott Koenig, MacroGenics Inc.

B gone

Mathis thinks retrospective analyses of patients already on B cell-depleting therapies for autoimmune indications might reveal whether such an approach would work in type 2 diabetes.

“There must be a lot of people treated with rituximab” who are at risk for type 2 diabetes, said Mathis. “You could ask if they have altered insulin resistance” compared with untreated controls.

Biogen Idec Inc. and **Roche’s Genentech Inc.** unit co-market the anti-CD20 mAb rituximab as Rituxan in the U.S., while Roche markets it as MabThera in Europe, to treat a range of cancer and autoimmune indications including non-Hodgkin’s lymphoma (NHL), multiple sclerosis (MS) and RA.

Mathis suggested that other B cell targets, such as BLyS (BAFF), also might be worth exploring for type 2 diabetes. BLyS is the target of Benlysta belimumab, a mAb from **Human Genome Sciences Inc.** and **GlaxoSmith-Kline plc** that is approved to treat systemic lupus erythematosus (SLE).

Mathis cautioned that B cell-depleting approaches could be risky because of the broad systemic effects of such therapies and the safety-oriented regulatory environment for diabetes. “There’s more and more interest in targeting B cells for autoimmune indications, but my feeling is that I would be rather surprised if drug development in the metabolic disease field would go toward B cell-depleting therapies,” said Mathis.

Engleman’s ultimate goal is to develop a therapeutic vaccine that could forestall type 2 diabetes progression.

In the paper, his group reported a list of 20 antigens preferentially recognized by autoantibodies in serum from 32 patients. The researchers now hope to winnow that list down to a few targets that might be the most relevant to disease.

“We’d very much like to know what the specificities” of the diabetes-associated autoantibodies are, said Engleman. “If we can identify one or a few antigenic species that are responsible, you could potentially develop a vaccine” that promotes tolerance to the self-antigens that trigger pathogenic autoantibodies.

Mathis said understanding the order of events leading to autoantibody production will be critical in designing a vaccine. If T cells come into play before autoantibodies, there may be a therapeutic window for vaccines or immunomodulatory therapeutics. However, if autoantibody production “is happening late in the disease process, vaccinating against these antigens wouldn’t make much of a difference,” she noted.

Stanford University and the **University of Toronto** have filed patents in connection to the study. The IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Dendreon Corp. (NASDAQ:DNDN), Seattle, Wash.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Genentech Inc., South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Harvard Medical School, Boston, Mass.
Human Genome Sciences Inc. (NASDAQ:HGSI), Rockville, Md.
MacroGenics Inc., Rockville, Md.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
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