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Role of Autoimmunity in Development of Type 2 Diabetes

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ABSTRACT

The mechanisms that underlie Type 2 diabetes are complex and far less illustrated compared to Type 1 diabetes which has been acknowledged as an autoimmune disease. It has been hypothesized that autoimmunity, autophagy, or/and dedifferentiation of islet β cells and other factors could be involved in the development of Type 2 diabetes, in which autoimmunity may also play a critical role.

Keywords: Diabetes, Autoimmunity, Immune Cells, Insulin, Islet B Cells, Autophagy, Dedifferentiation, Insulin Resistance, Hyperglycemia.

INTRODUCTION

Type 2 diabetes is characterized by hyperglycemia, insulin resistance, and insufficiency or relative lack of insulin.[1-3]. In some patients with type 2 diabetes, insulin resistance causes cells to respond inadequately to normal insulin levels, resulting in a relative lack of insulin [3]. In contrast, other patients exhibit insufficient insulin production from dysfunctional pancreatic β cells [2,3]. In most cases, people with insulin resistance do not develop irreversible diabetes without impairing insulin secretion by β cells [4,5], indicating β cell damage(apoptosis) or/and dedifferentiation [4] is a critical factor in developing type II diabetes. It was found that the β cell mass expands, increasing the insulin output to compensate for the insulin insensitivity in the early stages of insulin resistance [4,6], and the loss of 50% of β cells when type 2 diabetes has been clinically developed [4,6,7]. Other studies also found β cell reduction in type 2 diabetes [8]. These findings are consistent with most clinical observations [2]. However, the mechanism of β cell loss in type 2 diabetes has not been fully elucidated, although many studies have been done and various hypotheses have been posited. [1-4,6,7].

Contribution of Autoimmunity to Insulin Resistance

Insulin resistance can be found in almost every tissue of type 2 diabetes patients whose adipose, muscle and liver tissue are well studied [2]. In obesity-induced insulin resistance, the chronic tissue inflammation in adipose tissue is caused by increased cytokines and chemokines as well as macrophages and other immune cells. More than ten cytokines

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and chemokines such as IL-1, TNF, IL-6, leptin, and chemo attractant protein-1 (MCP-1), are associated with the insulin resistance in adipose, muscle and liver cells. These cytokines and chemokines play important roles in attracting immunocytes, inducing macrophage polarization, and causing inflammation [9,10]. Auto-antibodies against intracellular antigens, such as GOSR1 (a golgi complex protein), GFAP1 (an inter mediate filament protein), BTK (a tyrosine kinase important in B cell development), and enzymes such as aspartoacylase, glutathione-s-transferase, and RNA polymerase, were found in adipose tissue and serum of high fat diet-fed mice [3,11,12]. These antigens, when exposed to the immune system, can stimulate T cell immune responses, causing T and B lymphocytes in the adipose tissue to release more cytokines and exacerbate insulin resistance. The excessive inflammatory factors released from adipose tissue enter other tissues or organs and further cause inflammation of the target tissues or organs. This is a hypothesized mechanism for the inflammation of pancreatic islets which may initiate β cell damage [2,13]. The more that immunocytes infiltrate the adipose tissue, the more cytokine is released, forming a vicious circle.

Many therapeutic measures of weight control can effectively break this cycle and reduce insulin resistance or retard its development. However, it is unknown if the insulin resistance can be remitted by blocking cytokines and/or chemokines pathway or depleting any subtype of T or B cells.

Hypothesized Mechanisms for β Cell Loss in Type 2 Diabetes

Cytokine mediated β cell loss

After being processed by antigen-presenting cells, such as dendritic cells and macrophages, the auto-antigens from the lipolysis caused by lipotoxicity are presented to CD4+ T cells in the pancreatic lymph nodes, which lead to the recruitment of proinflammatory cells to the pancreatic islets and to the production of proinflammatory cytokines, resulting in β cell loss [2,13]. This hypothesis does not explain why those cytokines only damage the β cells but not their adjacent α cells. One possibility could be that β cells are unusually sensitive to the stress from cytokines when they are overworking to produce and release insulin due to the excessive insulin needs triggered by insulin resistance. In our recent observations, more insulin was needed to bring the blood glucose down to normal levels in type 2 diabetes patients experiencing cytokine storm caused by severe COVID-19, suggesting the effects of cytokines on exacerbation of Type 2 diabetes.

