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Diabetes and Obesity

A NEW DAWN FOR TYPE 1 DIABETES: COMBINING A NANOTHERAPY TO HALT AUTOIMMUNITY WITH BETA-CELL REGENERATION

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1. Summary

Type 1 diabetes (T1DM) is a metabolic disease of unknown aetiology that mainly affects children and teens, impacting their quality of life and causing secondary complications. Unfortunately, the incidence of T1DM is increasing worldwide. T1DM is an autoimmune disease caused by the selective destruction of insulin-producing beta cells in the pancreas. One century ago, T1DM was a fatal disease, until the discovery of the hormone insulin. Exogenous insulin administration is the current treatment for this disease. The failure of clinical trials performed in the last decades highlights the urgent need for new strategies to prevent and cure T1DM. Our group has generated an innovative nanotherapy based on small particles (liposomes) that definitively arrests the destruction of beta cells in T1DM. This immunotherapy is not enough to cure the disease due to the reduced beta cell mass at the onset of the disease. However, in combination with a regenerative strategy, it could contribute to a cure. The aim of this project was to develop a combined therapy for T1DM, coupling liposomes and a drug with beta cell regeneration abilities identified by drug repositioning, a computational technique that identifies new uses for approved drugs. During the three-year development of the project, different liposome formulations were tested and we selected the most effective both in the mouse model of the disease and in immune cells from patients with T1DM. Liposome treatment also demonstrated optimal safety and tolerability in mice. Simultaneously, we selected a drug (Liraglutide) with the potential to regenerate beta cell mass and this effect was demonstrated in diabetic mice. The mechanism of action was double: on one hand Liraglutide induced neogenesis of beta cells from pancreatic ducts and on the other hand transdifferentiation from islet alpha cells. The next step was to merge both strategies, demonstrating that combined therapy (immunotherapy + regenerative) was able to revert experimental T1DM and without observed adverse effects. In conclusion, the combination therapy with Liraglutide and a liposome-based immunotherapy is a promising candidate strategy for T1DM.

Dissemination at the Societat Catalana d'Immunologia (in Catalan).
https://www.youtube.com/watch?v=boOlYaaj1RM

2. Project results

The results obtained after the three-year project development are detailed below:

1. First, the optimal nanoparticles for T1DM combined immunotherapy were selected after testing several formulations in the experimental model of disease, the non-obese diabetic (NOD) mouse, a spontaneous model of T1DM similar to the human disease. Liposome treatment demonstrated optimal safety and tolerability in NOD mice

2. The tolerogenic effect of the selected liposomes was assessed in dendritic cells obtained from patients with T1DM. Patients were selected at the Paediatrics and Endocrinology Dept. of the Germans Trias i Pujol University Hospital. The potential effect of liposomes in arresting autoimmunity was confirmed in adult and paediatric patients at several stages of the disease (onset and longstanding).

3. At the same time, a drug repositioning analysis based on systems biology was performed to identify the beta-cell regenerative potential of commercially available compounds. Drug repositioning is a strategy used for identifying new uses for approved drugs that are outside the scope of the medical indication. This analysis was carried out in collaboration with Anaxomics Biotech S.L. A list of candidates was obtained and we selected Liraglutide for its predictive efficacy values for neogenesis, transdifferentiation of alpha-cells and/or replication of pre-existing beta-cells. Liraglutide is an analogue of glucagon-like peptide-1, a drug used in patients with type 2 diabetes. The effect of Liraglutide was confirmed in mice, demonstrating neogenesis of beta cells from the pancreatic ducts and transdifferentiation from glucagon producing alpha cells, as represented in Figure 1.

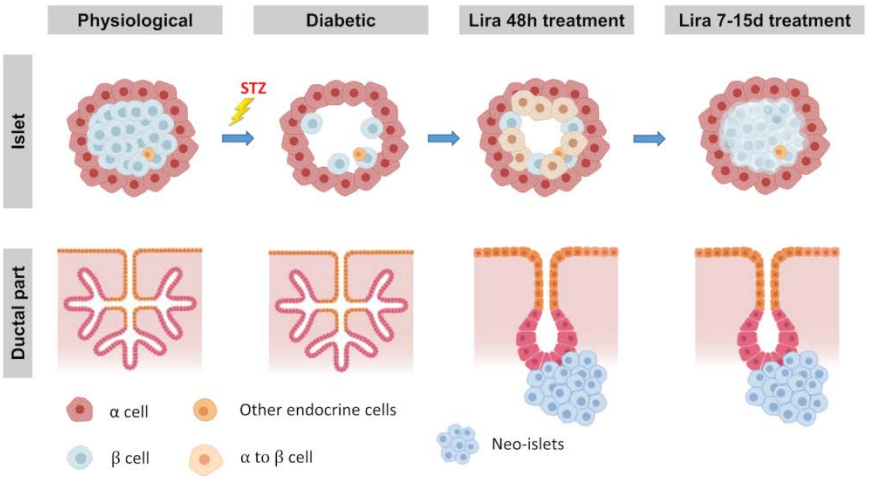

Figure 1. Proposed model of Liraglutide-induced β-cell regeneration. Top row: Islet β-cells were depleted when treated with streptozotocin (STZ), while the ductal part of the pancreas remains unaffected. We propose that Liraglutide can induce a regeneration process in two steps. The first consists in the transdifferentiation from alpha-cells (glucagon-producing) into new insulin-expressing β-like cells, while in the second step neo-islets formed by insulin-expressing β-like cells arise from the pancreatic ducts (lower row).

