The anti-inflammatory feature of glucagon-like peptide-1 and its based diabetes drugs – Therapeutic potential exploration in lung injury

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Abstract

Since 2005, GLP-1 receptor (GLP-1R) agonists (GLP-1RAs) have been developed as therapeutic agents for Type 2 diabetes. GLP-1R is not only expressed in pancreatic islets but also in other organs, especially the lung. Extra-pancreatic expression of GLP-1R triggered intensive investigations on extra-pancreatic functions of GLP-1RAs, aiming to repurpose them into therapeutic agents for other disorders. Intensive studies have demonstrated promising anti-inflammatory features of GLP-1RAs. Whether those features are directly mediated by GLP-1R expressed in majority of immune cells remains controversial. Following a brief review on GLP-1 as incretin and the development of GLP-1RAs as therapeutic agents, we summarized our current understanding on anti-inflammatory features of GLP-1RAs. The main part of this review is literature discussions on GLP-1RA utilization in chronic and acute lung injuries, including studies on combined use of MSC-based therapy and the GLP-1RA liraglutide in LPS-induced acute lung injury. This is followed by a summary and perspective.

The anti-inflammatory feature of glucagon-like peptide-1 and its based diabetes drugs – Therapeutic potential exploration in lung injury

Short title : GLP-1 based drugs in anti-inflammation

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Abstract (149 words)

Since 2005, GLP-1 receptor (GLP-1R) agonists (GLP-1RAs) have been developed as therapeutic agents for Type 2 diabetes. GLP-1R is not only expressed in pancreatic islets but also in other organs, especially the lung. Extra-pancreatic expression of GLP-1R triggered intensive investigations on extra-pancreatic functions of GLP-1RAs, aiming to repurpose them into therapeutic agents for other disorders. Intensive studies have demonstrated promising anti-inflammatory features of GLP-1RAs. Whether those features are directly mediated by GLP-1R expressed in majority of immune cells remains controversial. Following a brief

review on GLP-1 as incretin and the development of GLP-1RAs as therapeutic agents, we summarized our current understanding on anti-inflammatory features of GLP-1RAs. The main part of this review is literature discussions on GLP-1RA utilization in chronic and acute lung injuries, including studies on combined use of MSC-based therapy and the GLP-1RA liraglutide in LPS-induced acute lung injury. This is followed by a summary and perspective.

Key words: Anti-inflammation; GLP-1R; Exenatide; Liraglutide; Lung injury; TxNIP

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List of Abbreviations: ALI, acute lung injury; ANP, natriuretic peptide; ARDS, acute respiratory distress syndrome; BALF, brochoalveolar lavage fluid; BMI, body mass index; COPD, chromic obstructive lung disease; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase 4; DPP-4i, DPP-4 inhibitor; EMA, European Medicines Agency; eNOS, endothelial NO synthase; FDA, FGF10, fibroblast growth factor 10; FOXA2, forkhead box A2; Food and Drug administration; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; GLP-1RA, GLP-1R agonist; GLP-2, glucagon-like peptide-1; GWAS, genome-wide association study; HBA1c, Hemoglobin A1c; hMSCs, human MSCs; hs-CRP, high-sensitivity CRP; ICAM, intercellular adhesion molecule-1; IEL, intraepithelial lymphocyte; IFN-γ, interferon γ· IL-1α· IL-β, IL-1RA, interleukin 1 receptor antagonist; interleukin β· IL-4, interleukin 4; IL-6, interleukin 6; IL-8, interleukin 8; IL-13, interleukin 13; IL-33, interleukin 33; ILC2s, group 2 innate lymphoid cells; i.p, intraperitoneal; KGF, keratinocyte growth factor; KO, knockout; LPL, lipoprotein lipase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MPGF, major pro-glucagon fragment; MSC, mesenchymal stem cells; NEP24.11, neutral endopeptidase 24.11; NF-ϰB, nuclear factor-kappa B; NO, Nitric Oxide; NLRP3, NLR family pyrin domain containing 3; PBMC, peripheral blood mono-nuclear cells (also known as MNC, mononuclear cells); PC1/3, pre-hormone convertase 1/3; PC2, pre-hormone convertase 2; PGF-2α, 8-iso-prostaglandin F2a; PKA, protein kinase A; PKG, protein kinase G; PMN, polymorphonuclear neutrophil; PPAR, peroxisome proliferator-activated receptor; sGC, soluble guanylyl cyclase; SGLT-2, sodium-glucose cotransporter-2; SP-1, surfactant protein A; STZ, streptozotocin; SVF, sromal vascular fraction; T1D and T2D, type 1 and type 2 diabetes; TG, triglyceride; Th2, T helper 2; TNF-α, tumor necrosis factor α· Tregs regulatory T cells; TxNIP, thioredoxin-interacting protein; TTF-1, thyroid transcription factor-1; VCAM-1, vascular cell adhesion molecule-1.

Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin hormone produced in endocrine L cells, located mainly in distal ileum and the colon (1-4). Postprandial GLP-1 secretion leads to reduced plasma glucose level by mechanisms including the stimulation of insulin secretion, the inhibition of glucagon release, as well as the delay of gastric emptying (5). Furthermore, plasma GLP-1 elevation or GLP-1-based drug administration may directly reduce food intake, involving its function in the brain, mediated by GLP-1 receptor (GLP-1R), which is known to be expressed in brain hypothalamus and elsewhere (6-8). Various GLP-1 based drugs (also known as GLP-1R agonists, GLP-1RAs) have been developed and approved by Food and Drug administration (FDA), European Medicines Agency (EMA), or other authorities for diabetes treatment since 2005 (9). They are now widely utilized in treating type 2 diabetes (T2D) without side effects of weight gain and hypoglycemia, compared with various sources of commercial insulin (10). GLP-1 based drugs, such as

liraglutide (commercially known as Victoza®) and semaglutide (Ozempic®) were also approved by FDA for chronic weight management in patients with obesity, overweight, or a weight related comorbid condition.

Studies on native GLP-1 and the use of these drugs in animal models or in treating patients with T2D have also uncovered their potent anti-inflammatory functions (11, 12). Since inflammatory responses also play important roles in the development and progression of diseases other than T2D, repurposing GLP-1 based drugs has been attracting researcher's attention in various fields.