Critical role of macrophages

Although T cells did not increase in pancreatic islets in Type 2 diabetes, a significant increase in macrophages was found around the islets [14,15]. In adipose tissue, macrophage polarization from M1/M2 balance to M1 dominance increases the inflammation of adipose tissue and further increases the insulin resistance of adipose cells [14,15]. If the same macrophage polarization occurs around the pancreatic islets, it could explain β cell loss or damage because M1 polarization can enhance the inflammation reaction (M1 represents the classically activated proinflammatory macrophages and M2 represents the alternatively activated anti-inflammatory macrophages). This hypothesis still has a specificity problem in which only the β cells are damaged but not their adjacent α cells in the islet.

Changes in immunocyte subsets in obese condition

Mukul Prasad, et al. [2,9,10] summarized previous studies and posited that immunocyte subset changes caused by intake of high fat diet in the observed obese subjects can play an important role in the development of type 2 diabetes. They found a marked decrease in the anti-inflammatory immunocyte subsets and an increase in the proinflammatory immunocyte subsets at various physiologic sites, including (1)anti-inflammatory Tregs, Bregs, iNKT cells, ILC2 cells, M2 macrophages, eosinophils decrease, and the proinflammatory TH1, CD8+ T cells, $\gamma\delta$ T cells, B cells, NK cells, and M1 macrophages increase in adipose tissue; (2) loss of TFH cells and IgA plasmablasts in digestive system; (3) the microglia become more proinflammatory and circulatory macrophages accumulate in the brain; (4) proinflammatory TH1 cells and macrophages accumulate in skeletal muscles; (5) loses the anti-inflammatory CD40+CD11c+ dendritic cells and the Kupffer cells become proinflammatory in liver; and (8) macrophages, CD4+ T cells and B cells accumulate in pancreas. These changes are part of the insulin-resistance mechanism and the changes in the pancreas could more directly contribute to the development of type 2 diabetes, although the significant amounts of CD8+ cytotoxic T lymphocytes found in pancreatic islet of type 1 diabetes were not found in type 2 diabetes. This hypothesis also lacks specificity for β cell damage.

Controversial role of TNF-α

Unlike many other cytokines, TNF-α can directly lead to cell death by inducing apoptosis. Its role in the pathogenesis of insulin resistance and type 2 diabetes has been studied and reported by many authors [16,17]. Many studies found that TNF-α impaired the insulin action in the animal models and/or cell cultures [2,18,19], induced inflammation in pancreatic islets, and caused apoptosis in β-cells of pancreatic islets [20,21] by activating transcriptional factor, NF-κB, to modulate pancreatic cell death [3,22,23].

The above studies posited that TNF-α plays a critical role in the development of insulin resistance, the impairment of β-cells of pancreatic islets, and the pathogenesis of type 2 diabetes. Therefore, several anti-TNF-α treatment strategies have been used to confirm the effects of TNF-α in the development of type 2 diabetes. In experimental animal studies, anti-TNF-α treatment compromised the insulin resistance [24], and neutralization of TNF-α reduced hepatic insulin resistance [25]. However, results from clinical trials with anti-TNF-α treatment strategies in the patients with type 2 diabetes are controversial [19,26-28]. The inconsistency in the clinical observations has raised questions about the central role of TNF-α. In addition, this hypothesis also lacks the specificity on the impairment of β cells, the same as other cytokines. It is possible that TNF-α is only one of many important factors in the pathogenesis of type 2 diabetes and that a more complicated mechanism needs to be explored.

