GDF15: a potential therapeutic target for type 1 diabetes

Article highlights

- The stress-induced growth differentiating factor-15 (GDF15) has been documented to play a critical role in a number of diseases.

- The recent discovery of potential receptor targets of GDF15 has brought significant attention to the field due to its therapeutic possibilities.

- Recently we have demonstrated that GDF15 ameliorates β-cell death during the initial stages of T1D progression.

- However, the pleotropic nature of GDF15 poses a significant challenge for its therapeutic potential.

- There remains a gap in knowledge regarding GDF15's pharmacokinetic and pharmacodynamic characteristics in various diseases, including T1D. Therefore, further in-depth research is warranted.

Abstract

Introduction: Current treatment for Type 1 diabetes (T1D) is centered around insulin supplementation to manage the effects of pancreatic β cell loss. GDF15 is a potential preventative therapy against T1D progression that could work to curb increasing disease incidence.

Areas Covered: Here, we discuss the known actions of GDF15, a pleiotropic protein with metabolic, feeding, and immunomodulatory effects, connecting them to highlight the open opportunities for future research. We then examine the role of GDF15 in the prevention of insulitis and protection of pancreatic β cells against pro-inflammatory cytokine-mediated cellular stress. We then discussed the current state of GDF15's pharmacological promise as well as critical areas of future research.

Expert Opinion: GDF15 shows promise as a potential intervention but still requires further development. Current preclinical trials have shown poor efficacy, but that result may be confounded by the measurement of gross GDF15 instead of the active form. Additionally, the effect of GDF15 in the induction of anorexia and nausea-like behavior and short-half-life present significant challenges to its deployment, but a systems pharmacology approach paired with chronotherapy may provide a possible solution to therapy for a currently unpreventable disease.

1.0 Introduction –

Type 1 diabetes (T1D) is an autoimmune disorder marked by the destruction of insulin-producing β cells in the pancreas. The International Diabetes Federation (IDF) estimates T1D cases increase by 3% per year globally, with the 2nd highest number of new cases of T1D estimated to be from the USA [1]. Epidemiological studies indicate ~40% of T1D cases reported globally are associated with polymorphism in the human leukocyte antigen (HLA) gene; however, the recent increase in the T1D numbers among children, in parallel with reduced frequency of HLA genotype, indicate increased environmental pressure, as a responsible factor [2-4]. As a result, our understanding of the disease pathology has evolved to the current model that T1D results from a combination of genetic predisposition and various environmental triggers that activate and accelerate disease severity.

The combinatorial disease concept underlying T1D was first proposed by Eisenbarth, who defined and parsed the T1D progression stage from the initiation stage [5]. This work redefined strategies for therapeutic development targeting each stage of the disease. For instance, insulin replacement, which remains the gold-standard therapy, was developed and used as a first-line therapeutic option to treat T1D [6,7]. Several advances, such as the development of the insulin pump and genetically modified long-lasting insulins, have shown promise for minimizing injections and better controlling insulin delivery. There have also been significant efforts in developing preventative therapies targeting the immune responses responsible for pancreatic β cell death. While immunomodulatory therapies like Cyclosporine A, anti-CD3/20 antibodies, and IL-1 inhibitors are only able to delay the onset of the disease, there remains significant interest in developing next-generation immunomodulators targeting immune systems Treg cells, B lymphocytes, and CD3 coreceptor [6,8-10]. Lastly, combinatorial treatment strategies that act at

multiple stages of T1D, including the artificial pancreas, stem cell mobilization, β cell encapsulation, and SGLT2 inhibitors, show promising returns in the clinic [6]. However, trials are still in the early stages, and the cost-benefit of these therapies compared to traditional treatments has yet to be determined.

Current therapeutic options only manage T1D, demanding novel and efficient therapies that prevent or delay disease onset. Growth differentiation factor 15 (GDF15 - also known as macrophage inhibitory cytokine 1 & NSAID-activated gene 1 protein and placental TFG-β) a known diabetes biomarker, has triggered widespread interest in this regard due to its impressive tissue-protective actions over the last 2 decades in broad range of metabolic disorders (**Fig. 1A, B & Table S1**) [11]. The discovery of GDF15's primary receptor and associated signaling pathway has further bolstered its potential as a druggable target [12]. A recent study by our team has specifically demonstrated the benefits of GDF15 in reducing insulitis and T1D onset [13]. In this review, we map multiple GDF15-relevant pathways in T1D pathology and discuss the therapeutic potential of GDF15 in the treatment of T1D.