In this review, we have briefly summarized the discovery of GLP-1 as an incretin hormone and the development of GLP-1 based diabetes drugs. We then discussed studies leading to the recognition of the anti-inflammatory and immune regulatory functions of GLP-1 and its based drugs. The focus of this review, however, is on literature discussions of the discovery and functional assessment of potential therapeutic effects of GLP-1 based drugs in chronic and acute lung injuries. For more detailed discussions on utilization or potential utilization of GLP-1 based drugs in the treatment of diabetes, cardiovascular diseases, and neurodegenerative brain disorders, please see excellent review articles elsewhere (1, 13-18).

The incretin GLP-1 and its elevation during inflammation

GLP-1 was recognized as the 2nd incretin hormone back to 1983 (19, 20). Ebert and colleagues have observed that in the rat model, incretin activity was still preserved after gastric inhibitory polypeptide (GIP, the 1st incretin identified in 1960s, also known as glucose-dependent insulinotropic polypeptide) was removed from gut extracts by immune-adsorption (20). Following the isolation of the proglucagon gene (*GCG* /*Gcg*) cDNA from fish, hamster, rat, mice, and humans, it was evident that in addition to encoding glucagon, a counter-regulatory hormone of insulin;*GCG/Gcg* cDNAs also encode two additional polypeptides defined as glucagon-like peptide 1 (GLP-1) and glucagon-like peptide 2 (GLP-2) (19, 21-27).

Gcg (*GCG* in humans) is abundantly expressed in pancreatic α-cells, intestinal endocrine L cells, and certain neuronal cells in the brain (3, 22, 28). Post-translational processing of the pro-hormone proglucagon occurs in tissue-specific manners via prohormone convertases (PC) known as PC1/3 and PC2. As shown in Figure 1A, in pancreatic α-cells, which mainly expresses PC2, the pro-hormone proglucagon is cleaved to produce the active hormone glucagon and other products including major proglucagon fragment (MPGF). In the brain and the intestinal endocrine L cells, expression of PC3 (also known as PC1) leads to the catalysis of pro-glucagon into GLP-1 and GLP-2, as well as glicentin and oxyntomodulin (23, 25, 26, 29-33).

Full length GLP-1 consists of 37 amino acid residues, and it becomes biologically active after it is truncated at the *N* -terminus to form GLP-1$_{7\text{-}37}$ (Figure 1B) or GLP-1$_{7\text{-}36\ \text{amide}}$ (not shown), with the latter to be more abundant in the circulation after meals (34, 35). As mentioned above, GLP-1 is the 2nd incretin hormone recognized to date (36-39) while GIP being the first one (20, 40, 41). Incretins are defined as gut produced hormones that can stimulate insulin secretion in glucose-concentration dependent manner. The inhibitory effect of GLP-1 on glucagon secretion, however, was not shared by GIP (42). Instead, a study showed that GIP might stimulate glucagon secretion from pancreatic islet α-cells (42). Native GLP-1 (both GLP-1$_{7\text{-}37}$ and GLP-1$_{7\text{-}36\ \text{amide}}$) can be cleaved by the ubiquitously expressed enzymes dipeptidyl peptidase 4 (DPP-4) to produce GLP-1$_{9\text{-}37}$ or GLP-1$_{9\text{-}36\text{amide}}$, while further cleavage by neutral endopeptidase 24.11 (NEP 24.11) leads to the production of GLP-1$_{28\text{-}36}$ and GLP-1$_{32\text{-}36}$(43-48). Although certain biological functions of GLP-1$_{9\text{-}36\text{amide}}$, GLP-1$_{28\text{-}36\text{amide}}$ and GLP-1$_{32\text{-}36\text{amide}}$ have been described in pre-clinical investigations by our team and others (46-49), those are generally considered as inactive "degradation" products of GLP-1. Half-life of GLP-1 is relatively short, around 5-6 min in human plasma (34). For mechanisms underlying GLP-1 secretion, please see review articles by our team and by others elsewhere (50-53).

In humans, circulating GLP-1 level starts to ramp up only a few minutes after nutrient intake. It reaches the peak around 1 hour (54). Among the nutrient components, glucose was shown to be the strongest stimulus of GLP-1 secretion followed by sucrose, starch, triglycerides (TG), and certain amino acids (50, 51). Animal model studies have demonstrated that systemic inflammation induced by endotoxin (lipopolysaccharide, LPS) can also stimulate GLP-1 secretion in mice (55-57). Kahles and colleagues observed that among the inflammatory stimuli including endotoxin, interleukin 6 (IL-6), and IL-1β, it appears that IL-6 was sufficient

and necessary to directly stimulate GLP-1 production and release, as in IL-6 knockout mice, endotoxin induced GLP-1 secretion was blunted (57). Kahles and colleagues have also reported that in an intensive care unit (ICU) cohort, GLP-1 plasma levels correlated with inflammation markers and the disease severity (57). Consequently, they suggested that GLP-1 serves as a link between the immune system and the gut (57). Indeed, metabolic illness and inflammatory diseases share certain common therapeutic targets (58). Individuals underwent cardiac surgery or autologous stem cell transplantation had up to 2-fold higher levels of circulating GLP-1, reported by Lebherz and colleagues, as well as Ebbesen and colleagues (59, 60). Patients with severe burn injury produced 3-fold more plasma GLP-1, while patients who died from severe burn injury had 5-fold higher GLP-1 levels than those who survived (61). In addition, patients that suffered from sepsis combined with T2D displayed an enhanced activation of endogenous GLP-1 system compared to non-diabetic patients (62). Thus, in both animal models and in human subjects, systematic inflammation can cause plasma GLP-1 elevation. Further investigations are required to determine whether plasma GLP-1 level can be developed as a biomarker for diagnosis and prognosis of inflammatory responses and inflammatory diseases. Patho-physiologically, elevated GLP-1 level during systematic inflammation may serve as a self-defence mechanism.

GLP-1R agonists as diabetes drugs

Although GIP was discovered more than a decade earlier compared with GLP-1, for various reasons, it has not yet been developed as a therapeutic agent. In 2005, the first GLP-1 based drug, exenatide (with the commercial name Byetta®), was approved by FDA for T2D treatment. Since then, ten additional GLP-1R agonists (GLP-1RAs) have been approved for T2D treatment. Table 1 lists those GLP-1RAs, as well as four DPP-4 inhibitors (DPP-4i) and DPP-4i based compound drugs.

