FGF23 in Diabetes

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The incidence of Type 2 diabetes mellitus (T2DM) results from a combination of genetic, environmental, and behavioral risk-factors that include sedentary lifestyle and diet. Related to diet, small elevations in the levels of Pi in blood also constitute a risk factor for the appearance of prediabetes situations, particularly, impaired glucose tolerance and IR, as well as for the development of T2DM. Pi serum range is maintained by diverse hormones that regulate the intestinal uptake, its mobilization from bone, and the renal excretion. Importantly, the pathophysiological repercussions of Pi imbalances also involve to these regulatory factors. Disbalances in phosphataemic regulatory-factors traditionally related to an increase in morbidity are the decrease in calcitriol (the active form of vitamin D) and the increase in parathyroid hormone (PTH) levels. Fibroblast growth factor 23 (FGF23) is considered the main regulator of phosphorus and vitamin D metabolism. FGF23 is secreted from bones, especially by osteoblasts and osteocytes, after phosphate intake and acts primarily on the kidneys to inhibit phosphate reabsorption in urine. FGF23 also inhibits calcitriol renal synthesis and the secretion of PTH in the parathyroid glands.

Keywords: diabetes ; chronic kidney disease ; fibroblast growth factor 23

1. FGF23 Signaling Pathway

FGF23 belongs to the FGF superfamily, which in humans consists of 22 signaling peptides that participate in a broad diversity of biological processes. FGF23, together with FGF19 and FGF21, form the particular group of endocrine (hormone-like) FGFs segregated from the wide FGF ligand superfamily by phylogenetic and sequence analysis [1][2]. Since both FGF19 and FGF21 are implied in the regulation of lipid and glucose metabolism [3][4][5][6][7], it is plausible that FGF23 may also be involved in some metabolic processes, especially in the metabolism of glucose.

The lack of active heparan–sulfate (HS) binding domains in endocrine FGFs prevents the formation of hydrogen bindings with the HS-rich extracellular matrix [8] and allows entry to the bloodstream. However, this feature of endocrine FGFs also determines a low affinity for their cell surface tyrosine kinase receptors, termed FGF receptors (FGFRs). There are four FGFRs (FGFR1–4) that present a similar structure and a high degree of amino acid sequence homology [9] and that are practically ubiquitous, being expressed in multiple organs and tissues [10]. A new FGFR called FGFR5 has recently been added to this group of receptors, which lacks the tyrosine-kinase domain and which is believed to regulate FGFR1 responses [11]. The alternative splicing of the codifying genes produces several FGFR subtypes, including b and c subtypes of FGFR1 to FGFR3 [12]. To enhance the affinity for FGFRs in their target organs, endocrine FGFs use Klotho proteins as cofactors. Since FGFRs are expressed in a wide range of tissues, tissue-specific expression of Klotho proteins is considered to be the determinant for an organ to be targeted by endocrine FGFs. Furthermore, it has been reported that the soluble form of αKlotho, generated by proteolytic cleavage of the membrane-anchored form, may also function as a coreceptor for FGFR1c [10][13], although the significance of soluble αKlotho in the transmission of FGF23 signaling is unknown.

The components of the canonical receptor complex for FGF23 are FGFR1c and the membrane-anchored protein αKlotho, which is expressed in several restricted tissues, including the kidneys and the parathyroid glands [14]. Recently, the crystal structure of the FGFR1c/αKlotho complex has been described, demonstrating that αKlotho is a nonenzymatic molecular scaffold for FGF23 signaling [13]. In addition to kidneys and parathyroid glands, the expression of αKlotho has also been detected in the choroid plexus, vascular tissue, peripheral blood cells (PBCs), and recently in pancreatic ß cells [14][15][16][17][18][19][20]. The presence of αKlotho in ß cells suggests that this protein may play a role related to the synthesis and/or release of insulin through its role as a coreceptor for FGF23. Furthermore, it is also plausible that circulating FGF23 directly mediates off-target effects independently of αKlotho, and it has been proposed that, at high concentrations, FGF23 is capable of establishing independent low-affinity αKlotho binding to FGFRs other than FGFR1c, thus causing deleterious effects on multiple organs and tissues.