2.0 GDF15: A functionally pleiotropic molecule

GDF15 is a secreted cytokine, independently discovered by three research groups in 1997 [14-16]. Despite its low sequence homology to TGF-β, GDF15 has been classified as a distant member of the TGF-β family due to the presence of a unique cysteine knot characteristic of this class of molecules. GDF15 is expressed in most tissues as a 308 amino acid propeptide monomer form, which dimerizes via a disulfide linkage between the cysteines in the C-terminus. The pro-protein dimer undergoes proteolytic cleavage at an RXXR residue by a furine-like protease to release the mature GDF15 dimer of 25 kDa into the extracellular space [15,17-21]. In plasma, GDF15 exists

in a broad concentration ranging from 0.15 to 1.15 ng/mL and potentially in both proGDF15 and mature GDF15 forms [21,22]. Levels of GDF15 are impacted by plethora of metabolic factors, exercise, tissue injury, pregnancy, hypoxia, and drugs like metformin and rapamycin represented in **Fig. 2**. Given its central role and metabolic sensitivity, GDF15 is emerging as a premier biomarker to determine prognoses in a number of health disorders, including T1D [11,23,24].

Recently, the interest in GDF15 has spiked due to multiple landmark studies that independently identified the Glial-cell-derived neurotrophic factor (GDNF) family receptor α-like (GFRAL) receptor as the primary receptor for GDF15 [25-28]. GFRAL is primarily expressed in the area postrema (A.P.) and the nucleus of the hindbrain's solitary tract (NST) neurons. Using GFRAL deficient mice, it has been demonstrated that GDF15 acts on GFRAL in the hindbrain, signaling through AKT, ERK, and PLCγ pathways which reduce appetite and ultimately result in weight loss [25,28]. In addition, it was observed that administration of GDF15 accelerates lipid oxidation and was thought to be secondary to AKT/ERK signaling, which contributes to the observed weight loss phenotype [26,27,29]. Taken together, these studies suggest that GDF15 has a significant impact on pathways critical for energy expenditure. This notion was reinforced by Shuang and colleagues, who demonstrated that GDF15 could specifically regulate lipid metabolism by stimulating hepatic triglyceride secretion via β adrenergic signaling [30]. In addition, multiple studies have demonstrated improved glucose tolerance and insulin sensitivity [31,32]. Whether this improvement is an indirect effect of weight reduction or directly induced by ectopic expression of GDF15 has yet to be determined. Regardless, these studies make GDF15 a highly enticing therapeutic target for treating obesity and other metabolic epidemics currently plaguing the USA [29,33,34].

While GDF15 is best recognized for its influence on metabolism, it acts in several homeostatic mechanisms in the body. Multiple studies have now shown that GDF15 plays a critical anti-inflammatory role in tissue injury. Most of our mechanistic insights on the role of GDF15 in inflammation come from an early study by Kempf and colleagues, who reported that GDF15 inhibits integrin activation and thereby dampens cytokine signaling and infiltration of pro-inflammatory cells in heart infarcts [35]. In addition, Abulizi et al. and Santos et al. demonstrated that GDF15 deficiency exacerbates the inflammatory response to the sepsis affected tissue, but its role is highly contextual [36,37]. Similarly, in animal models of T1D, Deelman and colleagues showed that GDF15 deficiency results in increased expression of inflammatory markers [38]. In contrast, Santos et al. showed that GDF15's immunomodulatory role has also been demonstrated in tumorigenesis and cancer progression with contradictory viewpoints, making it difficult to clearly define its underlying mechanism of action as an anti-inflammatory molecule [39-41]. However, the above studies indicate a tissue-protective role of GDF15 in addition to the parasympathetic signaling axis.

Apart from systemic effects, GDF15's direct impact on tissues and cells has been well documented. For example, GDF15 was found to directly interact with avian erythroblastosis oncogene B 2(ErbB2) receptor, which activates AKT and ERK pathways [42,43]. Likewise, upregulation of GDF15 by Tumor protein 53 (TP53) activates the Phosphoinositide 3-kinase/endothelial nitric oxide synthase (PI3K/eNOS) pathway and downregulates the Nuclear Factor kappa-light-chain-enhancer of activated B cells/c-Jun N-terminal Kinase (NF-κB/JNK) pathways [44]. Recently two groups independently have identified novel interactions of GDF15 with surface receptors of immune cells [45,46]. Wang et al., shows GDF15 interacts with CD48 on T cells and regulates the function and population of competent Treg cells against hepatocellular

carcinoma [45]. Whereas, Gao et al., outlines the mechanism of immune escape of ovarian cancer regulated by GDF15-CD44 interaction in dendritic cells [46]. As GFRAL receptors are reported to be exclusively in the hindbrain, the above studies indicate the existence of a potentially non-GFRAL receptor. Nonetheless, reports of GFRAL receptors detected in pancreatic ductal adenocarcinoma tissue and our unpublished preliminary data from pancreatic islets imply that GFRAL might not be as exclusive as previously thought [47]. Therefore, these pieces of evidence point towards a gap in our understanding of GDF15's molecular mechanism. Consequently, further studies are warranted, which eventually would aid in developing a robust GDF15 therapy for multiple disease modalities, including T1D.