As shown in Figure 1C, there are six GLP-1RAs currently approved by FDA as treatment options for T2D, including exenatide, liraglutide, lixisenatide, dulaglutide, albiglutide and semaglutide. Exenatide was developed based on studies on a peptide isolated from the saliva of the Gila monster, known as exendin-4. Exendin-4 contains 39 amino acid residues with a half-life longer than 10 min and sharing 53% amino acid sequence homology with human GLP-1 (63, 64). As a synthetic version of exendin-4, exenatide is resistant to DPP-4-induced degradation which contributes to a longer half-life about 2.4 h (65, 66). Lixisenatide, another derivative of exendin-4 with a half-life of about 3 h, was approved by FDA in 2016 (67, 68). Liraglutide (Victoza®) was approved by FDA in 2010, which is a modified human GLP-1, sharing 97% sequence identity with native GLP-1. The non-covalent binding with albumin further enhanced its stability. It is the first long-acting compound of GLP-1RAs, with a much longer half-life of 13 h (69-71). The other two long-acting GLP-1RAs, albiglutide and dulaglutide, consist of a dimer of human GLP-1 molecules that are fused to recombinant human albumin and a modified human immunoglobulin G4 heavy chain, respectively. Therefore, they have further extended half-life of about 5 days (10). Semaglutide (Ozempic) is the most recent approved long-acting GLP-1RAs for T2D in 2017, with a half life of 7 days (72, 73). Specifically, an equipotent once-daily oral administration form of semaglutide was approved in 2019 and greatly improved medication compliance (74).

As shown in Figure 1B, native GLP-1 can be cleaved by DPP-4, which is a ubiquitously expressed peptidase. DPP-4 can also inactivate GIP. Thus, DPP-4 inhibition can prevent degradation of both native GLP-1 and GIP. DPP-4i can specifically inhibit the enzymatic degradation activity of DPP4 by over 80%, leading to a doubling of active GLP-1 level (75). Sitagliptin (Januvia), developed by Merck & Co, was the first DPP-4i approved by the FDA as a T2D drug in 2006, followed by saxagliptin, linagliptin and alogliptin (76-78). DPP-4i can be administered orally and formulated either as a single-ingredient product or in combination with other diabetes medicines, including metformin (Table 1).

The anti-inflammation features of GLP-1 and its based diabetes drugs

Systemic inflammation is usually characterized by elevated pro-inflammatory cytokines and imbalanced immune cells in the circulation. As the first FDA approved GLP-1-based diabetes drug, the anti-inflammatory features of exenatide have been intensively investigated in patients with T2D. As early as 2007, Viswanathan

and colleagues have demonstrated that in subjects with T2D, exenatide had two "non-metabolic actions": the effect on attenuating plasma C-reactive protein (CRP) levels and the effect on lowering systolic blood pressure (11). A few years later, Kim and colleagues showed in mice that cardiomyocyte GLP-1R activation promoted the translocation of the rap guanine nucleotide exchange factor Epac2 to the membrane, leading to atrial natriuretic peptide (ANP) elevation, which lowers blood pressure (79). Interestingly, they have also located GLP-1R expression in mouse cardiac atria (79). In 2011, Wu and colleagues showed that in patients with T2D, 16-week exenatide treatment had not only reduced body mass index (BMI) and improved hemoglobin A1c (HbA1c) and glucose profile; but also decreased circulating levels of inflammatory markers including high-sensitivity C-reactive protein (hs-CRP) and monocyte chemoattractant protein-1 (MCP-1) (80). Furthermore, the level of oxidative stress marker 8-*iso* -prostaglandin F2a (PGF2α), was also reduced following exenatide treatment (80). The protein and mRNA levels of a battery of pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-α), IL-1β and IL-6 in peripheral blood mono-nuclear cells (PBMC or MNC) were also shown to be suppressed by exenatide treatmentin subjects with T2D (81, 82). Moreover, both investigations observed the anti-inflammatory effect of exenatide in the absence of body weight loss in patients with T2D with 12-week exenatide treatment (81, 82). Thus, the anti-inflammatory effect of exenatide may not always be secondary to its body weight lowering effect (81-83). The anti-inflammatory effect of liraglutide was also demonstrated very recently by Zobel and colleagues in subjects with T2D (84). In this clinical trial, subjects with T2D were on 26-week liraglutide treatment. Zobel and colleagues observed discrete modulatory effect of liraglutide on the expression of inflammatory genes in PBMCs. Importantly, such modulatory effect was not observed in the *in vitro* settings with direct liraglutide treatment in the human monocytic cell line THP-1 (84). Furthermore, Zobel and colleagues reported that GLP-1R expression cannot be detected in the THP-1 cell line or in PMBCs (84).

The anti-inflammatory effect of GLP-1 based diabetes drugs was also investigated in various animal models. Although GLP-1 based diabetes drugs showed no improvement in patients with type 1 diabetes (T1D), Sherry and colleagues demonstrated that exenatide could facilitate the reversal of T1D in NOD mice treated with the "therapeutic" anti-CD3 monoclonal antibody (85). Mechanistically, the facilitation is likely involving the increase of anti-inflammatory subsets of T lymphocytes, such as T helper 2 (Th2) and regulatory T cells (Tregs) in mice (85-87). More recent studies have further demonstrated the T lymphocyte regulatory function of liraglutide and dulaglutide, as well as the DPP-4i sitagliptin (88-90). The DPP-4i linagliptin was also shown to attenuate obesity-related insulin resistance and inflammation by modulating M1/M2 macrophage polarization, reported by Zhuge and colleagues (91). In a Wistar rat model with intraperitoneal (*i.p* .) LPS challenge, exenatide treatment was shown to attenuate neutropenia, associated with decreased levels of a battery of pro-inflammatory cytokines, including IL-1α, IL-1β, IL-6, TNFα, and IFNγ (92). Utilizing the pro-adipocytic 3T3-L1 and RAW264.7 macrophage cellular models, several studies have shown that the DPP-4i anagliptin or liraglutide can inhibit nuclear factor-kappa B (NF-ϰB) pathway and secretion of a battery of pro-inflammatory cytokines (93-95). Although a few studies have indicated the expression of GLP-1R in rodent immune cells (87, 90), as mentioned above, a more recent human study by Zobel and colleagues showed that the repressive effect of liraglutide on expression of inflammatory genes in PBMCs was not observed in the*in vitro* settings with direct liraglutide treatment (84). In addition, Zobel and colleagues cannot detect GLP-1R in the THP-1 cell line or in primary MNCs (84). Figure 2 summarizes our current knowledge on the anti-inflammatory features of GLP-1 based diabetes drugs. It remains to be determined whether those anti-inflammatory and immune cell modulatory effects of GLP-1RAs are mediated directly by GLP-1R that are expressed in majority of immune cells, or by a small portion of immune cells, or by yet to be further explored mechanism.