FGF23 regulates circulating Pi levels by decreasing blood Pi and calcitriol levels [21][22][23]. In the kidneys, FGF23 reduces reabsorption of phosphate from the urine by reducing the abundance of type IIa and IIc sodium–phosphate cotransporters (NaPis) in the apical membrane of epithelial cells in the proximal renal tubule [24][23]. Additionally, FGF23 also reduces renal calcitriol synthesis by reducing the transcription of renal 1α-hydroxylase (CYP27B1), the key enzyme for 1.25 $(OH)_2D_3$ synthesis [21][22][23]. These actions are mediated by FGFRs that can activate several intracellular signal transduction pathways, including the extracellular signal-regulated kinase (ERK), protein kinase B (Akt) and phospholipase C-γ (PLCγ) pathways [25]. The canonical αKlotho-dependent signal transduction that FGF23 is believed to employ to regulate phosphate and vitamin D metabolism is the Ras/MAPK/ERK [10]. The transduction is initiated by activation through autophosphorylation of tyrosine kinase enzymes in the cytoplasmic tail of FGFR1c, which induces the activation of the Ras/MAPK/ERK pathway and, posteriorly, the expression of the early growth response 1 (EGR1) protein, which acts as a differential transcription factor.

2. Potential Diabetogenic Actions of FGF23

Most of the studies that relate FGF23 to the appearance of imbalances in glucose and insulin metabolism are merely descriptive, and currently, there are no mechanisms explaining these relationships. One of the possible explanations may be the combined effects of high levels of FGF23 and reduced expression of its specific cofactor αKlotho.

In conditions characterized by the presence of supraphysiological levels of FGF23, the unspecific binding of this hormone could mediate off-target effects in tissues and organs not previously considered to be targets, explaining part of these effects. Several data support the existence of this complementary mechanism of action of FGF23 that can be activated in certain circumstances. A few alternatives to canonical FGF23 signal transduction have been proposed. αKlotho can be found in blood and cerebrospinal fluid as a soluble protein, and as mentioned above, it has been proposed that this soluble form may act as a widely available cofactor for the FGFR1c receptor [13]. A second possibility is that the new onset or the stimulation of the expression of αKlotho in tissues where it is not generated or is in a very low proportion could generate a functional receptor complex when it is colocalized with the ubiquitously expressed FGFR1c. Finally, signal transduction in response to FGF23 may occur independently of αKlotho by binding to receptors FGFR2, 3, and 4 since only FGFR1c requires the presence of αKlotho to bind FGF23 with sufficient affinity [26]. This possibility has been demonstrated in a small group of cells and tissues including myocardial tissue, hepatocytes, and neutrophils, which only express FGFR2 and FGFR4 [27][28][29].

The existence of this multiplicity of bindings for FGF23, even in the same target organ if it co-expresses different FGFRs, has important repercussions on the potential activation of different intracellular signals and, consequently, on the effects elicited by this hormone. The PLCγ/calcineurin (CN)/nuclear factor of activated T cells (NFAT) signaling pathway is a noncanonical pathway activated by non-αKlotho-dependent FGF23 binding. The overactivation of this pathway results in hypertrophic effects in cardiac myocytes that, at the clinical level, is associated with the appearance of left ventricular hypertrophy (LVH), and in the induction of an inflammatory response in hepatocytes [30][27][28]. Similarly, the suppression of PTH expression in the parathyroid glands, which is canonically mediated by the binding of FGF23 to the FGFR1c/αKlotho receptor complex, can also occur through the activation of the PLCγ/CN/NFAT pathway independently of αKlotho [31]. However, the chronic activation of this pathway derived from an excess of FGF23 generates maladaptive effects leading to hyperplasia of parathyroid cells and an increase in the secretion of PTH [32]. To date, the potential diabetogenic effects of the activation of this pathway by noncanonical binding of FGF23 remain unexplored. Although these effects can be at very different levels, there are two possibilities that we consider to deserve attention.

2.1. Effects on Pancreatic ß Cell

FGF signaling plays an important role in the maintenance of ß-cell physiology and glucose homeostasis, with disorders in the intracellular signaling response being associated with the onset and progression of diabetes [33][34]. FGF1 and 2 specifically stimulate insulin secretion in rodent pancreatic ß cells [35][36]. Conversely, the impairment of FGFR1 signaling leads to the appearance of the diabetic phenotype in mice, indicating that this receptor, but not FGFR2, has a crucial role in the control of glucose homeostasis [37].

