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A complex auxiliary: IL-17/Th17 signaling during type 1 diabetes progression

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ABSTRACT

Type 1 diabetes (T1D) is an autoimmune disease centered around the loss of the beta cells of the islets of Langerhans, and consequent inability of the islets to produce the insulin necessary to maintain glycemic control. While most therapeutic approaches have been centered on insulin replacement, newer approaches to target the underlying immune response have become an area of focus. However, the immune landscape in T1D is extremely complex, and the roles played by individual cytokines during disease progression are incompletely understood, making the development of immunotherapies very difficult. In this review, we discuss the complex auxiliary role played by IL-17, both around the islet and in peripheral tissues such as the gut and kidney, which might influence T1D progression. Through our re-analysis of the key factors involved IL-17 signaling in recently published single-cell sequencing and sorted-cell bulk sequencing datasets, we find supporting evidence for the general existence of the signaling apparatus in islet endocrine cells. We also explore the emerging evidence of IL-17 serving as an influential factor in diabetic complications that affect distal tissues. While anti-IL-17 therapies are emerging as an option for psoriasis and other autoimmune disorders, we highlight here a number of questions that would need to be addressed before their potential applicability to treating T1D can be fully evaluated.

1. Introduction

Type 1 diabetes (T1D) is an autoimmune disease centered around the loss of the beta cells of the islets of Langerhans, and consequent inability of the islets to produce the insulin necessary to maintain glycemic control. Most commonly diagnosed in juvenile patients, the incidence of T1D has been rising worldwide for reasons that are unclear. Although T1D has long been understood to be a chronic and progressive autoimmune disease as a result of histological findings of T cell infiltration into the islets, the nature of immune interactions at the onset and during disease progression are incompletely understood, with a number of recent reviews suggesting that there is in fact a prolonged persistence of beta cell mass in some patients (Wilcox et al., 2016; Lam et al., 2017). Instead, most of the treatment methods thus far have focused on insulin replacement and/or beta cell regeneration through regular insulin administration, islet transplant with protective carriers, and other more exploratory compounds (Lacy et al., 1990; Soon-Shiong et al., 1994; Wang et al., 2015). While these strategies are effective for regaining glycemic control, they typically require substantial lifestyle modifications and must be continuously administered, as they likely allow for immune-driven islet destruction to continue to progress.

In recognition of this problem, a number of more recent efforts have been made to also focus on the immune component of T1D in the hopes of being able to restrict the islet destruction from happening and to allow for effective islet regeneration. These include antibody-based concepts targeting CD3, interleukin-1, and thymocyte globulin, as well as cell-based transfers of cultured regulatory T cells and myeloid-derived suppressor cells (Orban et al., 2011; Moran et al., 2013; Gitelman et al., 2013; Haller et al., 2015; Bluestone et al., 2015; Yin et al., 2010). Other attempts have been made to specifically target autoantibody positive T cells through vaccination-like approaches. Although a number of these approaches have been screened in early clinical trials and have shown promise, broader application of these therapies has remained elusive, with the clinical parameters for which their use might be most effective unclear. This uncertainty is in part due to a lack of understanding regarding the complex cytokine milieu around the islets during disease progression, where any given factor might act in either protective or damaging ways. While three major cytokines (IFNγ, IL-1β, and TNF) are commonly used to mimic cytokine stress experienced by beta cells during in vitro experiments (primarily justified by the fact that mouse overexpression systems with these cytokines seems to induce beta cell death and immune response), how other cytokines

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may behave in conjunction with them remains incompletely known (Green and Flavell, 2000; Mandrup-Poulsen et al., 1985; Campbell et al., 1985). In this review, we focus on the evidence for potential direct involvement of IL-17 in T1D progression through signal transduction within islets, as well as the auxiliary interactions that may facilitate such an involvement. We also gather emerging evidence of more indirect and systemic impacts mediated by IL17 action in other organs that may further accelerate or restrict disease progression and influence diabetic complications. Through exploration of both an islet-centric and more generalist approach, we hope to expand the appreciation for the role a cytokine may play during chronic disease.

2. Islet-intrinsic defects in T1D

Before evaluating the potential for IL-17 effects on the islets, it is useful to consider briefly the stress environment in the islets that may support and respond to cytokine induction. Despite being relatively few in number compared to the exocrine cells in the pancreas, endocrine cells within the islets of Langerhans must act rapidly to tightly regulate glucose levels across the body. As such, each of the major endocrine cell types (alpha, beta, delta) tend to contain large amounts of their signature hormone in both protein and mRNA forms. These hormones can thus be rapidly secreted as protein in response to the appropriate stimuli, with sufficient reserves to allow for continued release. However, excess stress on the protein production and secretion capabilities of the cells over time (whether from intrinsic defects or extrinsic pressure such as metabolic imbalance) may lead to severe ER and general cellular stress. While the body may be able to adaptively respond to some level of stress through some combination of islet cell hypertrophy/proliferation (commonly observed during development in both humans and mice), chronic stress that exceeds the capabilities of the response result which may induce loss of identity and/or cell death (Gregg et al., 2012). It has recently shown that continued expression of a number of transcription factors (such as Foxo1, Nk2.2, Sox5, and Pax6) are essential for maintenance of beta cell function, and that loss of expression may lead to a reversion to a progenitor-like state (Axelsson et al., 2017; Talchai et al., 2012; Rutter, 2017). It has also been shown that while the key cellular sensor mTOR is essential for maintenance of normal beta cell mass and function, hyperactivation of mTOR and its downstream targets, such as S6kinase, ultimately leads to beta cell failure, in part due to the simultaneous reduction of damage-clearing autophagic pathways in the cells that hyperactivate mTOR to compensate (Bartolomé et al., 2014; Elghazi et al., 2010). Reversal of the mTOR hyperactivation by chemical means and/or dietary approaches has been reported to help regenerate beta cells by recovering expression of several transcription factors (Cheng et al., 2017). Combined, these metabolic stresses contribute to beta cell damage independently of any immune response.