GLP-1 based drugs in lung injury studies

During the past decade, there are substantial controversies in literature regarding GLP-1R expression in a few extra-pancreatic organs, including that in the liver, adipose tissues and immune cells (9, 96-98). Nevertheless, *in vivo* effects of GLP-1 based drugs in the liver and other extra-pancreatic organs are clear and substantial (96-101). The controversies could be partially due to the lack of reliable anti-GLP-1R antibodies (96, 97). It remains to be determined whether those extra-pancreatic functions of GLP-1 and its based drugs are

mediated by certain brain-peripheral tissue axis or by a small portion of GLP-1R-producing cells scattered within each of those organs. However, we have learned for more than 25 years that lung is an extra-pancreatic organ, which exhibits the highest GLP-1R expression (102, 103). Hence, great efforts have been made in clinical trials and in various lung injury models, seeking for the possibility to repurpose GLP-1-based drugs in chronic and acute lung injury treatment. Here we will present our literature review on clinical investigations as well as studies with chronic lung injury and acute lung injury animal models. We will then summarize a few more recent studies on "therapeutic effect" of combined use of human mesenchymal stem cells (hMSCs) and GLP-1 based drugs in mouse acute lung injury models.

V.I. Studies in chronic obstructive lung diseases and chronic lung inflammation

Chronic obstructive lung diseases mainly include asthma and chronic obstructive pulmonary disease (COPD). In a study of meta-analysis, Wei and colleagues have reported that the utilization of GLP-1-based drugs showed reduced trends in the risks of nine categories of respiratory diseases, including pneumonia, asthma, and COPD. However, GLP-1 based drug utilizations were shown to increase trends in interstitial lung disease (104). In a recent retrospective cohort study, Foer and colleagues compared rates of asthma exacerbations and symptoms between patients with T2D and asthma prescribed GLP-1RAs and those prescribed sodium-glucose cotransporter-2 (SGLT-2) inhibitors, or DPP-4 inhibitors, or sulfonylureas, or basal insulin. They observed that patients prescribed GLP-1RAs had lower counts of asthma exacerbation and encounters for asthma symptoms after 6 months of the treatment (105). In another human study, Mitchell and colleagues reported that GLP-1R is expressed in both human eosinophils and neutrophils but the numbers were reduced in allergic asthmatics (106). Their *ex vivo* study showed GLP-1 analog decreased the expression of eosinophil-surface activation markers, as well as IL-4, IL-8 and IL-13 produced by eosinophils (106).

IL-33, a member of the IL-1 family, is constitutively produced in fibroblasts, endothelial cells, and epithelial cells of skin, lung, and gastrointestinal tract (107). It is among crucial mediators of both innate and adaptive immune responses induced by aeroallergens. Genome-wide association studies (GWAS) have revealed the implication of*IL33* locus in the development of asthma (108, 109). To date, there is no known therapeutical agent that can inhibit the release of IL-33 from airway cells (110). When *Alternaria* extract, an aeroallergen with protease activity, is intranasally administrated in mice, acute asthma can be induced. In this mouse model, Toki and colleagues assessed both "preventative" and "therapeutic" effects of liraglutide. Either administrated before or after *Alternaria*extract challenge, liraglutide suppressed IL-33 secretion, associated with decreased numbers of group 2 innate lymphoid cells (ILC2s), reduced mucus production, and airway responsiveness (110). However, further mechanistic explorations are needed for clarifying the involvement of GLP-1R and the downstream signaling events. In another chronic asthma mouse model challenged with ovalbumin for 81 days, *i.p* . injection of liraglutide at 2mg/kg twice daily in the last 66 days inhibited airway inflammation and mucus hyper-secretion through a protein kinase A (PKA)-dependent signaling pathway (111).

COPD is among the top leading cause of death worldwide. Up to date, here is no approved therapy that is able to reverse lung injury caused by COPD. Huang and colleagues have reported that expression of GLP-1R in PBMC isolated from COPD patients is lower than that in non-COPD subjects (112). E*x vivo* liraglutide treatment, however, upregulated GLP-1R expression and restored antigen-stimulated interferon γ (IFN-γ) production in T lymphocytes (112). Considering the intensive literature controversy on GLP-1R expression in extra-pancreatic organs, further investigations are needed for clarifying GLP-1R expression in immune cells with newly developed GLP-1R antibodies and other tools such as RNAseq (96, 100, 101, 113, 114). There is an on-going clinical trial operated by Hospital South-West Jutland, University of Southern Denmark on assessing effects of liraglutide treatment in patients with COPD. This prospective, randomized, placebo-controlled, double-blinded, parallel group two-center clinical trial, headed by Dr. Claus B Juhl, will determine various pharmacological effects and functional outcomes of 4-, 20-, 40- and 44- week liraglutide treatment in 40 patients with COPD.

Pulmonary surfactant is a surface-active complex of proteins and phospholipids formed by type II alveolar cells, which plays important roles in regulating alveolar size and lung innate immunity, as well as in preventing

fluid accumulation and maintaining dryness of the airway. In human type II pneumocytes isolated from cadaveric organ donors, Vara and colleagues found that native GLP-1 or exenatide could stimulate cAMP formation and phosphatidylcholine secretion; and such effects were shown to be reversed by the GLP-1R antagonist exendin (9–39) (115). Early investigations have generated ovalbumin and long-term LPS induced rodent COPD models (116, 117). Combining these two models, Viby and colleagues have assessed the effect of liraglutide on improving lung functions in a female COPD mouse model (118). They found that mice treated with liraglutide or exenatide showed much better clinical appearance and increased survival rate. They also observed reduced expression of surfactant proteins in their COPD female mouse model, associated with increased expression of pro-inflammatory cytokines. However, levels of surfactants and pro-inflammatory cytokines in the lung were largely unaffected with liraglutide treatment in female COPD mouse model (118). One may speculate that long-term ($>$ 10 days) liraglutide administration may exert more profound "metabolic" beneficial effects in addition to its anti-inflammatory effect observed in the acute injury model. Nevertheless, the stimulatory effect on surfactant secretion was not observed in this *in vivo* model, in contrast with the *in vitro* assay with human type II pneumocytes isolated from cadaveric organ donors (115). Thus, mechanisms underlying the improvement effect of liraglutide treatment in COPD is complicated, involving not only surfactants and pro-inflammatory cytokines, but also other yet to be identified components.