3.0 GDF15: a bridge between T2D and T1D

Obesity is a known risk factor for type 2 diabetes (T2D), as it is considered one of the environmental triggers for genetically predisposed individuals [48]. Obesity is marked by metabolic dysregulation and is associated with increased GDF15 levels [49-52]. The connection between GDF15 and T2D has also been reported by several studies [53,54]. Further, various papers have looked at increased GDF15 levels in obese and diabetic patients, with GDF15 being regarded as a marker for both [20,49,55,56]. GDF15, primarily identified as macrophage inhibitory cytokine 1(MIC-1), has been associated with ameliorating inflammation-mediated cellular stress [14]. Accordingly, interleukin-13 (IL-13) has been known to regulate glucose metabolism, insulin sensitivity, and glucose tolerance via GDF15 [57]. Plus, in a comprehensive human study, an increase in GDF15 levels in early-stage T2D indicated GDF15's anti-inflammatory response to the onset of diabetes [55]. Therefore, as obesity and diabetes are both associated with chronic

inflammation, there exists a strong connection between GDF15 and diabetes in the context of the immune response that needs to be explored further [58].

In addition to inflammation, endoplasmic reticulum (ER) stress is also considered a common contributor to T1D and T2D pathogenesis [59]. As a link between GDF15 and a known ER stress protein C/EBP Homologous Protein (CHOP) exists, the possibility of a relationship between GDF15, T1D, and T2D through ER stress is not farfetched [60]. Moreover, clinical studies have implicated that metformin, an insulin-sensitizer widely used to treat T2D patients, exerts its function by activating endogenous GDF15, which reduces ER and mitochondrial oxidative stress [61-65]. Together, these studies assert GDF15 as a bridge between T1D and T2D, which could help develop treatment strategies for both diseases.

4.0 GDF15's role in T1D pathogenesis

There is growing evidence indicating GDF15's involvement in T1D pathogenesis. For instance, recent studies suggest that peroxisome proliferator-activated receptor (PPAR) and AMP-protein kinase (AMPK) both play vital roles in glucose metabolism and can ameliorate T1D development in NOD mice through the activation of GDF15 [66-68]. Similarly, a study by Lertpatipanpong et al. reported that, in transgenic mice, overexpressing GDF15 improves insulin sensitivity and protects pancreatic islets against streptozotocin-mediated β cell destruction [69]. In line with these results, we have reported that human islets and human β cells exposed to pro-inflammatory cytokines have a significant decrease in GDF15, which is similar to pancreatic tissue sections obtained from human T1D cadaveric donors. To understand the mechanism of this reduction we found that GDF15 mRNA translation was blocked by pro-inflammatory cytokines, which acted as a bottle neck. Moreover, when we pretreated human islets with recombinant GDF15 (rGDF15),

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we saw enhanced protection against pro-inflammatory cytokine-mediated β cell apoptosis/death [13]. Finally, we were able to determine that rGDF15 significantly reduced insulitis and increase β cell survival. We are at present trying to understand the underlying mechanism of our observation and hypothesis that GDF15 effects transcend through the GFRAL receptor found on the β cell surface. Collectively, these data suggest that GDF15 could be a likely target for T1D prevention and management. Hence, these connections are discussed in detail with the relative gaps in knowledge and future area of research below.

5.0 GDF15: the makings of a T1D therapy

Studies since the early 1980's suggest that T1D is a multi-stage disease, broadly divided into three major stages and one pre-stage (**Fig. 3**) [70,71]. The pre-stage of T1D is mainly associated with genetic mutation of the HLA gene, triggered by various environmental factors such as β cell mass, β cell stress, pancreatic size, congenital rubella/enterovirus infections, or metabolic stress [72-74]. These factors initiate immune activation and response towards pancreatic β cells. Based on this classification, early treatment strategies have mainly focused on developing anti-inflammatory drugs to treat the onset of T1D, with no long-term success [6,8-10]. Nevertheless, interest in this area persists, as multiple clinical studies are being performed worldwide to develop next-generation immunomodulatory drugs against T1D initiation [75]. Following the trend, GDF15 has been associated with immunosuppressant activity and is regarded as the first anti-inflammatory cytokine to demonstrate regulation of chemokine-triggered leukocyte integrin activation [30,35,76,77]. Therefore, GDF15 could be deemed as a lucrative immunomodulatory target in the future. However, there is a growing paradigm shift in the field regarding T1D pathogenesis. According to the latest consensus, the pancreas is not considered the target of the immune response;

and instead, it is regarded as the initiator of immune activation [78,79]. Therefore, this could be a potential rationale for the lack of any successful immunomodulatory drug so far.