At the same time however, there must be another defect on either the beta cell or immune side for T1D to develop, since damaged cells that undergo traditionally regulated apoptosis may be cleared without inflammatory immune cell activation. The most prominent demonstration of this is the Akita mouse, carrying a point mutation in the Ins2 gene that leads to protein misfolding and ER stress-driven beta cell death, which has been commonly used as a diabetic model (Yoshioka et al., 1997; Wang et al., 1999). However, no appreciable insulitis can be detected in the mice, even though Akita males are diabetic by 4 weeks of age and continue to lose beta cell mass over time, and are understood to be immunocompetent. As such, the mice were first reported to be, and remained commonly classified as, a MODY model. It is not clear why the heavy beta cell death that occurs in Akita mice is immunologically silent and tolerated, given reports that ER stress-induced cell death in other tissues has been shown to promote necrotic/necroptotic signals that activate immune cells (Nakagawa et al., 2014). One possibility may be that the cells are dying too quickly for there to be effective presentation of self-antigens. A similar phenotype has been reported in infant patients with Wolcott-Rallison syndrome, featuring mutations in the PERK gene (which may normally help manage ER stress), in which insulitis is not typically observed despite severe beta cell death (Delépine et al., 2000). These observations have also been replicated in mice, where various forms of PERK-/- and Xbp1-/- animals have been demonstrated to be hyperglycemic at maturity with lower beta cell mass, but with no reported insulitis (Gao et al., 2012; Zhang et al., 2006; Lee et al., 2011). Furthermore, it has been suggested in a mouse model that beta cells without any intrinsic defect can still persist without obvious functional defects in a model of alpha cell destruction mediated by immune recruitment and islet inflammation (Skak et al., 2005). While the possibility of rapid and vanishing immune activation in any of these animals cannot be entirely ruled out (especially given a recent report that PERK-/- animals have increased expression of the cytokine receptor IFNΓR1), they are nonetheless illustrative of the insufficiency of beta cell fragility alone in inducing a persistent autoimmune response (Yu et al., 2015).

3. Cytotoxic t cells, class I MHC, and targeted killing

Indeed, based on the current genetic understanding of T1D gleaned from large cohort GWAS and smaller family studies, it is well appreciated that a large portion of the genetic risk for T1D is linked to HLA typing on both class II and class I MHC (Aly et al., 2006; Nejentsev et al., 2007; Varney et al., 2010; Redondo et al., 2008). Under conventional situations, class I MHCs are broadly expressed across almost all nucleated cells in the body, and serve to present proteasome-degraded peptide fragments of intracellular proteins to cell surface, where they may then be surveilled by immune cells. CD8 + T cells can activate upon recognition of a MHC class I presented epitope, while NK cells are understood to ignore cells that express class I (Cruz et al., 2017). While antigen surveillance is essential for adaptive immunity, the expansion of T cell clones that target islet peptides (islet autoantigens) presented through MHC class I can lead to targeted killing of beta cells (Roep and Peakman, 2012). It has been suggested that class I expression in beta cells may increase in many patients with T1D relative to healthy controls, which would support efficient presentation of autoantigens from defective cells (Richardson et al., 2016). As such, one long standing hypothesis has been that beta cells may act to directly recruit autoantigen responsive CD8 + T cells into the islets to perform targeted killing. Consistent with this understanding, studies have demonstrated that high levels of autoantibodies against GAD, IA2, and ZnT8 can be found in circulation near disease onset, together with increased frequencies of CD8 + T cells responsive to the insulin autoantigen (Spanier et al., 2017; Miao et al., 2013; Énée et al., 2012). A more general TCR sequencing exploration study has also reported the occurrence of several public TCRs in a small cohort of T1D patients, which be responsive to autoantigens (Seay et al., 2016). Interestingly however, a recent study has also reported that CD8+ clonotypes responsive to ZnT8 persist at similar frequencies in the circulation regardless of disease status, and only differ in the islet periphery, suggesting that not all autoantigens will behave in the same fashion (Culina et al., 2018). Furthermore, results from a class I APC-bald mice has suggested that while the presentation of antigen from beta cells may be sufficient to promote lymphocyte recruitment to the islets, it remains insufficient to induce diabetes or spark infiltration of immune cells into the islets themselves (de Jersey et al., 2007).

While the overall origin of the islet-reactive cytotoxic T cells in T1D is unclear, it is nonetheless well appreciated that these cells are able to infiltrate into the islets in diabetic patients (who are presumed to have functional APCs) and kill beta cells. The most specific of these mechanisms is mediated through direct cell-cell interactions, with autoantigen-responsive CD8 + T cells binding onto cells displaying autoantigen and inducing their apoptosis/lysis through directed secretion of perforin and granzymes (Thomas et al., 2010). This primary mechanism is supported by auxiliary capabilities like cytokine production

(especially of IFNγ), which may more non-specifically affect peripheral cells, and which is conditioned by the overall cytokine environment (Freeman et al., 2012). These directly cytotoxic functions are also not necessarily restricted to CD8 + T cells; CD4 + T cells may also produce substantial amounts of perforin and granzyme upon activation under certain contexts. These lysis-driven deaths may then induce further inflammation by promoting release of cellular debris as the stimulus for APCs.

