negatively regulates autophagy via modulation of mTOR activity. How this relates to the autoimmune function is yet to be determined.

In our previous work in type-1 diabetes, the protective *CLEC16A* alleles were associated with higher levels of CLEC16A (formally known as *KIAA0350*). We also recently showed that ubiquitous loss of CLEC16A led to disrupted mitophagy in immune cells.

Given the large number of autoimmune and other disorders correlated with CLEC16A loss or dysfunction, it is clear that new treatments and therapeutic agents which ameliorate the effects of malfunctioning CLEC16A are urgently needed.

Summary

The current disclosure implicates CLEC16A as a critical regulator of lipophagy and endoplastmic reticulum (ER) stress, involving a robust cytokine response that results in a systemic inflammatory response and lipolytic processes responsible for substantive weight loss. As CLEC16A is a major autoimmune gene associated with at least 16 autoimmune diseases, including type-1 diabetes, multiple sclerosis, lupus and inflammatory bowel disease.

In accordance with the present disclosure, a combination therapy for the treatment of at least one autoimmune disorder associated with aberrant CLEC16A function is provided. In one aspect, the present disclosure provides a use of one or more agents selected from a mitophagy suppressor/modulator, an ER suppressor, a JAK2 inhibitor and SOCS1 inhibitor in the manufacture of a medicament for treating a CLEC16A-associated autoimmune disorder in a subject in need thereof. In another aspect, the present disclosure provides a use of an agent that modulates expression of one or more of CD163, Bcl-2, Pax-5, V-cam1, CD8 and FoxP3 in the manufacture of a medicament for treating CLEC16A-associated degeneration of the thymus, thereby altering the medulla cortex ratio in thymus and ameliorating symptoms associated with degeneration of the thymus.

In yet another aspect, the present disclosure provides a use of an agent that modulates one or more of CD163, CD68, Bcl-2, CD40, Pax5, Vcam1, CD3, and GzmB in the manufacture of a medicament for treating CLEC16A-associated degeneration of spleen, thereby altering the white red pulp ratio in the spleen and ameliorating symptoms associated with degeneration of the spleen. In a further aspect, the present disclosure provides a use of an agent which modulates

CD163 expression and/or immune cell infiltration and/or acini cell degeneration in the pancreas in the manufacture of a medicament for treating CLEC16A-associated degeneration of the pancreas, thereby reducing autoimmune symptoms.

In one example a method for treating CLEC16A-associated degeneration of the thymus is provided comprising administration of an agent that modulates expression of one or more of CD163, Bcl-2, Pax-5, V-cam1, CD8 and FoxP3, thereby altering the medulla cortex ratio in thymus and ameliorating symptoms associated with degeneration of the thymus. In another embodiment, a method for treating CLEC16A-associated degeneration of spleen is provided comprising administration of an agent that modulates expression of one or more of CD163, CD68, Bcl-2, CD40, Pax5, Vcam1, CD3, and GzmB, thereby altering the white red pulp ratio in the spleen and ameliorating symptoms associated with degeneration of the spleen. The disclosure also discloses a method for treating CLEC16A-associated degeneration of the pancreas comprising administration of an agent which modulates CD163 expression and/or immune cell infiltration and/or acini cell degeneration in the pancreas, thereby reducing autoimmune symptoms.

As noted above, the disclosure includes a combination the combination therapy that can include at least two of a mitophagy suppressor/modulator, ER suppressor, a JAK2 inhibitor and

SOCS1 inhibitor. Inhibitors of the JAK-Stat pathway will also have utility in the present disclosure. In certain embodiments, the agents are rapamycin and tofacitinib. In other embodiments, a nucleic acid encoding CLEC16A is obtained from the subject and assessed for the presence of genetic alterations.

Brief Description of the Drawings

Figure 1. Percent body weight from initial body weight over time. Mice were weighted 3 times per week during the study.

Figure 2. Clec16a KO male and female mice exhibit complete loss of body and visceral fat.

Figure 3. Foot intake in KO mice as compared to controls.

Figures 4A – 4D. Fig. 4A) Representative immunoblot depicting CLEC16A expression. Fig. 4B) mRNA levels of ER stress markers in control and KO gWAT. Fig. 4C) Representative immunoblot depicting ER stress in KO gWAT. Fig. 4) Organ weight ratio.

Figure 5. Hormone sensitive lipase (HSL) phosphorylation in control and KO mice.

Figures 6A -6C. Fig. 6A) The mRNA expression and Immunoblot (Figs. 6B and 6C) of lipid catabolism genes (*Cpt1b, Ppara*), adipogenic genes (*Pparg and Adipoq*) and thermogenic genes (*Ucp1 and Cidea*) from gWAT of control and KO mice.

Figure 7. Lipid analysis (cholesterol, triglyceride, and free fatty acid) from Clec16a KO vs. control mouse serum.

Figures 8A – 8D. Fig. 8A) Clec16a KO mice exhibit decreased adiponectin, leptin, and LDL-R in comparison to control. Fig 8B) Clec16a KO mice exhibit up increased cytokines, chemokines, growth factors compared to control adipose. Fig. 8C) Clec16a KO mice exhibit up increased cytokines, chemokines, growth factors compared to control adipose. Inhibitor U0126 reverses the upregulation. Fig. 8D) High constitutive expression of IL-16 precursor in Clec16a KO splenocytes and release of bioactive IL-16 by active caspase-3.

Figure 9. Decreased expression of SOCS1 and SOCS3 in Clec16a KO splenocytes.

What is claimed is:

1. Use of one or more agents selected from a mitophagy suppressor/modulator, an ER suppressor, a JAK2 inhibitor and SOCS1 inhibitor in the manufacture of a medicament for treating a CLEC16A-associated autoimmune disorder in a subject in need thereof.

2. Use of an agent that modulates expression of one or more of CD163, Bcl-2, Pax-5, V-cam1, CD8 and FoxP3 in the manufacture of a medicament for treating CLEC16A-associated degeneration of the thymus, thereby altering the medulla cortex ratio in thymus and ameliorating symptoms associated with degeneration of the thymus.

3. Use of an agent that modulates one or more of CD163, CD68, Bcl-2, CD40, Pax5, Vcam1, CD3, and GzmB in the manufacture of a medicament for treating CLEC16A-associated degeneration of spleen, thereby altering the white red pulp ratio in the spleen and ameliorating symptoms associated with degeneration of the spleen.

4. Use of an agent which modulates CD163 expression and/or immune cell infiltration and/or acini cell degeneration in the pancreas in the manufacture of a medicament for treating CLEC16A-associated degeneration of the pancreas, thereby reducing autoimmune symptoms.

5. The use of any of claims 1 - 4 , wherein said CLEC16A associated autoimmune disorder is selected from type-1 diabetes, multiple sclerosis, primary adrenal insufficiency, Crohn's disease, primary biliary cirrhosis, juvenile idiopathic arthritis, rheumatoid arthritis, and alopecia areata, uveitis, neurodegeneration and lupus.

6. The use of any of claims 1 - 5, wherein said agents are rapamycin and tofacitinib.

7. The use of any of claims 1-5, wherein a nucleic acid from said subject is first assessed for an alteration in a CLEC16a encoding nucleic acid.