Subsequently, scientists in the field have diverted their attention to understanding T1D β cell physiology that potentially instigates immune response [73,74,79]. Out of the number of factors, cytokines from neighboring macrophage cells or immune cells initiate β cell stress, which activates STAT1, IRF1, and NFκB pathways to hyper-express HLA class 1 protein, which is responsible for initiating a full-blown immune response [80-83]. GDF15 has been associated with the downregulation of the NFκB/STAT pathways in endothelial cells to attenuate cell apoptosis in response to high glucose stimulus [44]. As GDF15 in islets increases cell survival and decreases insulitis, together, the above studies imply a direct effect of GDF15 on β cell fate through NFκB/STAT pathways, which counteracts cytokine-mediated HLA-induced immune response [13]. Furthermore, GDF15 is associated with regulating mitochondrial dysfunction and ER stress, both of which are considered crucial in aggravating β cell stress and initiating inflammation [60,80,84-86]. Evidence of GDF15 being the target of p53 and its role in activating pro-survival pathways(AKT/ERK) suggests GDF15 could have a direct protective role towards pancreatic β cells [42,44]. In summary, GDF15 can be developed as a holistic therapy, focusing on its direct β cell function against T1D initiation, whereas the indirect effect of GDF15 through the immune system should be explored with caution (**Fig. 3**).

As outlined previously, T1D is an autoimmune disease; however, metabolic and neurological implications contribute significantly to the progression of T1D. It is well documented that the sympathetic and parasympathetic nervous systems regulate various branches of glucose homeostasis, including regulation of hormone secretion (insulin & glucagon) and maintenance of β cell populations in our body [87]. Therefore, researchers have started investigating the neuronal

contribution to diabetes pathology [88-90]. To this end, as mentioned earlier, GFRAL receptors are present in the brainstem, nucleus of the solitary tract (NTS), and hypothalamus, implying a possible regulation of glucose homeostasis by GDF15 through stimulation of sympathetic and parasympathetic signaling [12,91,92]. This link is another addition to the growing list of potential GDF15 crosstalk with factors responsible for T1D, ultimately bolstering the therapeutic potential of GDF15 (**Fig. 3**).

The current standards of T1D therapy have not changed significantly in that Insulin replacement is still considered the most cost effective and easily available treatment options worldwide. However, the push for developing therapeutics which target multiple stages of T1D is gaining ground in preclinical studies. In alignment with this, we have reported that GDF15 prevents from insulitis and delays the development of diabetes in prediabetic mice [13]. Plus, other research discussed above, points to a direct or indirect β cell protection by GDF15, which makes it a potential concomitant therapy with Insulin. This strategy is particularly beneficial in the early stages of T1D, where the patients are not completely dependent on insulin and have some functional β cells in the islets. GDF15 could delay T1D clinical onset by potentially preserving the remaining β cells and could increase the success of islet replacement therapies. Overall, these additional benefits of GDF15 could significantly improve T1D patient outcomes.

6.0 Therapeutic future of GDF15

The discovery of GDF15's dedicated receptor has helped clear some of the ambiguity regarding GDF15's mechanism of action and related effects, which has opened a plethora of new therapeutic possibilities in the field. Initial studies have shown that manipulating GDF15/GFRAL signaling cascade in mice and nonhuman primates causes weight loss and regulates body metabolism [25,29].

Consequently, GDF15 related therapies are being developed to treat obesity, cancer-induced cachexia, heart disease, and many more metabolic disorders [29,93,94]. In addition, there is a steady rise in the number of GDF15-related clinical trials. According to *ClinicalTrial.gov*, 104 clinical trials are looking into GDF15 as a biomarker or potential drug target. Interestingly, only six studies in this list are related to T2D, while none are on T1D, indicating a large area for future studies with a therapeutic focus (**Table S1**).

Often increased circulating GDF15 levels documented in various disease pathologies are contradictory, yet the exogenous administration of GDF15 has consistently been demonstrated to be beneficial in regulating normal cellular functions [95-99]. Generally, GDF15 expression levels play a vital role in transcending its effect in the body, and therefore most treatment strategies focus on regulating its level in the system. However, developing GDF15 as a potential therapy has been challenging due to its very short half-life and its susceptibility to proteolytic cleavage in the serum [29,100]. The addition of recombinant modifications like human serum albumin (HAS) and fragment crystallization region of immunoglobulin G (FC) has significantly extended GDF15 protein half-life without hampering its associated anorexia and weight loss phenotypes [28,29,101]. Direct targeting of GDF15 transcription regulators like MKKK/p38, p53, and Egr-1, or post-transcriptional regulators like tristetraprolin (TTP), are also being explored as therapeutic options [102,103].