As mentioned above, Kim and colleagues have located mouse GLP-1R expression in mouse cardiac atria and shown that GLP-1R activation increased cardiac atria ANP secretion, leading to the reduction of blood pressure (79). As an atrial natriuretic peptide hormone, ANP is also recognized as a potent pulmonary vasodilator (119). Although ANP is mainly produced in the heart, pulmonary ANP expression was reported, at least in rodent species at its mRNA level (120). Utilizing the mouse COPD model, Balk-Moller and colleagues have assessed lung function of GLP-1-based drugs. Although mouse lung functions did not differ between mice receiving PBS and exendin (9-39) (a GLP-1R antagonist) treatment, or between GLP-1R knockout mice and their wild-type littermates, COPD mice receiving GLP-1-based drugs (liraglutide or exenatide) showed improved pulmonary functions, with less inflammation and 10-fold more ANP at the mRNA level. In isolated mouse bronchial sections, direct ANP treatment showed a moderate broncho-dilatory effect, while such effect was also observed, although less effective, with direct liraglutide treatment. Based on this finding, the authors suggested a link between GLP-1 and ANP in COPD. Balk-Moller and colleagues, however, did not assess pulmonary ANP production at peptide hormone level. Hence, it remains to be determined whether observed beneficial effect of liraglutide treatment is generated by ANP produced in cardiac atria only, or with the contribution of pulmonary produced ANP (120).

Nosocomial infections especially that in the lung is a critical complication world widely. Lung chronic infections can be generated by respiratory pathogens including the most notorious pathogen*Pseudomonas aeruginosa (P. aeruginosa)* . *P. aeruginosa* and its virulence factor, known as pyocyanin, was shown to attenuate expression of forkhead box A2 (FOXA2), a key transcription factor of a battery of genes that are involved in mucus homeostasis (121). Choi and colleagues have shown that FOXA2 expression was severely depleted in surface airway epithelial cells in patients with COPD, while exenatide treatment can restore FOXA2 expression in *P. aeruginosa*challenged mouse model (122).

V.II. Studies in acute lung injury

Acute lung injury (ALI) may lead to the development of acute respiratory distress syndrome (ARDS) which is the major cause of respiratory failure in ICU. To our knowledge, GLP-1-based drugs have not been utilized in clinical trials for ALI. Nevertheless, as mentioned above, a very recent retrospective study has shown that the utilization of GLP-1 based drugs reduced trends in the risks of pneumonia, in addition to asthma and COPD (104). Intensive investigations have, however, been conducted in ALI animal models, mainly with intratracheally LPS administration in mice (123).

In 2011, Lim and colleagues have developed a "nanomedicine" designated as GLP1-SSM, in which human GLP-1 (7-36) is self-associated with PEGylated phospholipid micelles (SSM). They then demonstrated that in LPS induce ALI mouse model, subcutaneous GLP1-SSM administration decreased lung neutrophil influx, myeloperoxidase activity and IL-6 levels in a dose-dependent manner (124). In 2017, GLP-1-SSM was shown

by this team to alleviate gut inflammation in a dextran sodium sulfate induced mouse colitis model (125).

Several recent studies have explored mechanisms underlying the attenuating effect of GLP-1R agonists in ALI animal models. Reduction of pulmonary surfactant is tightly associated with decreased pulmonary compliance and edema in ALI. Thyroid transcription factor-1 (TTF-1) is known to play an important role in regulating levels of surfactant protein-A (SP-A), the most abundant protein component of pulmonary surfactant. Romaní-Pérez and colleagues have reported that in rats, administering of exenatide or liraglutide to the mother from gestational day 14 to the birth increased SP-A and SP-B mRNA levels and the amount of SPs in the amniotic fluid at the end of pregnancy (126). Furthermore, they have reported that lung GLP-1R mRNA level increased 4-fold at the 1st day of life in both male and female rats, while the level of expression was subsequently maintained into the adulthood (126). In 2018, Zhu *et al* found that in the ALI mouse model, LPS administration reduced lung SP-A and TTF-1 levels, while the reduction was reversed by simultaneous administration of liraglutide with LPS challenge (127). In 2019, in a similar mouse model, Xu and colleagues found that LPS challenge induced polymorphonuclear neutrophil (PMN) extravasation, lung injury, along with alveolar-capillary barrier dysfunction. Concomitant liraglutide administration prevented PMN-endothelial adhesion by inhibiting expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (128). Other documented functions of GLP-1-based drugs in ALI models include the stimulation of eNOS/sGC/PKG signalling cascade, the induction of vasorelaxant expression, and the inactivation of the NF-ϰB inflammatory signalling (129-131). However, none of these investigations have directly assessed the involvement of pulmonary GLP-1R.

In 2020, our team has directly assessed the involvement of GLP-1R in mediating effect of liraglutide treatment in LPS-induced ALI mouse model. In this study, conducted by Zhou and colleagues, liraglutide was not administrated simultaneously with LPS challenge, but as a "preventative agent" which was subcutaneously administrated 2 hours before intratracheal LPS delivery (103). In such experimental settings, we observed that liraglutide pre-treatment significantly reduced LPS-induced acute lung injury, including the reduction on lung injury score, wet/dry lung weight ratio, immune cell counts, protein concentration in bronchoalveolar lavage fluid (BALF), and cell apoptosis in the lung. Those effects were highly associated with reduced pulmonary mRNA expression of genes that encode inflammatory chemokines and cytokines. Importantly, none of those "preventative" effects were observed in GLP-1R knockout (KO) mice, highlighting the essential role of lung GLP-1R in mediating the effect of liraglutide in preventing lung injury (103). Based on such "preventative" effect observed, we suggested that retrospective studies should be conducted in T2D subjects received with or without GLP-1 based drugs, asking whether T2D patients are less vulnerable to ALI as well as chronic lung inflammatory injury after receiving GLP-1 based drug treatment (103, 132, 133).