While CD8 + T cells have long been known to produce significant levels of IFNγ, recent studies have demonstrated that they may also become polarized to produce significant amounts of IL-17 or IL-4 under pathogenic conditions (Yen et al., 2009). The percentages at which these cells may naturally exist in the islets of T1D patients is unknown. However, a study using peripheral blood reported that in vitro stimulation of CD8+ cells from pediatric T1D patients led to a modest increase in the percentage of IL-17+ cells forming relative to cells from healthy controls, albeit at very low absolute percentages (Marwaha et al., 2010a). From mouse models, it has been observed that defective IL-4 production from CD8 + T cells can occur during disease onset of NOD mice, and that adoptive transfer of CD8+ IL-17 producing cells can also drive diabetes in a RIP-Ova model (Ciric et al., 2009). Collectively, these results have identified a possible role played by IL-17 from CD8+ cells that may be further clarified with future clinical observations and animal work.

4. Helper t cells, class II MHC, and the cytokine environment

It has become increasingly clear that CD4 + T cells also serve as key actors during insulitis. While CD8 + T cells are predominately characterized by their strong and direct cytotoxic function, CD4 + T cells are understood to help facilitate broader immune responses by secreting diverse cytokines to shape local cytokine environments. These can include factors like TNF, GM-CSF, and RANKL, which may promote the maintenance of a range of pro-inflammatory cell types, or inhibitory factors like IL-10 and TGF-β. It is also well appreciated that some of these secreted factors may be able to directly modulate beta cell behavior. For instance, the combination of TNF, IFNγ, and IL1β is commonly used to model cytokine-induced damage to beta cells, and it is clear that the provision of the cytokine mixture alone is sufficient to dysregulate insulin secretion and drive human and mouse beta cell apoptosis (Imai et al., 2016).

As with their CD8+ counterparts, exactly how the reactive CD4 + T cells in the islet periphery were recruited there and subsequently activated is also unclear. It is unknown if residential CD4+ cells exist in the islet, with very few cells being seen in healthy donors, so it is presumed that the infiltrating cells must be recruited from circulation, and then activated for specific clones in the islet periphery. Unlike CD8 + T cells which may respond directly to class I MHC, CD4 + T cells conventionally require activation through class II MHC that are typically understood to be present only on specialized antigen presenting cells. Since the islets are known to contain substantial numbers of resident macrophages under physiological conditions, the conventional theory has been that these macrophages act to phagocytize and process dying/dead beta cells before presenting the antigen to activate T cells during disease (Unanue, 2014). Dendritic cells and B cells may also enter into the islet periphery during disease, and serve as additional APCs to sustain T cell activation. These APCs can be expected to also express a number of additional surface receptors, such as CD86 and CD80, that may further strengthen the activation signal received and enhance the cytokine-production capabilities of T cells. These signals are also complemented by inhibitory proteins, such as CD95l and PDL1, to promote T cell apoptosis as part of a carefully regulated feedback loop. Both increased expression and deletion of these inhibitory receptors in NOD mice have been reported to lead to faster disease onset, highlighting the importance of APCs in regulating islet immune responses (Wang et al., 2005; Yoshida et al., 2008).

Very recently however, it has also been demonstrated in the NOD animal model that beta cells themselves may also express many components of the machinery necessary to present antigens on class II MHC, with this process only being activated during disease (Walter et al., 2003; Zhao et al., 2015). While this effect has thus far been shown on both protein and mRNA levels through several methods, the possibility that these results are due to technical and “biological” doublets (such as the possibility of an APC having engulfed parts of a beta cell) cannot be fully excluded yet. More precise scRNAseq and in vivo imaging interrogation of islets from human T1D patients may be able to clarify the situation. If the class II MHC expression of beta cells can be confirmed to be real and functional, it would suggest that the large amounts of CD4 + T cells observable during insulitis are directly receiving a major part of their activation signal from beta cells, which may then support their prolonged presence around islets.

Regardless of precisely how the CD4 + T cells are activated however, it is abundantly clear from both human and animal data that large amounts of CD4 + T cells can localize around and infiltrate into the islets during T1D. Per the classic paradigm, activated CD4 + T cells can be polarized by cytokines in the environment into a number of different types that express unique cytokines. Three major (and commonly present) cytokine-producing varieties of CD4 + T cells have been described; Th1 cells defined by IFNγ production are generated primarily as a result of IL-12p40, Th2 cells secrete IL-4 in response to IL-4, and Th17 cells produce IL-17 A/F (henceforth IL-17) following signal from TGF-β and IL-6. These effector populations are also complemented by a Foxp3+ population of Tregs, conventionally polarized by TGF-β, which can limit the proliferation and activity of the effector subsets (Zhu et al., 2010). More recent studies have identified a large number of transcription factors and other proteins to be involved in the polarization process for these cells, leading to an appreciation of the significant degree of plasticity between these cell populations. For instance, it is now appreciated from fate mapping studies that Th17 may be able to transdifferentiate into Tregs following chronic inflammation, and Th1 cells have also been suggested to be capable of being converted into Th17 (Gagliani et al., 2015). Since many other reviews have already described the contributions of Th1 and Th2 cells to T1D, we will instead emphasize here the role played by Th17 and IL-17 as has been elucidated from newer work in the field.