High GDF15 levels induce vomiting and nausea in patients, posing a critical risk to GDF15 therapeutic endeavors [104,105]. As a result, exploring small molecules like XIB4035 and BT13, which can mimic GDF15 effects by targeting GFRAL/RET receptor signaling, could potentially increase the target specificity and reduce off-target effects [34,106]. In addition, approaches like reducing the dosage of GDF15 agonist should be explored for temporary relief. Furthermore, an

alternative strategy to achieve the targeted GDF15 effect could be by implementing antibody strategies targeting the GDF15/GFRAL signaling axis. As antibodies against GDF15 or GFRAL receptors have been utilized to outline the GDF15-GFRAL circuitry, multiple studies are underway to explore its efficacy in mitigating GDF15's side effects [26,29,93]. As GDF15 is pleiotropic, there is a high probability that any GDF15 agonist therapies might fail in the clinical trials due to unwanted effects in the body. Therefore, a combination of an agonist and an antagonist therapy targeting specific regions of the body, such that the agonist only affects the area of interest, could hold the key to increasing GDF15's precision and reducing its side effects. Such technology is being developed by Pondion therapeutics for targeting PDL1 and Ionis pharmaceutical for GLP1 receptor. However, whether such concepts can be applied to GDF15 therapy need to be explored and tested.

Overall, GDF15 holds tremendous potential to be a frontline treatment for T1D initiation, progression, or both. However, there are still significant questions that need to be addressed by thorough fundamental work to understand GDF15's precision, efficacy, and long-term effects in our bodies.

7.0 Expert Opinion

Generally, around 90% of therapies fail at the clinical development stage due to poor pharmacokinetics, toxicity, and/or lack of efficacy [107,108]. This high failure rate accounts for an enormous economic burden on the drug development process and eventually discourages real innovation. The common reasons for this lack of success are usually associated with the poor predictive ability of preclinical studies for human efficacy and randomized controlled clinical trials [109]. Recently, a study by Cheung et al. performed a Mendelian randomized study to look at

serum GDF15 relationship with cardiometabolic phenotype and reported no effect of GDF15 on anthropometric measurement in human subjects [110]. They further suggested that the effects observed in animal studies might be different in humans and advised caution for future drug development ventures. The study accounted for various SNPs found in serum GDF15; however, there is a possibility of GDF15 existing in 4 different protein forms in the serum, out of which only one is considered active and thought to produce the characteristic functions [21,111]. Therefore, the conclusion drawn by Cheung et al. might have looked at a mixed population of GDF15, which could explain the lack of GDF15 association with weight loss in humans. Nevertheless, the study points out a valid concern regarding GDF15's therapeutic blind spot, i.e., translation from bench to bedside. Therefore, we suggest the application of a systems pharmacology approach, which accounts for genome-wide association (GWA), proteome-wide association (PWA), and phenome-wide association studies (PheWAS) with exhaustive pharmacodynamic and pharmacokinetic (PD/PK) studies, to help develop a robust GDF15 therapy to target T1D.

As mentioned earlier, the pleiotropic nature of GDF15 makes it an exciting target but has the potential to be a therapeutic challenge. Its potential to cause several side effects upon administration can jeopardize its precision and efficacy. Therefore, research focusing on GDF15 fidelity is of utmost priority. One approach to curtail this unwanted outcome would be implementing chronotherapy strategies in the GDF15 drug development plan. Since the 1970's, various drugs are being evaluated with respect to chronotherapy which utilizes our body's innate time-keeping system called the circadian clock to determine the right time of drug/therapy administration, such that it reduces potential side effects and increases its efficacy and precision [112,113]. The circadian clock is a vital homeostatic mechanism present in almost every cell of our body and known to regulate about 50% of all protein-coding genes in humans, creating various

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physiological and biochemical rhythms synced to the natural night and day cycle [114,115]. Due to the circadian nature of multiple genes in the body, it is becoming evident that drugs show low to no effect, if administered at the wrong time of the day, when the target concentration is low. This can also in some cases lead to pronounced unwanted effect of the drug [116,117]. Therefore, knowing the drug target and its associated mechanism with respect to circadian timing could offer a solution.