The binding of FGF23 to the pancreatic ß cell would allow the existence of a mechanism of cellular regulation which is not yet known. This possibility has been reinforced by demonstration of the expression of coreceptor αKlotho, together with FGFR1c and FGFR2b, in the pancreatic ß cell [30][37]. Moreover, the recently identified FGFR5 is also expressed in adult pancreas [38][39] and exerts modulatory effects on FGFR1 activity, enhancing tyrosine phosphorylation of the Ras/MAPK/ERK signaling pathway [40].

Thus, FGF23 could act in the ß cell through this canonical signaling pathway and exert modulatory actions on the production and/or release of insulin in this cell. Furthermore, the feedback could be closed by an inhibition of the production of FGF23 by insulin: both insulin and insulin-like growth factor 1 (IGF1) are capable of suppressing FGF23 production through activation of phosphatidyl inositol triphosphate kinase (PI3K)/Akt/forkhead box protein O1 (FOXO1) signaling [41].

The PLCγ/CN/NFAT pathway is an important regulator of multiple biological functions, including the regulation of ß-cell growth and function as well as the biosynthesis and secretion of insulin. Administration of the CN inhibitors CsA and FK506 to rodents or humans induces hyperglycemia and hypoinsulinemia derived from a reduction in insulin biosynthesis and secretion [42]. However, sustained activation of the PLCγ/CN/NFAT pathway provokes similar deleterious effects on ß-cell proliferation, growth, and function [43]. Therefore, the activation of noncanonical pathways by FGF23-intracellular-signal transmission under certain conditions in which FGF23 is overexpressed and/or in which αKlotho, the membrane and/or the systemic soluble form, is absent or poorly expressed could generate a harmful effect by causing an overactivation of the CN pathway, resulting in a malfunction of the pancreatic ß cell. In this sense, αKlotho has been recently shown to play a role in glucose metabolism. Transgenic, αKlotho-deficient mice exhibit pancreatic islet atrophy with reduced pancreatic insulin mRNA and protein levels and serum insulin concentrations [44]. By contrast, αKlotho overexpression in mice resulted in increased plasma membrane retention of the Ca^{2+}-permeable, transient receptor potential cation channel V2 (TRPV2), enhanced calcium entry and glucose-induced intracellular calcium response, and insulin secretion, whereas knockdown of αKlotho attenuated these effects [45].

2.2. Effects on Inflammation

Chronic low-grade inflammation and activation of the innate immune system constitute key factors in the pathogenesis of diabetes mellitus [46][47][48]. Diverse inflammatory parameters are elevated in diabetic patients and constitute strong predictors of the development of this disease [49][50][51]. Given the prevalence of inflammation in T2DM and its role in the development of the disease, the potential effects of increased levels of FGF23 on the immune system may be of clinical relevance.

Similar to Pi, elevated FGF23 plasma levels have been independently associated with higher levels of inflammatory markers in patients with CKD or other inflammatory diseases. Results of the Chronic Renal Insufficiency Cohort (CRIC) showed that higher FGF23 levels are associated with higher levels of the inflammatory markers CRP, IL6, TNFα, and fibrinogen and with a higher odds ratio for severe inflammation independent of mineral metabolism and renal function [52]. This association is not limited to CKD, and the levels of FGF23 have been positively correlated with TNFα [45] and with IL6 [53] in general populations, and with CRP levels in the elderly [53][54]. Furthermore, inflammation is a major trigger of FGF23 production [55][56][57][58], indicating the potential existence of a feedback mechanism between FGF23 and inflammatory markers.