The study conducted by Zhou and colleagues has also revealed that liraglutide treatment attenuated LPS induced pulmonary thioredoxin-interacting protein (TxNIP) over-expression, and such attenuation is also GLP-1R dependent (103). TxNIP is a member of the NLR family pyrin domain containing 3 (NLRP3) inflammasome component (134-136), a mediator of glucotoxicity (137, 138), and a therapeutic target of T2D and other disorder (135, 138-141). In addition to high glucose challenge, TxNIP level in pancreatic β-cells was also shown to be stimulated by dexamethasone and streptozotocin (STZ), an antibiotic utilized in generating the T1D rodent model. Importantly, LPS challenge caused approximately 2.5-fold elevation in lung TxNIP levels in wild type littermates, while in GLP-1R KO mice, lung TxNIP increased about 7-fold after the challenge with the same amount of LPS. Thus, lung GLP-1R itself may represent a native defensing system. In contrast to the observation made by Balk-Moller and colleagues in their COPD model, we did not see a stimulatory effect of liraglutide treatment on pulmonary *nppa* (which encodes ANP) expression (120). However, we observed that LPS challenge led to a 3-fold activation on pulmonary *nppa* level. Whether such activation represents a protective or defensive response remains to be further explored (103). Figure 3 summarizes our current understanding on pulmonary GLP-1R mediated protection in ALI mouse model, in response to GLP-1R agonist treatment, involving the attenuation of the inflammasome component TxNIP.

V.III. Combined effect of MSC and GLP-1 based drugs

Multipotent mesenchymal stem cell (MSC) based therapy may apply to lung injuries including ALI and

radiation-induced lung injury, as well as other disorders (142-147). More than 18 years ago, Ortiz and colleagues have demonstrated that when male mouse bone marrow derived MSCs were intravenously administrated, they were able to home to the recipient female mouse lung in response to bleomycin-induced injury (148). Those MSCs were shown to adopt an epithelium-like phenotype, reducing both inflammation and collagen deposition (148). Mechanistic exploration studies have then demonstrated that those MSCs can produce paracrine factors, such as IL-1 receptor antagonist (IL-1RA), IL-10, keratinocyte growth factor (KGF), and prostaglandin E2 (146, 149). In LPS challenge induced ALI mouse model, Mei and colleagues demonstrated that bone-marrow derived MSCs with overexpressed angiopoietin 1 (Agn-1) further reduced the severity of lung injury (150). Gupta and colleagues then demonstrated that in LPS-induced ALI mouse model, intrapulmonary delivery of bone marrow-derived MSCs four hours after LPS-challenge was still able to improve survival and attenuate lung injury (151). During the last decade, functions of MSCs from various sources including bone marrow, adipose tissue, lung tissue, as well as human chorionic villi were also assessed in multiple disease models. For studies on additional paracrine factors released by MSCs and mechanistic exploration on MSC therapy in lung injuries, please see review articles elsewhere (152-155). In below we will only discuss recent studies that involve GLP-1 and GLP-1R.

In 2010, Sanz and colleagues reported the detection of GLP-1R in hMSC, derived from bone marrow. They found that in hMSC, GLP-1 treatment stimulated cell proliferation and reduced cell apoptosis. Furthermore, GLP-1 treatment prevented cell differentiation into adipocytes, associated with the repression of peroxisome proliferator-activated receptor-γ (PPARγ), C/EBPβ, and lipoprotein lipase (LPL) (156). A few studies then tested the effect of combined use of MSC and GLP-1 in myocardial infarction (157-159). MSC with GLP-1 conditioned media were shown to possess antiapoptotic effects on ischaemic human cardiomyocytes (159). MSCs that engineered to secrete a GLP-1 fusion protein were shown to possess therapeutic effects in myocardial infarction in a pig model (157, 159).

More recently, attempts have also been made in testing combined use of hMSC and liraglutide in ALI mouse model (160, 161). Last year, Yang and colleagues reported that LPS treatment could attenuate proliferation of human chorionic villus-derived MSCs (hCMSCs), human bone marrow-derived MSCs (hBMSCs), and human adipose-derived MSCs (hAMSCs). In LPS-induced ALI mouse model, liraglutide combined with MSCs showed a more significant therapeutic effect (160). Dose dependent reduction effect of LPS on hCMSC proliferation and expression of GLP-1R, Ang-1 and FGF-10 were then demonstrated in another study conducted by the same group by Fang and colleagues (161). Furthermore, the study by Fang and colleagues demonstrated that liraglutide treatment dampened the above reductions, involving the cAMP/PKAc/β-catenin-TCF4 signaling pathway. The same study also reported that combined use of liraglutide and hCMSCs exhibited enhanced therapeutic efficacy than liraglutide alone in reducing lung injury in their mouse ALI model (161).

Conclusion and perspectives

Shortly after the clinical utilization of GLP-1-based drugs in patients with T2D, the anti-inflammatory features of them were immediately observed. As chronic inflammation contributes to the pathobiology and etiology of T2D, these observations have further expanded our mechanistic understanding on the therapeutic functions of GLP-1R agonists. Importantly, these observations have triggered intensive exploration of anti-inflammatory features of GLP-1 based drugs in general and in translational investigations, aiming to repurpose them for other inflammation related disorders.

In this review, we have discussed both clinical and pre-clinical investigations on the anti-inflammatory and immune cell modulatory features of GLP-1R agonists. Importantly, we commented on the controversy regarding direct *in vitro* effect of GLP-1R agonist treatment in immune cells. We have discussed that the *in vivo*repressive effect of liraglutide treatment on expression of inflammatory genes in PBMCs were not recaptured in the *in vitro* settings with direct liraglutide treatment in THP-1 and primary PBMCs by Zobel and colleagues, and they cannot detect GLP-1R in those immune cells (84). Thus, it remains to be determined whether GLP-1 based drugs exert their anti-inflammatory and immune modulatory functions via indirect mechanisms. This could involve a brain-peripheral tissue axis, or via interacting with a small specific portion of immune cells that do express GLP-1R. Indeed, a study by Yusta and colleagues in 2015 showed

that GLP-1R expression is enriched in intestinal intraepithelial lymphocytes (IEL) (162). In mouse adipose tissues, GLP-1R expression is known to be enriched in stromal vascular fraction (SVF) (97). Very recently, McLean and colleagues have located GLP-1R expression in the liver in a small portion of T lymphocytes (γδ cells). They reported that metabolic and anti-inflammatory effect of semaglutide treatment observed in wild type mice were absent or attenuated in *Glp1rTie2*$^{-/-}$ mice (163). Hence Tie2-targeted GLP-1R+ cells are required for a subset of the anti-inflammatory actions of semaglutide in the liver, and possibly elsewhere (163). It appears that the regulatory effect of liraglutide treatment on blood pressure is also mediated by a small portion of GLP-1R expressing cells in mouse cardiac atria, followed by sending signal to produce ANP (79).