5. Th17 and IL-17 in T1D

First reported to be a distinct subtype of CD4 + T cells following treatment with TGFbeta and IL-6, and uncovered in vivo in models of EAE and IBD, Th17 cells have since been demonstrated to be distributed across a number of tissues and be involved in the pathogenesis of multiple autoimmune diseases, including lupus, psoriasis, and asthma (Korn et al., 2009). While Th17 and IL-17 have been suggested to be essential for maintenance of a healthy microbiome in both the skin and gut, dyresgulated increases in IL-17 secretion can also directly contribute to autoimmune disease progression (Stockinger and Omenetti, 2017). This observation has led to the development of a number of therapeutics for targeting IL-17 in autoimmune diseases, and has thus far yielded two FDA-approved anti-IL-17antibodies (ixekizumab and secukinumab) for treating psoriasis, as well as an anti-IL-17 receptor antibody (brodalumab) (Isailovic et al., 2015a; Balato et al., 2017). A plethora of additional small molecule approaches and other antibodies are also in various stages of study to inhibit Th17 cell differentiation and function.

While anti-IL-17 treatments have not been explored clinically for treating T1D thus far, several lines of evidence have suggested that IL-17 may also negatively contribute to disease progression. Early studies in NOD mice and STZ-induced diabetic models have reported significant increases in the percentage of IL-17+ T cells in the islet periphery following disease onset (Li et al., 2014). Deletion of IL-17 in NOD mice has been shown to delay disease onset together with lower

degrees of insulitis for approximately 1 month, although it was insufficient to lower total disease incidence by 40 weeks of age, demonstrating that it is insufficient to stop disease progression (Kuriya et al., 2013). This delaying effect of IL-17 knockdown has also been recapitulated with the use of anti-IL-17 antibody and RORC inhibitor in NOD mice (Emamaullee et al., 2009; Solt et al., 2015). It does not appear that any studies using IL-17 transgenic mice have been performed to ascertain the disease status in the reverse case. On a cellular level, it has been reported that when added in an environment with IFNγ, IL-17 exposure can directly increase levels of beta cell apoptosis in vitro, though provision of IL-17 on its own was largely insufficient for doing so (Honkanen et al., 2010). Even without direct apoptosis however, IL-17 will likely be capable of inducing a NF-kb driven response to influence beta cell homeostasis, similar to signals from other NF-kb activators.

Several clinical studies performed have also suggested that Th17 cells are more highly present in the circulation of children with T1D close to time of diagnosis, and circulating CD4+ memory cells from these patients may also be more prone to differentiation into Th17, albeit at low absolute frequencies (Marwaha et al., 2010b; Baharlou et al., 2016). This increase might be facilitated in part by a predisposition of macrophages in T1D patients to secrete IL-6 and IL-1β (Bradshaw et al., 2009). Since it is understood that significant amounts of immune-driven beta cell death need to occur prior to initial diagnosis, it has often been presumed that the cell types with increased presence at that juncture likely contribute to disease onset. The presence of Th17 markers on a RNA level within the pancreas has also been reported in a single case of a patient who perished 5 days after initial diagnosis, while an ELISPOT study found an increased percentage of IL-17 response following stimulation with a panel of known beta cell autoantigen peptides (Arif et al., 2011). A graphical summary of many of these possible IL-17-linked proinflammatory interactions is included as (Fig. 1).

At the same time however, recent studies have also suggested that a pure population of Th17 cells transferred into NOD/SCID cannot induce hyperglycemia of themselves, but instead require a partial conversion of the population into Th1 cells, and treatment with anti-IL-17 antibody in the context of the adoptive transfer model did not significantly ameliorate disease progression (Bending et al., 2009; Martin-Orozco et al., 2009). It is unknown if such a conversion process also occurs in T1D patients where insulitis has been understood to be less severe, but will likely be an important caveat to take into account. Furthermore, another study using a lentiviral-driven knockdown of IL-17 at the embryonic stage in NOD mice reported no change in disease incidence at maturity, although it is unclear if the whole body and developmental impacts of the depletion might be a confounding factor (Joseph et al., 2012). One potential explanation may be that the animal also lacked IL-17 production in rarer gamma-delta T cells which might be protective against T1D (Han et al., 2010). Additional experiments using inducible and/or conditional knockout animals may help clarify the situation by ruling out impact on distal organs and during early development.

6. Islet endocrine cell expression of IL-17 receptors

As with most other interleukins, IL-17 signaling requires specific binding between the cytokine and a heteromeric receptor complex. While IL-17 is a family of six cytokines, two members, IL-17 A and IL-17 F, seem to be preferentially secreted by Th17 cells and appear to have the greatest relevance to both T1D and autoimmunity in general. IL-17 A and IL-17 F both bind onto a complex of IL-17RA and IL-17RC to initiate a signaling cascade through the ACT1 adaptor through TRAF family members that may then reach common transcription factors of broad impact, such as p38, C/EBP, and/or NF-kB, through diverse mechanisms (Gaffen, 2009). This signaling cascade has been shown to influence the behavior of a number of different immune cell types and has been extensively reviewed elsewhere (Isailovic et al., 2015b). While most of these downstream effects are thought to be pro-inflammatory (even if protective), recent work has also suggested that the signaling might also be turned into an inhibitory circuit within T and B cells by ACT1 to instead restrict STAT3 by outcompeting IL-23R (Zhang et al., 2018a). Whether this inhibitory effect may also exist in other cell types is unknown. Three other receptors, IL17RB, IL17RD, and IL17RE, also exist, but their functions are less clearly understood. IL17RB and IL17RE have both been reported to be capable of independently forming heterodimers with IL17RA to mediate the signaling of IL17E and IL17C, respectively, but the conditions under which these two cytokines may be produced are not well understood. It is also unknown if IL-17 A/F might also be able to signal directly through other receptors at lower affinity, or if other ligands may be able signal through IL-17RA/RC complexes.