With regards to T1D, circadian clock is known to regulate body glucose metabolism and immune response in our body [118-120]. Plus, a study by Takahashi & Bass's group has demonstrated that loss of clock in pancreatic islets can trigger diabetes onset due to impaired β cell function [121]. Indeed, the connection between the circadian clock and T1D seems logical. Likewise, studies have reported GDF15 as a clock-controlled gene with a nominal diurnal circadian rhythmicity in human serum, and the GFRAL receptor being expressed in the hippocampus, spinal cord, and thalamus regions of the brainstem, NTS and area postrema (AP), which are associated with the suprachiasmatic nucleus (SCN), aka master circadian clock, solidifies the possibility of a connection [12,91,114,122-124]. Therefore, applying chronotherapy strategies in the GDF15 therapeutic undertaking might be beneficial to determine a specific time of the day to administer GDF15, such that it produces a precise effect with no or minimal side effects. However, the lack of a defined GDF15 mechanism in T1D presents a significant challenge to develop it as a chronotherapy. Tools are being developed to measure the internal timing of the effector tissue, or measure daily rhythms of sleep and temperature by wearable sensors (less invasive) which can speed up the development of chronomedicines in the future [113,125]. Such advances can offer an avenue for honing and improving GDF15 therapy for T1D treatment as well.

In addition, exploring tissue/cell type-specific delivery or activation of GDF15 to reduce possible side effects might be of worth as well.

Finally, in our opinion, the absence of a well-defined GDF15 mechanism of action in T1D pathology is an imperative hurdle that needs immediate attention. Though discovering the GFRAL receptor helped alleviate some mysticism, identifying the receptor exclusively in the brain tissue creates ambiguity regarding the evidence showing GDF15's direct action on peripheral tissue. Thus, presenting the question of whether GDF15 can act on peripheral tissue directly or indirectly through the GFRAL-β adrenergic signaling pathway. Further, studies showing a difference in effect based on GDF15 structures, i.e., matured vs. proGDF15, have brought into question the established signaling pathways [21,22]. Therefore, these crucial gaps in knowledge needs to be addressed in future studies.

In conclusion, with the increasing number of T1D cases in pediatric patients, new and efficient strategies are needed more than ever. None of the current therapies for T1D are sufficient to prevent the disease by themselves, plus they have been known to have severe drawbacks in the long run. Therefore, a systems approach in developing a therapy for T1D is necessary. As our knowledge regarding T1D pathogenesis has grown, we have evolved from the initial viewpoint of T1D being only a pancreatic disease to a more complex macro and micro environmental dysfunction. In alignment with this thought, GDF15 possesses the potential to address T1D holistically and could push us closer to a cure.

8.0 Declaration of Interest

Refrences

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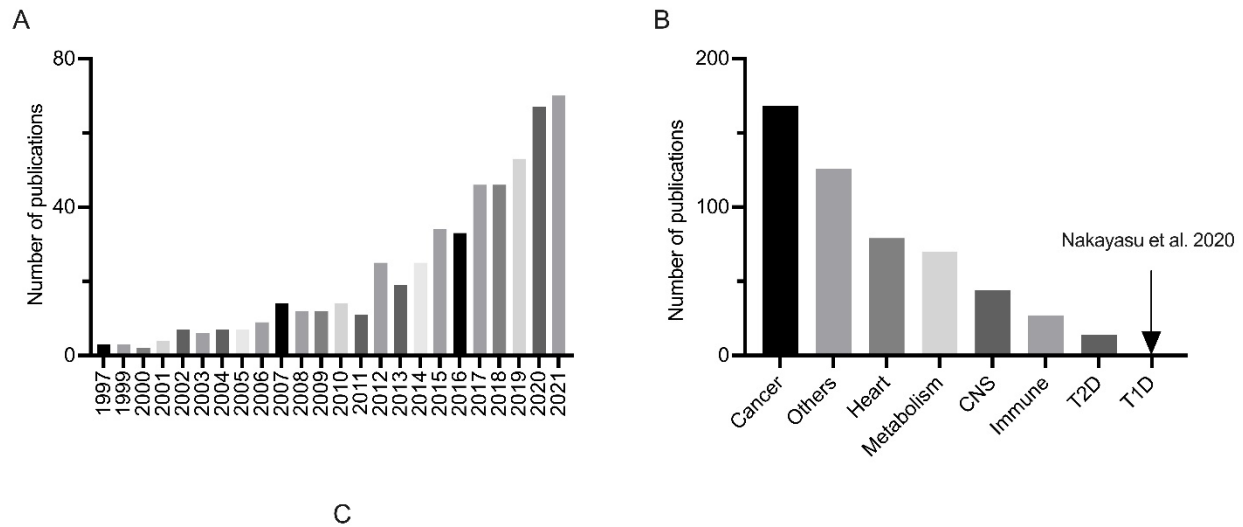
Figures