4. Taking all this information into account, an experimental combined therapy consisting of an immunotherapy based on liposomes to arrest autoimmunity and Liraglutide to promote beta-cell regeneration was designed and tested in NOD mice to determine metabolic, immunologic and regenerative effects. The results showed that this strategy is able to ameliorate hyperglycaemia in experimental T1DM.

5. To go closer to clinical practice, we explored the effect of the combined therapy in the immune system cells from adult patients with T1D (Endocrinology Dept., Germans Trias i Pujol University Hospital), both in vitro and in vivo using humanized mouse models. Liraglutide was not detrimental for the tolerogenic effect of liposomes, and no adverse effects in human immune system cells were detected.

In summary, the aims of the project were achieved. While additional research is still needed to explore the potential of the combined therapy, this strategy could be useful for the treatment of T1DM. Moreover, the approach reported here could be adapted to other autoimmune diseases.

2. Impact

This project resulted in the optimisation of the liposome-based immunotherapy generated by our group in 2015 and in the demonstration of its effect in the human immune system. Importantly, the drug repurposing analysis has identified a candidate drug (Liraglutide) that stimulates the regeneration of insulin-producing beta cells, the target tissue in autoimmune diabetes. In fact, Liraglutide (trade name Victoza®, Novo-NordiskA/S) improves beta-cell replacement by two mechanisms, transdifferentiation and neogenesis, and contributes to glucose homeostasis restoration in T1DM. We have therefore taken a step towards a new therapeutic strategy for this autoimmune disease, based on a combined therapy. The impact derived from the results of this project on T1DM are described below.

- Liposomes to be tested in a future clinical trial for T1DM have been designed, generated, evaluated and selected.

- By drug repurposing analysis, we have identified a candidate drug (Liraglutide) capable of inducing insulin producing beta cell regeneration. The mechanism of action has been elucidated. Finding new uses for existing drugs accelerates the development of novel products with safety, provides further protection to embattled pipelines, and efficiently generates innovation in disease.

- Combined therapy is effective in ameliorating hyperglycaemia in diabetic mice. We previously demonstrated that liposomes alone were able to prevent T1DM but not enough to cure the disease in overt diabetic mice. Both a regenerative strategy and the immunotherapy are imperative to definitively arrest the autoimmune attack and to restore insulin producing cells lost before the onset of the disease. Importantly, Liraglutide does not interfere with the tolerogenic effect that liposomes exert on the immune system cells from patients with type 1 diabetes.

While additional research is still needed to explore the regenerative potential of Liraglutide, the combined therapy could be useful in the reversal of T1D.

4. Articles and Thesis

ORIGINAL ARTICLES

- Rodriguez-Fernandez S, Pujol-Autonell I, Brianso F, Perna-Barrull D, Cano-Sarabia M, Garcia-Jimeno S, Villalba A, Sanchez A, Aguilera E, Vázquez F, Verdaguer J, Maspoch D, Vives-Pi M. Phosphatidylserine-Liposomes Promote Tolerogenic Features on Dendritic Cells in Human Type 1 Diabetes by apoptotic Mimicry. Frontiers in Immunology 9:253, 2018.

- Rodriguez-Fernandez S, Murillo M, Villalba A, Perna-Barrull D, Cano-Sarabia M, Gomez-Muñoz L, Aguilera E, Maspoch D, Vazquez F, Bel J, Vives-Pi M. Impaired phagocytosis in dendritic cells from pediatric patients with type 1 diabetes does not hamper their tolerogenic potential. Frontiers in Immunology 10:2811, 2019.

- Villalba A, Rodriguez-Fernandez S, Ampudia RM, Cano-Sarabia M, Perna-Barrull D, Bertran-Cobo C, Ehrenberg C, Maspoch D, Vives-Pi M. Preclinical evaluation of antigen-specific nanotherapy based on phosphatidylserine-liposomes for type 1 diabetes. Artif Cell Nanomed Biotech. 48 (1):77-83, 2020.

- Villalba A, Rodriguez-Fernandez S, Perna-Barrull D, Ampudia RM, Gomez-Muñoz L, Pujol-Autonell I, Aguilera E, Coma M, Cano-Sarabia M, Vazquez F, Verdaguer J, Vives-Pi M. Repurposed analogue of GLP-1 ameliorates hyperglycaemia in diabetic mice through pancreatic cell reprogramming. Frontiers in Endocrinology, May 2020, 11:258, 2020.

- Villalba A, Rodriguez-Fernandez S, Perna-Barrull D, Ampudia RM, Gomez-Muñoz L, Pujol-Autonell I, Aguilera E, Risueño RM, Cano-Sarabia M, Maspoch D, Vazquez F, Vives-Pi M. Antigen-specific immunotherapy combined with a regenerative drug in the treatment of experimental type diabetes. Sci Rep 10:18927, 2020.

PhD THESIS

Adrian Villalba Felipe. Combined therapy for type 1 diabetes: Immunotherapy and regenerative strategies. October 2020 (Excellent Cum Laude)

PUBLISHED ARTICLES

Vives-Pi M. 'Reeducar al sistema inmunitario para detener el ataque a las células beta (páginas 20-23. La tolerancia es la clave'. Revista Diabetes (SED), 20-23, Dec 2019. https://fundacion.sediabetes.org/wp-content/uploads/2019/10/Revista_Diabetes_60/