However, despite the general appreciation for the importance of IL-17 signaling in autoimmune disease, the distribution of IL-17 receptors across different tissues is not fully understood. Furthermore, the question of whether this signaling apparatus is also intact in human beta cells and/or other cells in the islets has not been carefully addressed, despite there being a significant amount of data published that have explored islet expression profiles As such, we decided to survey a number of these datasets, to offer a cursory examination of the information available on the expression of IL-17 receptors in the pancreas during T1D (Fig. 1).

The first major efforts to clarify changes in the islet transcriptome involved microarray and RNAseq studies of whole islets from human donors with or without manipulation. Examination of several representative datasets demonstrates a substantial expression of the IL-17 signaling components in general, comparable in magnitude to other cytokine receptors of established functional expression, such as IFNΓR1 and TNFRSF1 A (Ling, 2018). Furthermore, expression levels of these components did not appear to change under acute cytokine insult using a cocktail of TNF, IL-1β, and IFNγ, or following hyperglycemic stress when transplanted into mice, suggesting that they may be stably maintained (Fig. 2) (Lopes et al., 2014; Kennedy et al., 2010; Marselli et al., 2010). These results are also consistent with profiling results of purified endocrine populations. A study that identified four subsets of beta cells also did not show significant variance in expression of these IL17 signaling components across the four types (Dorrell et al., 2016). Similarly, two sets of sequencing data that compared expression at different ages also showed some weak expression of these genes without a clear change driven by age (Fig. 3) (Arda et al., 2016; Blodgett et al., 2015). This lack of a difference as a function of development is particularly interesting given reports that stressed islets may feature increased numbers of less-differentiated beta cells which may be less sensitive to cytokine insult (Rui et al., 2017); these results would suggest that human beta cells may still be sensitive to IL-17 from early on. Overall, these bulk and purified transcriptome analysis results seem to confirm that IL-17 signaling may indeed occur directly within islets.

While the amount of data available on T1D islets is much more limited than that of healthy controls, a number of studies have also profiled expression changes that occur during the disease. Expression of IL17 signaling components appears to be largely unaffected by disease status on a whole islet level (Yin, 2018), and sorted alpha cells from T1D islets also did not appear to show appreciable differences (Brissova et al., 2018). Similarly, a case-control study exploring markers of disease progression in children with T1D did not see significant changes in expression of these components among the immune cells in peripheral blood, but did show detectable expression levels, consistent with other reports (Kallionpää et al., 2014). In fact, no obvious separation could be seen in the clustering of this cohort based on the expression of these IL-17-related factors. Collectively, these results indicate that IL-17 signaling can be generally transduced into both endocrine and immune cell types, and that this signaling is not lost during T1D (Fig. 4).