In human PBCs, which express αKlotho and the receptors FGFR1c, 2, and 4, FGF23 is able to inhibit calcitriol production, a well-known immune system modulator, through the activation of the Ras/MAPK/ERK signaling pathway [59]. Although this inhibition mediated by FGF23 may contribute to the suppression of innate immunity, indirectly explaining the effects of FGF23 on the inflammatory status, experimental data indicate that FGF23 can directly promote the synthesis of inflammatory factors. Although the effects of FGF23 in the immune system are unknown, mice models of FGF23 excess have revealed an overactivation of genes regulating inflammation such as *TGFß1*, *TNF*, *IL1ß*, and *NF-kB* [60]. Experimental studies show that hepatocytes treated with FGF23 increase CRP and IL6 expression, and that this effect is blocked by anti-FGFR4 or Cyclosporin A (CsA), pointing to the activation of the PLCγ/CN/NFAT signaling pathway as a mechanism responsible for these actions [27]. Similarly, the injection of the carboxi-tail peptide of FGF23, which prevents iFGF23 signaling, in a diabetic nephropathy mouse model reduced the renal expression as well as the serum levels of inflammatory cytokines IL6 and TNFα without affecting serum FGF23 and Pi levels [61]. These taken together, there is evidence of a role of FGF23 in the modulation of the inflammatory response, although the regulatory mechanism as well as its physiological function are barely understood.

The activation of noncanonical pathways could be involved in the association between FGF23 and inflammation. The pro-inflammatory effect promoted by FGF23 in hepatocytes described above is mediated by an αKlotho-independent activation of FGFR4 [27]. On the other hand, FGF23 has been reported to affect macrophages and stimulate TNFα expression via the Ras/MAPK/ERK signaling pathway, also through an αKlotho-independent mechanism [62]. The macrophage cell line RAW264.7 in nonpolarized M0 and anti-inflammatory M2 stages expresses FGFR1c and low levels of αKlotho. However, pro-inflammatory M1 macrophages, polarized with LPS and IFNγ, upregulated αKlotho gene expression and produced TNFα through the activation of ERK1/2 following exposure to FGF23 [62]. This finding suggests that high serum FGF23 levels might amplify the inflammatory response induced by primed macrophages, but to date, the

contribution of FGF23 to a pro-inflammatory status derived from the activation of the PLCγ/CN/NFAT pathway in macrophages, and also other immune cells such as lymphocytes, is unknown. αKlotho has been previously detected in CD4+ lymphocytes, and marked reductions in its expression have been related to aging [18], but currently, there are no data on the involvement in the function of either murine or human T lymphocytes.