GLP-1R is most abundantly expressed in mouse lung, demonstrated 25 years ago by Bullock and colleague, with the classical methods including RNAse protection, RT-PCR, and *in situ* hybridization (102). This investigation has also denied GLP-1R expression in adipose, liver, and skeletal muscle (102). As lung GLP-1R level elevated 4 times on the first day of birth, and elevated plasma GLP-1 level was observed in patients with systematic inflammation such as severe burn injury, it is likely that GLP-1 and lung GLP-1R represent a yet to be further explored defense system of our body. Observations made in a few clinical trials and retrospective studies have supported the beneficial effect of GLP-1 based drugs in asthma and lung injury. Detailed understanding of this defense system and properly utilizing the tools in regulating this system may allow us to treat both chronic and acute lung injuries.

The key inflammasome component TxNIP, a known therapeutic target of diabetes, is also among the major targets of GLP-1/GLP-1R signaling pathway activation in the lung. Lung TxNIP elevation can be stimulated by plasma glucose level elevation or the release of the stress hormone glucocorticoid (103), which is a recognized double-edged sword in ARDS treatment. Whether a moderate stimulation on lung TxNIP elevation in response to glucose and glucocorticoid elevation also represents a defensive response remains to be investigated. It is also worth to determine whether TxNIP knockout brings beneficial or deleterious outcome in mice with LPS or other inflammatory challenges.

Both nanomedicine and hMSC-based cell therapy are the cutting-edge skills in translational medicine. GLP-1-SSM, a putative nanomedicine tool has already been tested in ALI model and in bowl inflammation model, while combined hMSC and GLP-1 based drugs have been studied in a pig myocardial infarction model; and more recently, in the mouse ALI model. We anticipate seeing further development of the application of these two "therapies" in preclinical studies and in clinical trials in the near future.

The whole world has bene undergoing the astonishing Covid-19 pandemic. There are literatures debating on whether GLP-1-based drugs may serve as a cure or adjuvant for Covid-19 treatment (132, 133, 164, 165). A recent meta-analysis conducted by Hariyanto and colleagues covered nine studies with 19,660 patients of T2D who were infected by SARS-CoV-2 (166). The study suggested that pre-admission of GLP-1-based drugs was associated with reduced mortality rate (166). Further retrospective studies and pre-clinical studies should be conducted to determine the therapeutic and preventative potential of GLP-1R agonists on Covid-19 animal models, as our battle with such pandemic is likely a long journey.

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Disclosure

There is no conflict interest to disclose.

Figure legend

Figure 1. GLP-1 and GLP-1 based drugs. (A) The structure of proglucagon and proglucagon-derived

polypeptides (PGDPs). GRPP, glicentin-related pancreatic polypeptide. IP-1 and IP-2, intervening peptides 1 and 2; MPGF, major proglucagon fragment. GLP-1 and GLP-2, glucagon-like peptide 1 and 2. (B) The primary amino acid sequences of human GLP-$1_{7\text{-}37}$. GLP-$1_{7\text{-}37}$and GLP-$1_{7\text{-}36\text{amide}}$ (not shown) are functional active hormones. The ubiquitously expressed peptidase DPP-4 will cleave X-alanine dipeptides from the N-terminus of GLP-$1_{7\text{-}37}$ or GLP-$1_{7\text{-}36\text{amide}}$ to form GLP-$1_{9\text{-}37}$ or GLP-$1_{9\text{-}36\text{amide}}$, respectively. (C) Chemical structures of the six GLP-1R agonists (GLP-1RAs). Due to amino acid substitution or non-covalent binding to albumin or immunoglobulin, these GLP-1RAs are protected from DPP-4 mediated degradation, thus having a much longer half-life.

Figure 2. Illustration of intra-pancreatic and extra-pancreatic functions of GLP-1RAs. In pancreatic islets, GLP-1 stimulates insulin secretion and represses glucagon secretion by pancreatic β- and α-cells, respectively, events that are mediated by GLP-1R. GLP-1RAs were shown to exert their regulatory functions in both macrophages and T lymphocytes in human subjects and in animal models. It remains controversial whether GLP-1R is expressed in majority of immune cells. GLP-1RAs were shown to inhibit the differentiation of M1 macrophage and the production of its markers, such as CCR7, IL-6 and TNF-α. Conversely, the differentiation of M2 macrophage and the production of its markers, such as CD163, Arg-1 and IL-10 could be stimulated by GLP-1RA treatment. Meanwhile, GLP-1RAs were shown to inhibit the differentiation of pro-inflammatory T helper cells, including Th1 and Th17, leading to less pro-inflammatory cytokines, such as IFN-γ, TNF-α, IL-17 and IL-22. The differentiation of the anti-inflammatory Th2 and Treg, as well as the production of IL-4, IL-5, TGFβ and IL-10, however, could be promoted by GLP-1RA treatment.

Figure 3. The effect of GLP-1-based drugs on lung injury.GLP-1R is highly expressed in lung epithelia. Intratracheal LPS delivery induces overexpression of thioredoxin-interacting protein (TxNIP), a member of the NLRP3 inflammasome through Toll-like Receptor (TLR). This is followed by activation of Caspase 1 and production of active IL-1β, which initiates the apoptosis of alveolar epithelial cells and adhesion of immune cells (including monocyte-macrophages and neutrophils) to the capillary. Interaction between GLP-1RA and lung GLP-1R lead to elevated intracellular cAMP level and activation of PKA, which inhibits the expression of TxNIP. Meanwhile, GLP-1 based drugs have potent immuno-regulatory functions on reducing pro-inflammatory cytokines and increasing anti-inflammatory cytokines produced by immune cells in both the lung and in the circulation.