A

B

C

Figure 1. Trends of published research articles related to GDF15. **A.** represents the distribution of GDF15 research articles published since 1997. **B.** represents the number of GDF15 research articles arranged according to the topics (CNS: central nervous system, T2D: type 2 diabetes, T1D: type 1 diabetes). The articles titles with GDF15 or its aliases (i.e., MIC-1, NAG-1, PTGFB, PALB, & NRG1) were curated using PubMed search tool, specifically, excluding reviews, meta-analysis, commentary, & corrections in our analysis.
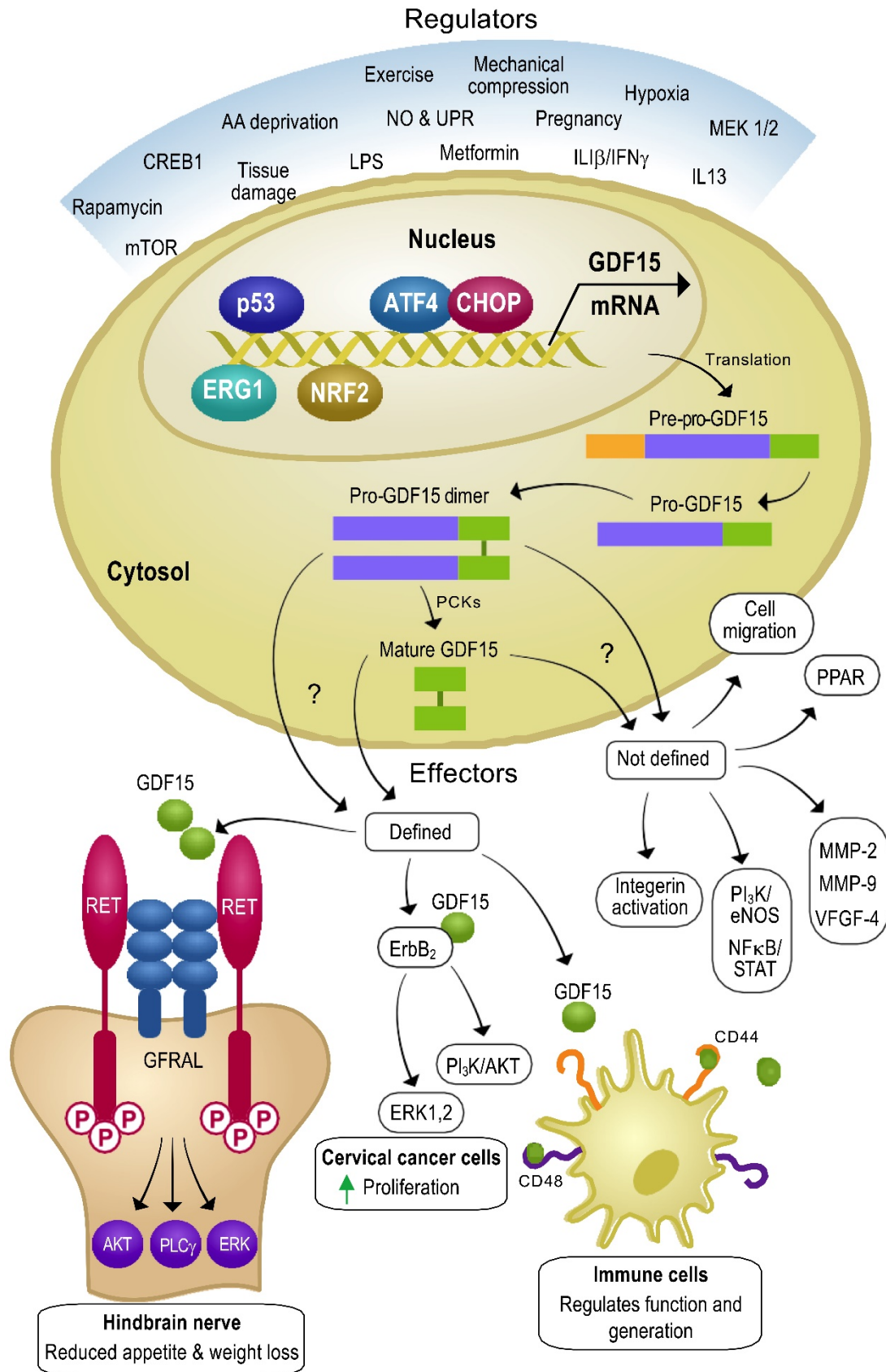
Figure 2. Regulators and effectors of GDF15. GDF15 is expressed in most tissues of our body in response to various signals including, tissue damage, hypoxia, mechanical compression and many more. The protein biosynthesis of GDF15 is well documented which results in pro-GDF15 dimer and mature GDF15 synthesis. It is still not very clear which of these protein forms are functionally relevant as they both are secreted in the plasma. Once released, they have plethora of effectors, which can be broadly classified as defined and not defined mechanism. Under defined mechanism, GDF15 has been shown to interact with 3 distinct receptors i.e., GFRAL, ErbB2 