References

1. Itoh, N.; Ornitz, D.M. Fibroblast growth factors: From molecular evolution to roles in development, metabolism and disease. J. Biochem. 2011, 149, 121–130.
2. Itoh, N. The Fgf families in humans, mice, and zebrafish: Their evolutional processes and roles in development, metabolism, and disease. Biol. Pharm. Bull. 2007, 30, 1819–1825.
3. Tomlinson, E.; Fu, L.; John, L.; Hultgren, B.; Huang, X.; Renz, M.; Stephan, J.P.; Tsai, S.P.; Powell-Braxton, L.; French, D.; et al. Transgenic mice expressing human fibroblast growth factor-19 display increased metabolic rate and decreased adiposity. Endocrinology 2002, 143, 1741–1747.
4. Fu, L.; John, L.M.; Adams, S.H.; Yu, X.X.; Tomlinson, E.; Renz, M.; Williams, P.M.; Soriano, R.; Corpuz, R.; Moffat, B.; et al. Fibroblast growth factor 19 increases metabolic rate and reverses dietary and leptin-deficient diabetes. Endocrinology 2004, 145, 2594–2603.
5. Kharitonenkov, A.; Shiyanova, T.L.; Koester, A.; Ford, A.M.; Micanovic, R.; Galbreath, E.J.; Sandusky, G.E.; Hammond, L.J.; Moyers, J.S.; Owens, R.A.; et al. FGF-21 as a novel metabolic regulator. J. Clin. Investig. 2005, 115, 1627–1635.
6. Coskun, T.; Bina, H.A.; Schneider, M.A.; Dunbar, J.D.; Hu, C.C.; Chen, Y.; Moller, D.E.; Kharitonenkov, A. Fibroblast growth factor 21 corrects obesity in mice. Endocrinology 2008, 149, 6018–6027.
7. Xu, J.; Lloyd, D.J.; Hale, C.; Stanislaus, S.; Chen, M.; Sivits, G.; Vonderfecht, S.; Hecht, R.; Li, Y.S.; Lindberg, R.A.; et al. Fibroblast growth factor 21 reverses hepatic steatosis, increases energy expenditure, and improves insulin sensitivity in dietinduced obese mice. Diabetes 2009, 58, 250–259.
8. Kuro, O.M. Overview of the FGF23–Klotho axis. Pediatr. Nephrol. 2010, 25, 583–590.
9. Mohammadi, M.; Olsen, S.K.; Ibrahimi, O.A. Structural basis for fibroblast growth factor receptor activation. Cytokine Growth Factor Rev. 2005, 16, 107–137.
10. Urakawa, I.; Yamazaki, Y.; Shimada, T.; Iijima, K.; Hasegawa, H.; Okawa, K.; Fujita, T.; Fukumoto, S.; Yamashita, T. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 2006, 444, 770–774.
11. Regeenes, R.; Silva, P.N.; Chang, H.H.; Arany, E.J.; Shukalyuk, A.I.; Audet, J.; Kilkenny, D.M.; Rocheleau, J.V. Fibroblast growth factor receptor 5 (FGFR5) is a co-receptor for FGFR1 that is up-regulated in beta-cells by cytokine-induced inflammation. J. Biol. Chem. 2018, 293, 17218–17228.
12. Ornitz, D.M.; Itoh, N. The fibroblast growth factor signaling pathway. Wiley Interdiscip. Rev. Dev. Biol. 2015, 4, 215–266.
13. Chen, G.; Liu, L.; Goetz, R.; Fu, L.; Jayaraman, S.; Hu, M.C.; Moe, O.W.; Liang, G.; Li, X.; Mohammadi, M. α-Klotho is a non-enzymatic molecular scaffold for FGF23 hormone signalling. Nature 2018, 553, 461–466.
14. Kuro, O.M.; Matsumura, Y.; Aizawa, H.; Kawaguchi, H.; Suga, T.; Utsugi, T.; Ohyama, Y.; Kurabayashi, M.; Kaname, T.; Kume, E.; et al. Mutation of the mouse Klotho gene leads to a syndrome resembling ageing. Nature 1997, 390, 45–51.
15. Donate-Correa, J.; Mora-Fernández, C.; Martínez-Sanz, R.; Muros-de-Fuentes, M.; Pérez, H.; Meneses-Pérez, B.; Cazaña-Pérez, V.; Navarro-González, J.F. Expression of FGF23/KLOTHO System in Human Vascular Tissue. Int. J. Cardiol. 2013, 165, 179–183.
16. Donate-Correa, J.; Henríquez-Palop, F.; Martín-Núñez, E.; Pérez-Delgado, N.; Muros-de-Fuentes, M.; Mora-Fernández, C.; Navarro-González, J.F. Effect of Paricalcitol on FGF-23 and Klotho in Kidney Transplant Recipients. Transplantation 2016, 100, 2432–3248.
17. Li, L.; Wang, Y.; Gao, W.; Yuan, C.; Zhang, S.; Zhou, H.; Huang, M.; Yao, X. Klotho Reduction in Alveolar Macrophages Contributes to Cigarette Smoke Extract-induced Inflammation in Chronic Obstructive Pulmonary Disease. J. Biol. Chem. 2015, 290, 27890–27900.
18. Witkowski, J.M.; Soroczyńska-Cybula, M.; Bryl, E.; Smoleńska, Z.; Jóźwik, A. Klotho-α common link in physiological and rheumatoid arthritis-related aging of human CD4+ lymphocytes. Immunol 2007, 178, 771–777.
19. Karami, M.; Mehrabi, F.; Allameh, A.; Pahlevan Kakhki, M.; Amiri, M.; Aleagha, M.S.E. Klotho gene expression decreases in peripheral blood mononuclear cells (PBMCs) of patients with relapsing-remitting multiple sclerosis. J. Neurol. Sci. 2017, 381, 305–307.

20. Lin, Y.; Sun, Z. In Vivo Pancreatic-Cell-Specific Expression of Antiaging Gene Klotho. A Novel Approach for Preserving b-Cells in T2 Diabetes. Diabetes 2015, 64, 1444–1458.

21. Shimada, T.; Mizutani, S.; Muto, T.; Yoneya, T.; Hino, R.; Takeda, S.; Takeuchi, Y.; Fujita, T.; Fukumoto, S.; Yamashita, T. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc. Natl. Acad. Sci. U SA 2001, 98, 6500–6505.