The hypotheses above have a common defect: they lack specificity to the β cells in pancreatic islet

We hypothesized that β cells are unusually sensitive to inflammatory stress when they are long-term overworking to produce and secrete insulin due to insulin's high demand triggered by insulin resistance. This hypothesis has evidence to support it. First, most early stage type 2 diabetes patients have elevated insulin level for several months or longer to fight the insulin resistance [4,29]. Afterwards, the insulin level declines. Second, after several months of insulin therapy, many early stage type 2 diabetes patients can recover to a level where only a proper diet is required and there is no need for insulin and other anti-diabetes medication [4,29]. Third, some type 2 diabetes patients with restricted carbohydrate intake (they mainly ate meat), such as those in our and others' studies [30,31] with low carbohydrate, ketogenic diet (LCKD), for several months can stay free of any anti-diabetes medication and keep the blood sugar and insulin levels normal. However, the diabetes of these patients would relapse if they take the diet with normal amount of carbohydrate. Although this hypothesis is supported by above mentioned evidences, it faces more challenging issues to confirm it is true. First, there is a need to confirm that overworked β cells are more susceptible to damage or death under inflammatory stress. Second, there is a need to clarify why overworked β cells are more sensitive to inflammatory stress. It can be caused by simple increased cell membrane permeability, abnormal molecule expression or cell internal antigen exposure on the cell surface. Third, if any abnormal antigen is expressed on the cell surface, the corresponding T cell response should be further investigated, although no T cell increase was found in pancreatic islets of type 2 diabetes in previous studies [2].

Other possible mechanisms

In recent years, some new hypotheses for β cell loss were proposed. Among them, autophagy[32-34] and dedifferentiation [35-37] of β cells were considered to important causative factors of the development of type 2 diabetes. However, it is not clear if and how autoimmunity play a role in inducing β cell autophagy or/and dedifferentiation. The inflammation caused by cytokines and immunocytes could be the major perpetrator in triggering the β cell autophagy and dedifferentiation [4,32-37].

Relevance of Other Autoimmune Diseases to Type 2 Diabetes

Obesity and many other diseases are associated with type 2 diabetes. Among these, some autoimmune diseases are often accompanied by type 2 diabetes [38]. The relationship between autoimmune diseases and type 2 diabetes strongly suggests that at least part of type 2 diabetes has a pathogenesis similar to those autoimmune diseases, or that those autoimmune diseases trigger the autoimmune response to islet β cells with aforementioned hypothesized mechanisms.

Kari Hemminki, et al. [38] investigated 757,368 patients with autoimmune diseases, and found that these patients were more susceptible to developing type 2 diabetes later, especially chorea minor (8.00), lupoid hepatitis (5.75), Addison disease (2.63), and immune thrombocytopenic purpura (2.46) and they have a higher risk of developing type

2 diabetes than most other diseases. Their data also showed that the risk of type 2 diabetes was higher in patients with rheumatoid arthritis (1.5), which is consistent with other findings by Piero Ruscitti, et al., [39,40] Solomon DH, et al. [41] and Dubreuil M. et al.[42] The studies from Solomon DH, et al. [43] and Dubreuil M, et al.[44] also found a higher risk of diabetes in patients with psoriatic arthritis and psoriasis.

Supporting Data from Type 2 Diabetes Animal Models

An animal model is an important tool for studying the etiology, pathology, pathogenesis and treatment of type 2 diabetes. Current animal models were mainly prepared by genetic manipulations to cause type 2 diabetes symptoms or imposing a high fat diet to induce obesity and type 2 diabetes symptoms.[45,46] However, mouse genetic model can model a few of them for induction of diabetes, and most patients get type 2 diabetes from their diet rather than their genetics. A great advantage of a high fat diet mouse model is that it engenders obesity, insulin resistance and chronic inflammation by increasing the cytokines, such as TNF-α, IL-1β, and IL-6, in circulation. [48,49] These are similar to those aforementioned changes observed in human type 2 diabetes. Therefore, a high fat diet model is a more appropriate model for type 2 diabetes [50]. The rat and cat high fat diet models are also used in the studies of type 2 diabetes [49,51].

Several studies were successfully conducted to demonstrate the effects of TNF blockage on insulin resistance with animal models [19,26,27], and other studies directly focused on the etiology and pathogenesis of type 2 diabetes [45-47], The data from these animal experiments provide evidence that autoimmunity is the main mechanism in the development of type 2 diabetes.

Indirect supporting data from mesenchymal stem cell (MSC) therapy

In past years, many clinical studies exhibited that MSC therapy significantly improved the condition of patients with type 2 diabetes, including ameliorating hyperglycemia, reducing insulin requirement increasing in fasting C-peptide levels and decreasing glycosylated hemoglobin levels [52,53]. Since MSC showed significant immunomodulatory effects in treatment of numerous autoimmune diseases, [54,55] its therapeutic effects seen in type 2 diabetes treatment suggest autoimmunity could be one of the type 2 diabetes causative factors.