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Table 1. FDA approved GLP-1 receptor agonists (GLP-1RA) and DPP-4 inhibitors (DPP-4i)

Brand Name	Active Ingredient(s)	FDA-Approved Year
GLP-1RA		
Byetta	Exenatide	2005
Bydureon	Exenatide (extended release)	2012
Victoza	Liraglutide	2010
Saxenda	Liraglutide	2014
Xultophy 100/3.6	Liraglutide and insulin degludec	2016
Tanzeum	Albiglutide	2014
Trulicity	Dulaglutide	2014
Adlyxin	Lixisenatide	2016
Soliqua 100/33	Lixisenatide and insulin glargine	2016
Ozempic	Semaglutide	2017
Rybelsus	Semaglutide (oral)	2019
DPP-4i		
Januvia	Sitagliptin	2006
Janumet	Sitagliptin and metformin	2007
Janumet XR	Sitagliptin and metformin (extended release)	2012
Steglujan	Sitagliptin and ertugliflozin	2017
Onglyza	Saxagliptin	2009
Kombiglyze XR	Saxagliptin and metformin (extended release)	2010
Qtern	Saxagliptin and dapagliflozin	2017
Qternmet XR	Saxagliptin, dapagliflozin and metformin (extended release)	2019
Tradjenta	Linagliptin	2011
Jentadueto	Linagliptin and metformin	2012
Jentadueto XR	Linagliptin and metformin (extended release)	2016
Glyxambi	Linagliptin and empagliflozin	2015
Tradjenta XR	Linagliptin, empagliflozin and metformin	2020
Nesina	Alogliptin	2013
Kazano	Alogliptin and metformin	2013
Oseni	Alogliptin and pioglitazone	2013

Figure 1

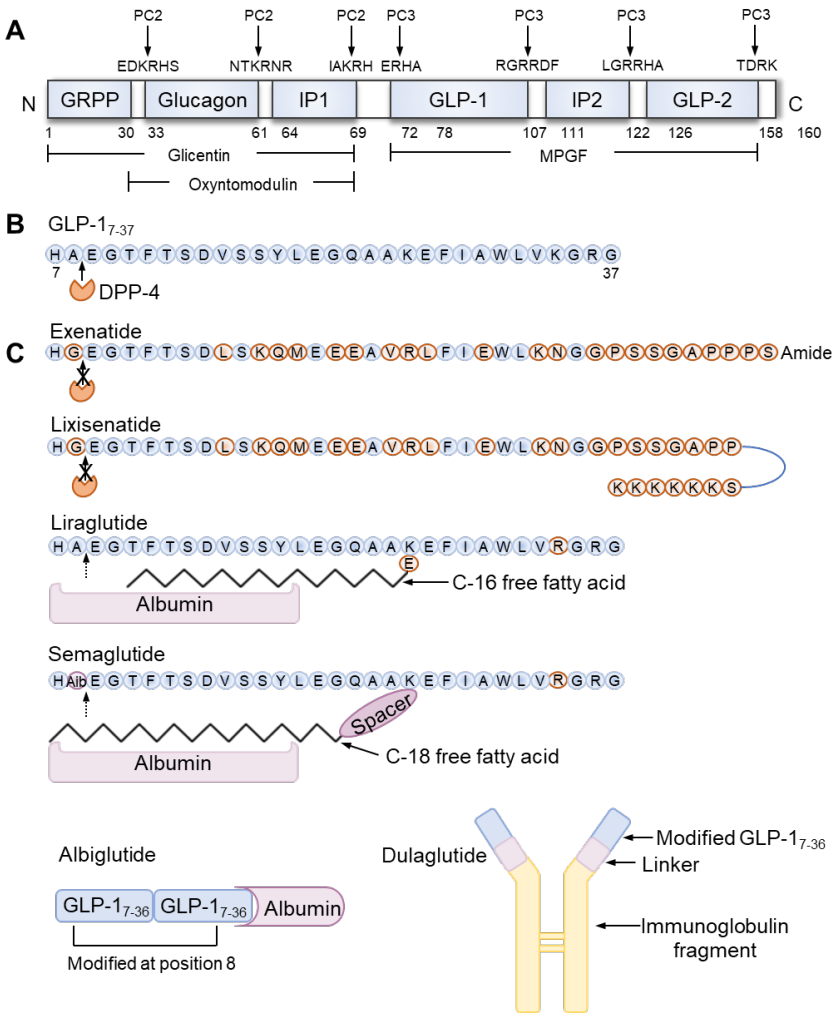

Figure 2

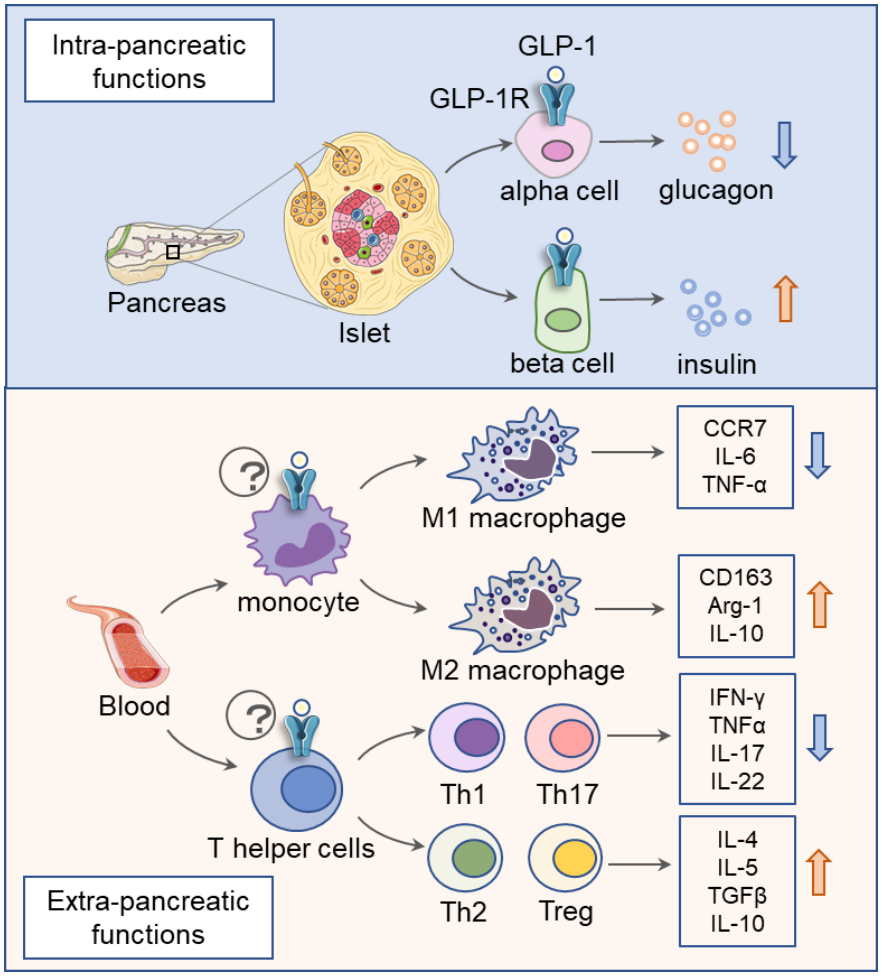

Figure 3