22. Shimada, T.; Hasegawa, H.; Yamazaki, Y.; Muto, T.; Hino, R.; Takeuchi, Y.; Fujita, T.; Nakahara, K.; Fukumoto, S.; Yama shita, T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J. Bone Miner. Res. 2004, 19, 429–435.

23. Shimada, T.; Yamazaki, Y.; Takahashi, M.; Hasegawa, H.; Urakawa, I.; Oshima, T.; Ono, K.; Kakitani, M.; Tomizuka, K.; Fujita, T.; et al. Vitamin D receptor-independent FGF23 actions in regulating phosphate and vitamin D metabolism. Am. J. Physiol. Renal Physiol. 2005, 289, F1088–F1095.

24. Shimada, T.; Kakitani, M.; Yamazaki, Y.; Hasegawa, H.; Takeuchi, Y.; Fujita, T.; Fukumoto, S.; Tomizuka, K.; Yamashita, T. Targeted Ablation of Fgf23 Demonstrates Essential Physiological Role of FGF23 in Phosphate & Vitamin D Metabolis m. J. Clin. Investig. 2004, 113, 561–568.

25. Goetz, R.; Mohammadi, M. Exploring mechanisms of FGF signalling through the lens of structural biology. Nat. Rev. M ol. Cell Biol. 2013, 14, 166–180.

26. Ornitz, D.M.; Itoh, N. Fibroblast growth factors. Genome Biol. 2001, 2, 3005.1–3005.12.

27. Singh, S.; Grabner, A.; Yanucil, C.; Schramm, K.; Czaya, B.; Krick, S.; Czaja, M.J.; Bartz, R.; Abraham, R.; Di Marco, G.S.; et al. Fibroblast growth factor 23 directly targets hepatocytes to promote inflammation in chronic kidney disease. Kidney Int. 2016, 90, 985–996.

28. Grabner, A.; Amaral, A.P.; Schramm, K.; Singh, S.; Sloan, A.; Yanucil, C.; Li, J.; Shehadeh, L.A.; Hare, J.M.; David, V.; e t al. Activation of cardiac fibroblast growth factor receptor 4 causes left ventricular hypertrophy. Cell Metab. 2015, 22, 1 020–1032.

29. Rossaint, J.; Oehmichen, J.; Van Aken, H.; Reuter, S.; Pavenstädt, H.J.; Meersch, M.; Unruh, M.; Zarbock, A. FGF23 si gnaling impairs neutrophil recruitment and host defense during CKD. J. Clin. Investig. 2016, 126, 962–974.

30. Faul, C.; Amaral, A.P.; Oskouei, B.; Hu, M.C.; Sloan, A.; Isakova, T.; Gutiérrez, O.M.; Aguillon-Prada, R.; Lincoln, J.; Ha re, J.M.; et al. FGF23 induces left ventricular hypertrophy. J. Clin. Investig. 2011, 121, 4393–4408.

31. Olauson, H.; Lindberg, K.; Amin, R.; Sato, T.; Jia, T.; Goetz, R.; Mohammadi, M.; Andersson, G.; Lanske, B.; Larsson, T. E. Parathyroid-specific deletion of Klotho unravels a novel calcineurin-dependent FGF23 signaling pathway that regulat es PTH secretion. PLoS Genet. 2013, 9, e1003975.

32. Kawakami, K.; Takeshita, A.; Furushima, K.; Miyajima, M.; Hatamura, I.; Kuro-o, M.; Furuta, Y.; Sakaguchi, K. Persisten t FGF23 signalling in the parathyroid glands for secondary hyperparathyroidism in mice with chronic kidney disease. Sc i. Rep. 2017, 7, 40534.

33. Kilkenny, D.M.; Rocheleau, J.V. Fibroblast growth factor receptor-1 signaling in pancreatic islet beta-cells is modulated by the extracellular matrix. Mol. Endocrinol. 2008, 22, 196–205.

34. Sun, M.Y.; Yoo, E.; Green, B.J.; Altamentova, S.M.; Kilkenny, D.M.; Rocheleau, J.V. Autofluorescence imaging of living pancreatic islets reveals fibroblast growth factor-21 (FGF21)-induced metabolism. Biophys. J. 2012, 103, 2379–2388.