Involvement of Th17 cells in the mechanism of type 2 diabetes development

Th17 cells are a subset of T helper cells characterized by their interleukin 17 production [56]. Some studies demonstrated they are implicated in autoimmune and inflammatory disorders, such as rheumatoid arthritis, multiple sclerosis, and psoriasis [57,58]. Excessive or over-activated Th17 cells were also found in type 2 diabetes patients and animal models [59-61]. It may suggest a new therapy for type 2 diabetes if further studies provide more direct evidence to show how Th17 cells affect the inflammation in the adipose tissue to cause insulin resistance and damages of exhausted islet β cells.

SUMMARY

In the past decade, more studies have suggested that type 2 diabetes is an autoimmune disease that involves both innate and adaptive immunity [2]. Chronic inflammation in the adipose tissue with cytokines, chemokines and immunocytes initiates the insulin resistance, extending to pancreas and resulting in islet β cells loss. There is a critical need to further clarify the mechanism of type 2 diabetes development by determining the specific factor for β cell loss for more effective treatment and prevention of type 2 diabetes.

REFERENCES

1. Olokoba AB, Obateru OA, Olokoba LB. (2012). Type 2 diabetes mellitus: a review of current trends. Oman Med J. 27(4):269-273. DOI: 10.5001/omj.2012.68.
2. Prasad M, Chen EW, Toh S-A, Gascoigne NRJ. (2020). Autoimmune responses and inflammation in type 2 diabetes. J Leukoc Biol. 107(5):739-748. DOI: 10.1002/JLB.3MR0220-243R.
3. Lebovitz HE. (1999). Type 2 Diabetes: An Overview. Clinical Chemistry. 45(8 Pt 2):1339-1345.
4. Sun T, Han X. (2020). Death versus dedifferentiation: The molecular bases of beta cell mass reduction in type 2 diabetes. Semin Cell Dev Biol. 103:76-82. DOI: 10.1016/j.semcdb.2019.12.002.
5. Chiasson JL, Rabasa-Lhoret R. (2004). Prevention of type 2 diabetes: insulin resistance and beta-cell function. Diabetes. 53(Suppl 3):S34-S38. DOI: 10.2337/diabetes.53.suppl_3.s34.

6. Tomita T. (2016). Apoptosis in pancreatic β-islet cells in Type 2 diabetes. Bosn J Basic Med Sci. 16(3):162-79. DOI: 10.17305/bjbms.2016.919.

7. Tomita T. (2010). Immunocytochemical localisation of caspase-3 in pancreatic islets from type 2 diabetic subjects. Pathology. 42(5):432-437. DOI: 10.3109/00313025.2010.493863.

8. Cnop M, Welsh N, Jonas JC, Jörns A, Lenzen S, Eizirik DL. (2005). Mechanisms of pancreatic beta-cell death in type 1 and type 2 diabetes: many differences, few similarities. Diabetes. 54(Suppl 2):S97-S107. DOI: 10.2337/diabetes.54.suppl_2.s97.

9. Kraakman MJ, Murphy AJ, Jandeleit-Dahm K, Kammoun HL. (2014). Macrophage polarization in obesity and type 2 diabetes: weighing down our understanding of macrophage function? Front Immunol. 5:470. DOI: 10.3389/fimmu.2014.00470.

10. Orliaguet L, Dalmas E, Drareni K, Venteclef N, Alzaid F. (2020). Mechanisms of Macrophage Polarization in Insulin Signaling and Sensitivity. Front Endocrinol (Lausanne). 11:62. DOI: 10.3389/fendo.2020.00062.

11. Islam MS, Loots du T. (2009). Experimental rodent models of type 2 diabetes: a review. Methods Find Exp Clin Pharmacol. 31(4):249-261. DOI: 10.1358/mf.2009.31.4.1362513.