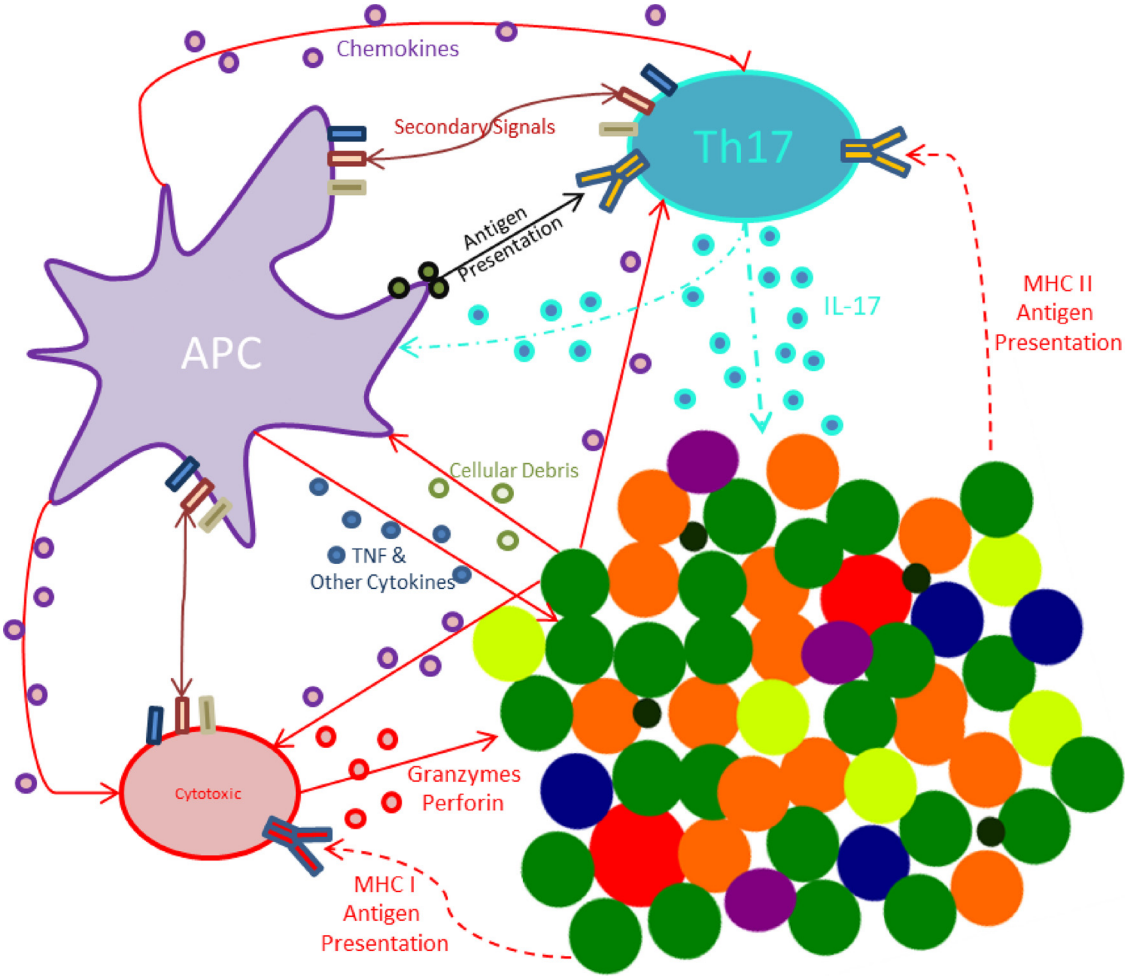

Fig. 1. Pro-inflammatory Interactions in the Islet Environment.
Cartoon showing some of the major pro-inflammatory interactions that may occur in the islet environment, and where Th17/IL17 might fit into the picture. This graphic is not intended to be an exhaustive, and many other interactions, such as degradation of the extracellular matrix around islets, nutrient regulation, and other signaling events are not shown. Potential roles of other immune cells such as neutrophils and natural killers are also not shown, and B cells, macrophages and dendritic cells are considered together here as antigen presenting cells, but each of these cells also possesses unique properties not reviewed her.

7. Insights from single-cell techonologies

With the recent advent of scRNAseq into human islet research, the potential heterogeneity of islet populations is becoming increasingly appreciated, especially as the number of cells sequenced and number of mappable reads continues to increase. Thanks to the sharp improvement in resolution offered by scRNAseq on the behavior of individual cells, novel insights such as the discovery of a substantial increase in somatic mutations in human islets over the course of aging, and of pseudotemporal relationships between markers of ER stress and beta cell function, have been made (Enge et al., 2017; Xin et al., 2018). Similar advances have been made using mouse islets to explore the gene profiles associated with beta and alpha cell development (Qiu et al., 2017; Zeng et al., 2017). Studies have also been conducted to explore the heterogeneity within particular endocrine cell subsets, and efforts have been made to find unique surface markers that might help to better identify subsets for targeted analyses. A number of these markers identified have also been further validated in a single-cell proteomics study conducted using mass cytometry (Wang et al., 2016).

Having already observed noticeable expression of parts of the IL-17 signaling apparatus within the major endocrine cell types in the bulk RNAseq data, we then performed a meta-analysis of scRNAseq data of human islets to try and clarify the distribution profile of these key genes, relying on the Seurat package in R (Butler et al., 2018). We explored the expression profiles of human endocrine cells across 6 datasets that used different protocols for sample preparation and sequencing to limit potential sources of bias. Consistent with the bulk sequencing results, average expression levels of the common adaptors also involved in other signaling pathways (TRAF6, TRAF3IP2, TRADD, and GSK3B) tended to be higher than the expression percentage levels of the five IL-17 receptors (Fig. 5) (Segerstolpe et al., 2016; Muraro et al., 2016; Lawlor et al., 2017; Xin et al., 2016). The relative expression levels of the five receptors to each other also varied significantly, with some sets showing strong expression percentages and absolute values of IL17RA but very little IL17RC, as well as vice versa. However, the sets all showed that IL17RE likely had the lowest expression percentage. These survey results thus seem to agree with the bulk RNAseq data.

After observing these further evidence that IL17R elements are expressed in human endocrine cells, we next looked at the mapping patterns of the IL17R + cells to look for possible selectivity in distribution. Visual inspection of the tSNE plots did not show any apparent clustering of the receptors that very strongly stood out, mainly due to the low percentage at which IL17R elements were detected among the clusters. One of the known weaknesses of single cell technologies is the dropout effect, whereupon weakly expressed genes may be undetected in individual cells, a difficulty for which a number of mathematical approaches have been devised (van Dijk et al., 2018). As such, we then