35. Hiriart, M.; Vidaltamayo, R.; Sánchez-Soto, M.C. Nerve and fibroblast growth factors as modulators of pancreatic beta cell plasticity and insulin secretion. Isr. Med. Assoc. J. 2001, 3, 114–116.

36. Rivas-Carrillo, J.D.; Navarro-Alvarez, N.; Soto-Gutierrez, A.; Okitsu, T.; Chen, Y.; Tabata, Y.; Misawa, H.; Noguchi, H.; M atsumoto, S.; Tanaka, N. Amelioration of diabetes in mice after single-donor islet transplantation using the controlled rel ease of gelatinized FGF-2. Cell Transplant. 2006, 15, 939–944.

37. Hart, A.W.; Baeza, N.; Apelqvist, A.; Edlund, H. Attenuation of FGF signalling in mouse beta-cells leads to diabetes. Nat ure 2000, 408, 864–868.

38. Kim, I.; Moon, S.; Yu, K.; Kim, U.; Koh, G.Y. A novel fibroblast growth factor receptor-5 preferentially expressed in the p ancreas. Biochim. Biophys. Acta 2001, 1518, 152–156.

39. Su, A.I.; Wiltshire, T.; Batalov, S.; Lapp, H.; Ching, K.A.; Block, D.; Zhang, J.; Soden, R.; Hayakawa, M.; Kreiman, G. A gene atlas of the mouse and human protein-encoding transcriptomes. Proc. Natl. Acad. Sci. USA 2004, 101, 6062–606 7.

40. Silva, P.N.; Altamentova, S.M.; Kilkenny, D.M.; Rocheleau, J.V. Fibroblast growth factor receptor like-1 (FGFRL1) intera cts with SHP-1 phosphatase at insulin secretory granules and induces beta-cell ERK1/2 protein activation. J. Biol. Che m. 2013, 288, 17859–17870.

41. Bar, L.; Feger, M.; Fajol, A.; Klotz, L.O.; Zeng, S.; Lang, F.; Hocher, B.; Föller, M. Insulin Suppresses the Production of Fibroblast Growth Factor 23 (FGF23). Proc. Natl. Acad. Sci. USA 2018, 115, 5804–5809.

42. Lawrence, M.C.; Bhatt, H.S.; Watterson, J.M.; Easom, R.A. Regulation of insulin gene transcription by a Ca2+-responsi ve pathway involving calcineurin and NFAT. Mol. Endocrinol. 2001, 15, 1758–1767.

43. Bernal-Mizrachi, E.; Cras-Méneur, C.; Ye, B.R.; Johnson, J.D.; Permutt, M.A. Transgenic Overexpression of Active Calc ineurin in β-Cells Results in Decreased β-Cell Mass and Hyperglycemia. PLoS ONE 2010, 5, e11969.

44. Utsugi, T.; Ohno, T.; Ohyama, Y.; Uchiyama, T.; Saito, Y.; Matsumura, Y.; Aizawa, H.; Itoh, H.; Kurabayashi, M.; Kawaz u, S.; et al. Decreased insulin production and increased insulin sensitivity in the klotho mutant mouse, a novel animal m odel for human aging. Metabolism 2000, 49, 1118–1123.

45. Lin, Y.; Sun, Z. Antiaging gene Klotho enhances glucose-induced insulin secretion by up-regulating plasma membrane l evels of TRPV2 in MIN6 b-cells. Endocrinology 2012, 153, 3029–3039.

46. Crook, M. Type 2 diabetes mellitus: A disease of the innate immune system? An update. Diabet. Med. 2004, 21, 203–2 07.

47. Pickup, J.C.; Crook, M.A. Is Type II diabetes mellitus a disease of the innate immune system? Diabetologia 1998, 41, 1 241–1248.

48. Pickup, J.C. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004, 2 7, 813–823.

49. Schmidt, M.I.; Duncan, B.B.; Sharrett, A.V.; Lindberg, G.; Savage, P.J.; Offenbacher, S.; Azambuja, M.I.; Tracy, R.P.; He iss, G. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities stud y): A cohort study. Lancet 1999, 353, 1649–1652.

50. Pradhan, A.D.; Manson, J.E.; Rifai, N.; Buring, J.E.; Ridker, P.M. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001, 286, 327–334.