12. Eldar-Finkelman H, Schreyer SA, Shinohara MM, LeBoeuf RC, Krebs EG. (1999). Increased glycogen synthase kinase-3 activity in diabetes- and obesity-prone C57BL/6J mice. Diabetes. 48(8):1662-1666. DOI: 10.2337/diabetes.48.8.1662.

13. Brooks-Worrell BM, Boyko EJ, Palmer JP. (2014). Impact of islet autoimmunity on the progressive β-cell functional decline in type 2 diabetes. Diabetes Care. 37(12):3286-3293. DOI: 10.2337/dc14-0961.

14. Lumeng CN, Bodzin JL, Saltiel AR. (2007). Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest. 117(1):175-184.

15. Prieur X, Mok CYL, Velagapudi VR, et al. (2011). Differential lipid partitioning between adipocytes and tissue macrophages modulates macrophage lipotoxicity and M2/M1 polarization in obese mice. Diabetes. 60(3):797-809.

16. Dula SB, Jecmenica M, Wu R, Jahanshahi P, Verrilli GM, Carter JD, et al. (2010). Evidence that low-grade systemic inflammation can induce islet dysfunction as measured by impaired calcium handling. Cell Calcium. 48(2-3):133-142. DOI: 10.1016/j.ceca.2010.07.007.

17. Imai Y, Dobrian AD, Morris MA, Nadler JL. (2013). Islet inflammation: a unifying target for diabetes treatment? Trends Endocrinol Metab. 24(7):351-360. DOI: 10.1016/j.tem.2013.01.007.

18. Dong Y, Kua ZJ, Khoo EY, Koo EH, Merchant RA. (2016). The Utility of Brief Cognitive Tests for Patients With Type 2 Diabetes Mellitus: A Systematic Review. J Am Med Dir Assoc. 17(10):889-895. DOI: 10.1016/j.jamda.2016.06.010.

19. Stanley TL, Zanni MV, Johnsen S, Rasheed S, Makimura H, Lee H, et al. (2011). TNF-alpha antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. J Clin Endocrinol Metab. 96(1):E146- E150. DOI: 10.1210/jc.2010-1170.

20. Akash MS, Shen Q, Rehman K, Chen S. (2012). Interleukin-1 receptor antagonist: a new therapy for type 2 diabetes mellitus. J Pharm Sci. 101(5):1647-1658. DOI: 10.1002/jps.23057.

21. Rehman K, Akash MS. (2016). Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? J Biomed Sci. 23(1):87. DOI: 10.1186/s12929-016-0303-y.

22. Parkash J, Chaudhry MA, Rhoten WB. (2005). Tumor necrosis factor-alpha-induced changes in insulin-producing beta-cells. Anat Rec A Discov Mol Cell Evol Biol. 286(2):982-993. DOI: 10.1002/ar.a.20229.

23. Donath MY, Shoelson SE. (2011). Type 2 diabetes as an inflammatory disease. Nat Rev Immunol. 11(2):98-107. DOI: 10.1038/nri2925.

24. Borst SE, Bagby GJ. (2002). Neutralization of tumor necrosis factor reverses age-induced impairment of insulin responsiveness in skeletal muscle of Sprague-Dawley rats. Metabolism. 51(8):1061-1064. DOI: 10.1053/meta.2002.34043.

25. Tzanavari T, Giannogonas P, Karalis KP. (2010). TNF-alpha and obesity. Curr Dir Autoimmun. 11:145-156. DOI: 10.1159/000289203.

26. Ofei F, Hurel S, Newkirk J, Sopwith M, Taylor R. (1996). Effects of an engineered human anti-TNF-alpha antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. Diabetes. 45(7):881-885. DOI: 10.2337/diab.45.7.881.

27. Paquot N, Castillo MJ, Lefèbvre PJ, Scheen AJ. (2000). No increased insulin sensitivity after a single intravenous administration of a recombinant human tumor necrosis factor receptor: Fc fusion protein in obese insulin-resistant patients. J Clin Endocrinol Metab. 85(3):1316-1319.

28. Dominguez H, Storgaard H, Rask-Madsen C, Steffen Hermann T, Ihlemann N, Baunbjerg Nielsen D, et al. (2005). Metabolic and vascular effects of tumor necrosis factor-alpha blockade with etanercept in obese patients with type 2 diabetes. J Vasc Res. 42(6):517-25. DOI: 10.1159/000088261.