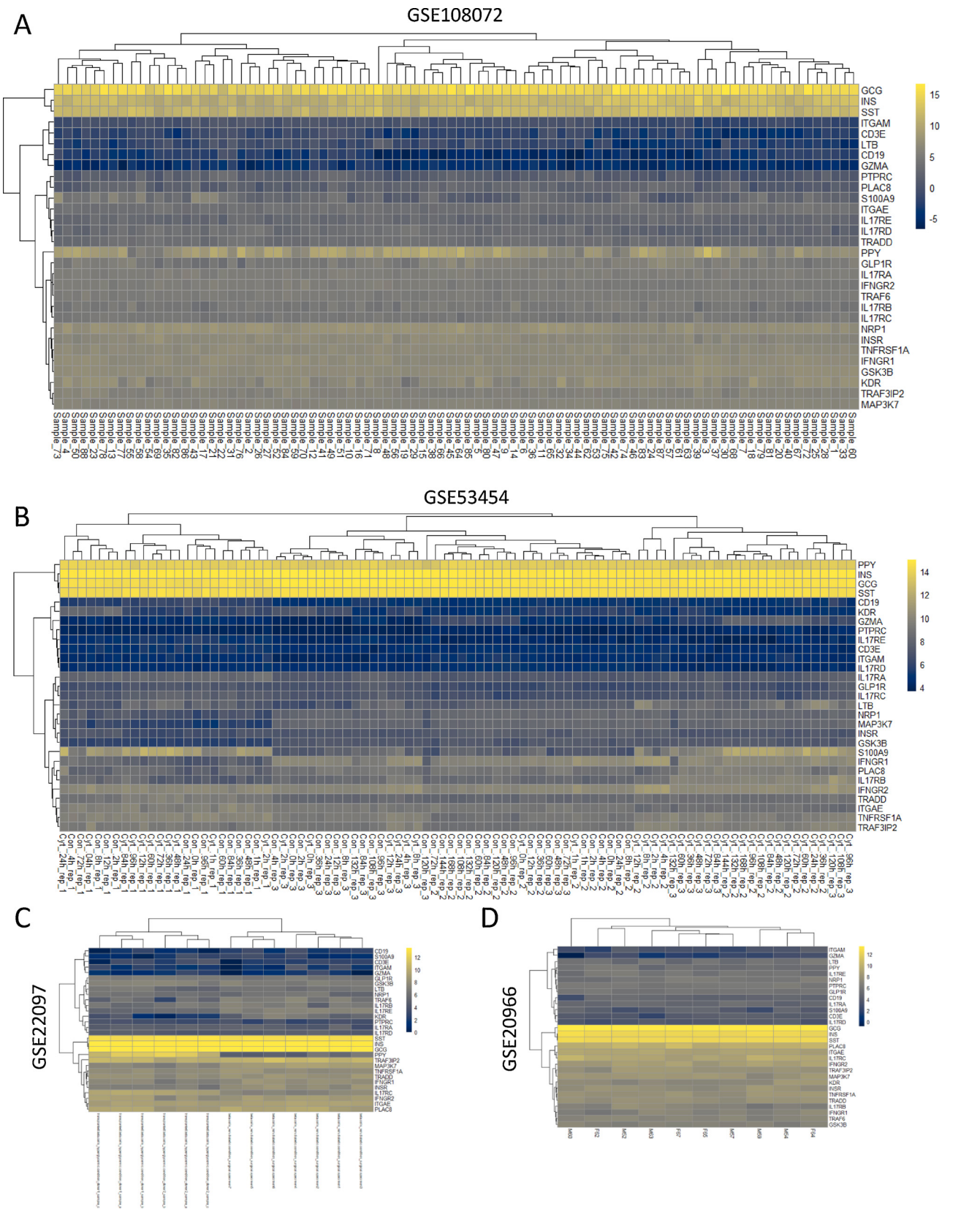

Fig. 2. Whole-islet expression of IL17 signaling elements.

Whole Islet profiling studies show positive expression of IL17 receptors and signaling components. A) A microarray study of 88 human islet samples shows considerable donor-to-donor variability, but expression of the primary components (at least one IL-17 family receptor, as well as the signal transducers TRAF3IP2, TRAF6, GSK3B) could still be generally seen in all subjects. B) A microarray study of human islet samples exposed to cytokine stress over time also shows detectable expression of IL17 receptors, but no clear changes in intensity as a result of stress. C) A microarray study of human islets transplanted into immunodeficient mice under euglycemic and hyperglycemic conditions (per mouse standards) and subsequently recovered also shows no apparent influence of the transplant or host glucose levels on the expression of these genes. D) A microarray study of the transcriptome of beta-cell enriched human islets from several middle-aged to elderly donors shows positive expression of the signaling elements, but no obvious age-dependent alterations.