and CD44, which have been reported to have different effects. Whereas there exists a large number of undefined correlational effects of GDF15, which could be the result of a direct or indirect mechanism.
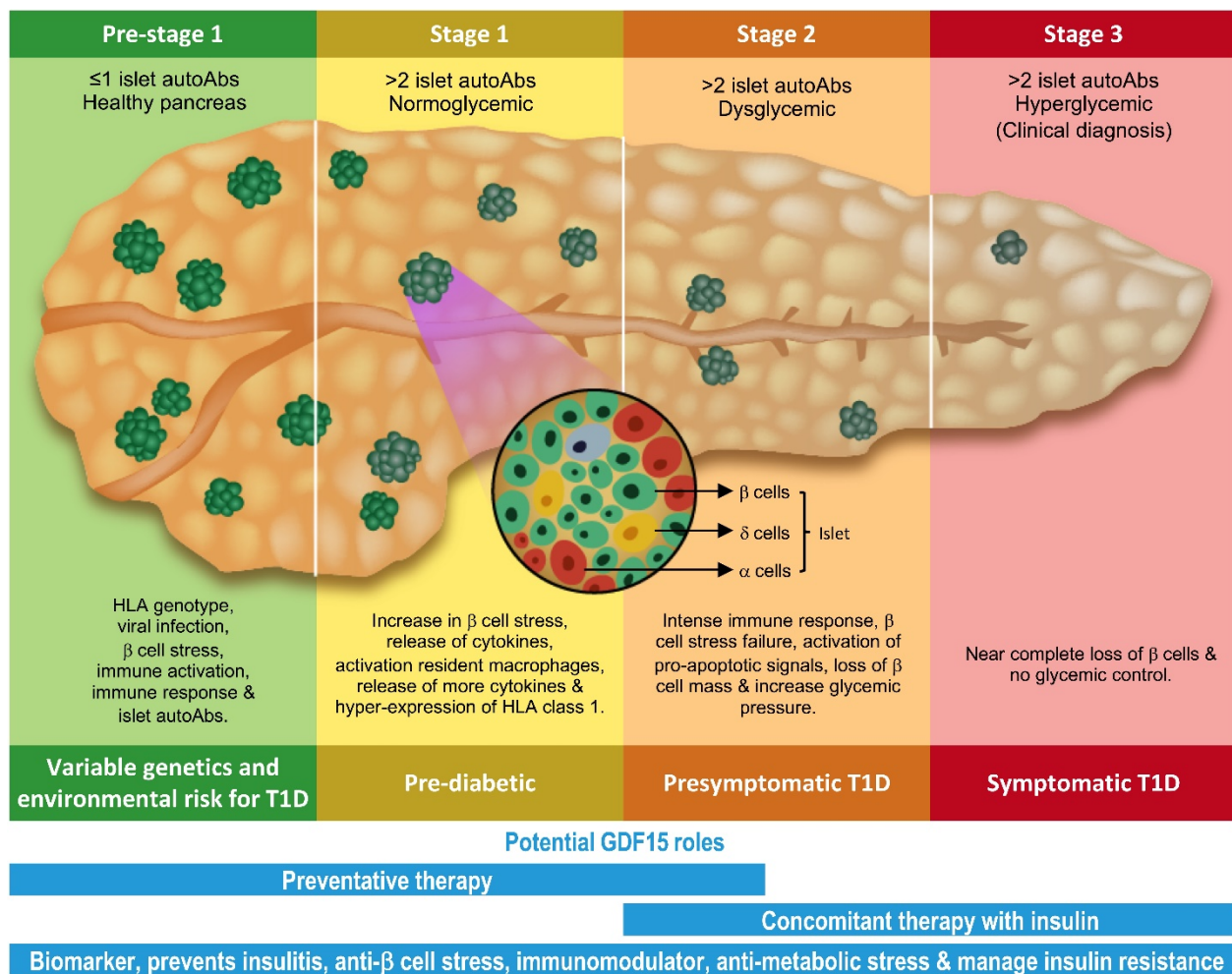
Figure 3. Schematic representing the stages of T1D and the potential GDF15 therapeutic roles. T1D is divided into 3 main stages and one pre-stage 1. The pre-stage 1 is marked by HLA genotype which gets triggered by an insult, such as viral infection, β cell stress or both. This initiates immune activation and response, leading to increased β cell stress and hyper HLA expression. Eventually, these events initiate pro-apoptotic signals and cause loss of β cell mass. GDF15 is an established biomarker for T1D and has been shown to reduce T1D insulitis. The potential roles of GDF15 in preventing or slowing the progression of T1D could be a combination of anti-β cell stress, immunomodulatory effect, management of metabolic stress and finally, restoration of glycemic control. Overall, GDF15 has the potential to be developed as a preventative

therapy for pre-stage 1 to stage 2, or a concomitant therapy along with insulin to reduce the progression of the disease in the later stages.