29. Ahrén B. (2005). Type 2 diabetes, insulin secretion and beta-cell mass. Curr Mol Med. 5(3):275-286. DOI: 10.2174/1566524053766004.

30. Yancy WS Jr, Foy M, Chalecki AM, Vernon MC, Westman EC. (2005). A low-carbohydrate, ketogenic diet to treat type 2 diabetes. Nutr Metab (Lond). 2:34. DOI: 10.1186/1743-7075-2-34.

31. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. (2012). Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. Nutrition. 28(10):1016-21. DOI: 10.1016/j.nut.2012.01.016.

32. Fujitani Y, Kawamori R, Watada H. (2009). The role of autophagy in pancreatic beta-cell and diabetes. Autophagy. 5(2):280-282. DOI: 10.4161/auto.5.2.7656.

33. Las G, Shirihai OS. (2010). The role of autophagy in β-cell lipotoxicity and type 2 diabetes. Diabetes Obes Metab. 12(s2):15-19. DOI: 10.1111/j.1463-1326.2010.01268.x.

34. Mukherjee N, Lin L, Contreras CJ, Templin AT. (2021). β-Cell Death in Diabetes: Past Discoveries, Present Understanding, and Potential Future Advances. Metabolites. 11(11):796. DOI: 10.3390/metabo11110796.

35. Efrat S. (2019). Beta-Cell Dedifferentiation in Type 2 Diabetes: Concise Review. Stem Cells. 37(10):1267-1272. DOI: 10.1002/stem.3059.

36. Bensellam M, Jonas JC, Laybutt DR. (2018). Mechanisms of β-cell dedifferentiation in diabetes: recent findings and future research directions. J Endocrinol. 236(2):R109-R143. DOI: 10.1530/JOE-17-0516.

37. Khin PP, Lee JH, Jun HS. (2021). A Brief Review of the Mechanisms of β-Cell Dedifferentiation in Type 2 Diabetes. Nutrients. 13(5):1593. DOI: 10.3390/nu13051593.

38. Hemminki K, Liu X, Försti A, Sundquist J, Sundquist K, Ji J. (2015). Subsequent Type 2 Diabetes in Patients with Autoimmune Disease. Sci Rep. 5:13871. DOI: 10.1038/srep13871.

39. Ruscitti P, Ursini F, Cipriani P, Ciccia F, Liakouli V, Carubbi F, et al. (2017). Prevalence of type 2 diabetes and impaired fasting glucose in patients affected by rheumatoid arthritis: Results from a cross-sectional study. Medicine (Baltimore). 96(34):e7896. DOI: 10.1097/MD.0000000000007896.

40. Ruscitti P, Cipriani P, Liakouli V, Iacono D, Pantano I, Margiotta DPE, et al. (2021). Occurrence and predictive factors of high blood pressure, type 2 diabetes, and metabolic syndrome in rheumatoid arthritis: findings from a 3-year, multicentre, prospective, observational study. Clin Exp Rheumatol. 39(5):995-1002.

41. Solomon DH, Love TJ, Canning C, Schneeweiss S. (2010). Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. Ann Rheum Dis. 69(12):2114-2117. DOI: 10.1136/ard.2009.125476.

42. Dubreuil M, Rho YH, Man A, Zhu Y, Zhang Y, Love TJ, et al. (2014). Diabetes incidence in psoriatic arthritis, psoriasis and rheumatoid arthritis: a UK population-based cohort study. Rheumatology (Oxford). 53(2):346-352. DOI: 10.1093/rheumatology/ket343.

43. Solomon DH, Love TJ, Canning C, Schneeweiss S. (2010). Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. Ann Rheum Dis. 69(12):2114-2117. DOI: 10.1136/ard.2009.125476.

44. Dubreuil M, Rho YH, Man A, Zhu Y, Zhang Y, Love TJ, et al. (2014). Diabetes incidence in psoriatic arthritis,

psoriasis and rheumatoid arthritis: a UK population-based cohort study. Rheumatology (Oxford). 53(2):346-352. DOI: 10.1093/rheumatology/ket343.

45. Srinivasan K, Ramarao P. (2007). Animal models in type 2 diabetes research: an overview. Indian J Med Res. 125(3):451-472.