51. Spranger, J.; Kroke, A.; Möhlig, M.; Hoffmann, K.; Bergmann, M.M.; Ristow, M.; Boeing, H.; Pfeiffer, A.F. Inflammatory c ytokines and the risk to develop type 2 diabetes: Results of the prospective population based European Prospective In vestigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes 2003, 52, 812–817.

52. Munoz Mendoza, J.; Isakova, T.; Ricardo, A.C.; Xie, H.; Navaneethan, S.D.; Anderson, A.H.; Bazzano, L.A.; Xie, D.; Kre tzler, M.; Nessel, L.; et al. Chronic Renal Insufficiency Cohort. Fibroblast Growth Factor 23 and Inflammation in CKD. Cl in. J. Am. Soc. Nephrol. 2012, 7, 1155–1162.

53. Mirza, M.A.; Alsiö, J.; Hammarstedt, A.; Erben, R.G.; Michaëlsson, K.; Tivesten, A.; Marsell, R.; Orwoll, E.; Karlsson, M. G.; Ljunggren, O.; et al. Circulating Fibroblast Growth factor-23 Is Associated with Fat Mass and Dyslipidemia in Two In dependent Cohorts of Elderly Individuals. Arterioscler. Thromb. Vasc. Biol. 2011, 31, 219–227.

54. Hanks, L.J.; Casazza, K.; Judd, S.E.; Jenny, N.S.; Gutiérrez, O.M. Associations of Fibroblast Growth factor-23 With Ma rkers of Inflammation, Insulin Resistance and Obesity in Adults. PLoS ONE 2015, 10, e0122885.

55. Egli-Spichtig, D.; Imenez Silva, P.H.; Glaudemans, B.; Gehring, N.; Bettoni, C.; Zhang, M.Y.H.; Pastor-Arroyo, E.M.; Sc hönenberger, D.; Rajski, M.; Hoogewijs, D.; et al. Tumor necrosis factor stimulates fibroblast growth factor 23 levels in c hronic kidney disease and non-renal inflammation. Kidney Int. 2019, 96, 890–905.

56. David, V.; Martin, A.; Isakova, T.; Spaulding, C.; Lixin, Q.; Ramirez, V.; Zumbrennen-Bullough, K.B.; Sun, C.C.; Lin, H. Y.; Babitt, J.L.; et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. Kidney Int. 2016, 89, 135–146.

57. Ito, N.; Wijenayaka, A.R.; Prideaux, M.; Kogawa, M.; Ormsby, R.T.; Evdokiou, A.; Bonewald, L.F.; Findlay, D.M.; Atkins, G.J. Regulation of FGF23 expression in IDG-SW3 osteocytes and human bone by pro-inflammatory stimuli. Mol. Cell. Endocrinol. 2015, 399, 208–218.

58. Imel, E.A.; Hui, S.L.; Econs, M.J. FGF23 concentrations vary with disease status in autosomal dominant hypophosphat emic rickets. J. Bone Miner. Res. 2007, 22, 520–526.

59. Bacchetta, J.; Sea, J.L.; Chun, R.F.; Lisse, T.S.; Wesseling-Perry, K.; Gales, B.; Adams, J.S.; Salusky, I.B.; Hewison, M. Fibroblast growth factor 23 inhibits extrarenal synthesis of 1, 25-Dihydroxyvitamin D in human monocytes. J. Bone Min er. Res. 2013, 28, 46–55.

60. Dai, B.; David, V.; Martin, A.; Huang, J.; Li, H.; Jiao, Y.; Gu, W.; Quarles, L.D. A comparative transcriptome analysis ide ntifying FGF23 regulated genes in the kidney of a mouse CKD model. PLoS ONE 2012, 7, e44161.

61. Zhang, X.M.; Guo, K.; Xia, F.; Zhao, X.; Huang, Z.; Niu, J. FGF23 (C-tail) improves diabetic nephropathy by attenuating renal fibrosis and inflammation. BMC Biotechnol. 2018, 18, 33.

62. Han, X.; Li, L.; Yang, J.; King, G.; Xiao, Z.; Quarles, L.D. Counter-regulatory paracrine actions of FGF-23 and 1,25(OH) 2D in macrophages. FEBS Lett. 2016, 590, 53–67.