46. Kleinert M, Clemmensen C, Hofmann SM, Moore MC, Renner S, Woods SC, et al. (2018). Animal models of obesity and diabetes mellitus. Nat Rev Endocrinol. 14(3):140-162. DOI: 10.1038/nrendo.2017.161.

47. Cefalu WT. (2006). Animal Models of Type 2 Diabetes: Clinical Presentation and Pathophysiological Relevance to the Human Condition. ILAR Journal. 47(3):186-198. DOI: 10.1093/ilar.47.3.186.

48. Stott NL, Marino JS. (2020). High Fat Rodent Models of Type 2 Diabetes: From Rodent to Human. Nutrients. 12(12):3650. DOI: 10.3390/nu12123650.

49. Skovsø S. (2014). Modeling type 2 diabetes in rats using high fat diet and streptozotocin. J Diabetes Investig. 5(4):349-358. DOI: 10.1111/jdi.12235.

50. Heydemann A. (2016). An Overview of Murine High Fat Diet as a Model for Type 2 Diabetes Mellitus. J Diabetes Res. 2016:2902351. DOI: 10.1155/2016/2902351.

51. King AJ. (2012). The use of animal models in diabetes research. Br J Pharmacol. 166(3):877-94. DOI: 10.1111/j.1476-5381.2012.01911.x.

52. Zang L, Hao H, Liu J, Li Y, Han W, Mu Y. (2017). Mesenchymal stem cell therapy in type 2 diabetes mellitus. Diabetol Metab Syndr. 9:36. DOI: 10.1186/s13098-017-0233-1.

53. Cho J, D'Antuono M, Glicksman M, Wang J, Jonklaas J. (2018). A review of clinical trials: mesenchymal stem cell transplant therapy in type 1 and type 2 diabetes mellitus. Am J Stem Cells. 7(4):82-93.

54. Rad F, Ghorbani M, Mohammadi Roushandeh A, Habibi Roudkenar M. (2019). Mesenchymal stem cell-based therapy for autoimmune diseases: emerging roles of extracellular vesicles. Mol Biol Rep.46:1533-1549. DOI: 10.1007/s11033-019-04588-y.

55. Munir H, McGettrick HM. (2015). Mesenchymal Stem Cell Therapy for Autoimmune Disease: Risks and Rewards. Stem Cells Dev. 24(18):2091-2100. DOI: 10.1089/scd.2015.0008.

56. Hartigan-O'Connor DJ, Hirao LA, McCune JM, Dandekar S. (2011). Th17 cells and regulatory T cells in elite control over HIV and SIV. Curr Opin HIV AIDS. 6(3):221-227. DOI: 10.1097/COH.0b013e32834577b3.

57. Zambrano-Zaragoza JF, Romo-Martínez EJ, Durán-Avelar Mde J, García-Magallanes N, Vibanco-Pérez N. (2014). Th17 cells in autoimmune and infectious diseases. Int J Inflam. 2014:651503. DOI: 10.1155/2014/651503.

58. Murdaca G, Colombo BM, Puppo F. (2011). The role of Th17 lymphocytes in the autoimmune and chronic inflammatory diseases. Intern Emerg Med. 6(6):487-495. DOI: 10.1007/s11739-011-0517-7.

59. Jagannathan-Bogdan M, McDonnell ME, Shin H, Rehman Q, Hasturk H, Apovian CM, et al. (2011). Elevated proinflammatory cytokine production by a skewed T cell compartment requires monocytes and promotes inflammation in type 2 diabetes. J Immunol. 186(2):1162-1172. DOI: 10.4049/jimmunol.1002615.

60. Chuang HC, Tan TH. (2017). MAP4K4 and IL-6+ Th17 cells play important roles in non-obese type 2 diabetes. J Biomed Sci. 24(1):4. DOI: 10.1186/s12929-016-0307-7.

61. Ip B, Cilfone NA, Belkina AC, DeFuria J, Jagannathan-Bogdan M, Zhu M, et al. (2016). Th17 cytokines differentiate obesity from obesity-associated type 2 diabetes and promote TNFα production. Obesity (Silver Spring). 24(1):102-112. DOI: 10.1002/oby.21243.