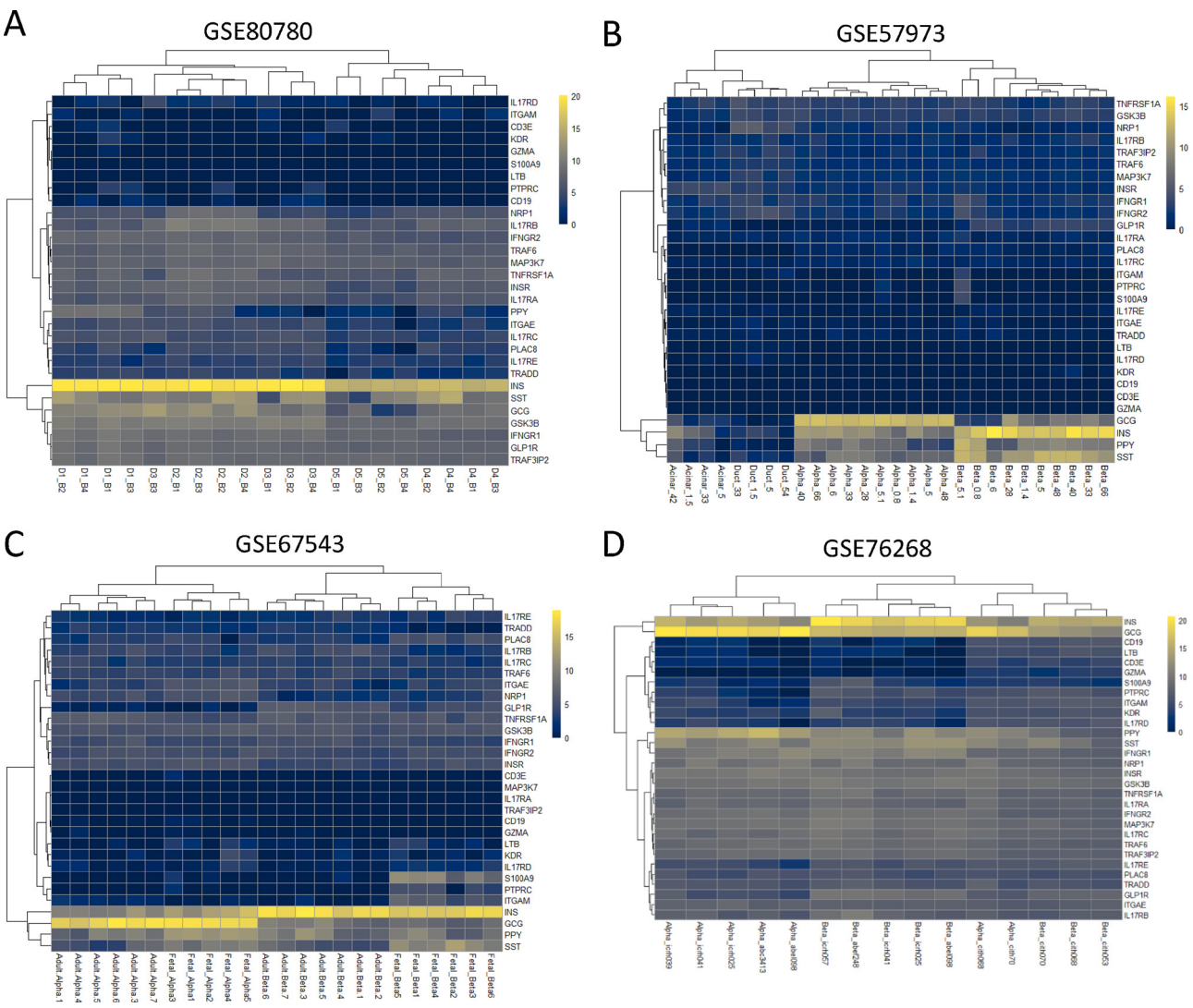

Fig. 3. Purified endocrine cell expression of IL17 signaling elements.
Purified endocrine cell expression of IL17 signaling elements. Bulk analysis of complex populations may sometimes hide the specific expression of a gene within a small subset of the whole, or otherwise lead to over-generalization of positive expression onto negative subsets. As such, we also looked at datasets generated by bulk-sequencing of sorted endocrine populations to gain further clarity. A) A study which reported the existence of four distinct beta cell subtypes that have distinct functional characteristics, but no apparent differences contributed by IL-17 signaling receptors. B) A study that compared endocrine cell types derived from very young and middle-aged donors. C) A study that compared purified beta and alpha cells taken from fetal and adult donors shows very low expression of the Act1 adaptor, but substantial expression of other components such as IL17RC and TRADD . D) A study that explored chromatin accessibility in alpha and beta cell and which also generated sequencing data of purified populations as reference for integrated analysis.

explored for potential dropout-driven lost effects with one of the datasets included. Interestingly, imputation suggested that IL17RA expression levels alone were not strongly correlated with co-expression of the ACT1 adaptor, or with high co-expression of the other heterodimer partners. On the other hand, IL17RC did appear to coexpress together with ACT1 and GSK3B following imputation, as well as with IL17RB and IL17RC (Figure S1). Whether or not this apparent co-expression is biologically real/significant is unclear. After all, despite the predictive value of these algorithms, they are still only guides that require careful validation with further evidence.

Collectively, our observations confirm that IL17 receptors are likely expressed across the endocrine cells in the islet, together with the downstream adaptors necessary for their signaling. These results thus agree with the existing data generated of mice and human islets that showed noticeable effects when exposed to recombinant IL-17 in vitro. If there is indeed functional expression of the IL-17 signaling apparatus in islets, a number of possible functional responses are possible once IL-17 is elevated during T1D. While NF-kb activation is commonly perceived to be a net negative, it may also serve a protective function. This is because at lower levels of activation (below the apoptotic threshold), NF-kb can trigger a range of protective responses to lower the metabolic activity of the cell (thus preventing excessive damage from oxidation), promote DNA damage repair (to preserve genome integrity), and barrier maintenance (Chen et al., 2003; Lawrence, 2009). Indeed, it is primarily as a result of the latter function that IL-17 has also been understood to be partly protective for the epithelium in the gut in inflammatory bowel diseases to restrict immune cell infiltration and exclude microbial expansion. It may be possible that early exposure with IL-17 may also desensitize beta cells against more damaging cytokine signaling from TNF and IFNγ that also require NF-kb for their primary effects. Additional in vitro studies on the spatio-temporal distribution of IL-17R and IL-17 signaling events will be required to clarify its direct role in beta cells. It may also be informative to generate IL-17R-deficient animals behind beta cell-specific promoters (such as a RIP-Cre) for direct in vivo experiments.

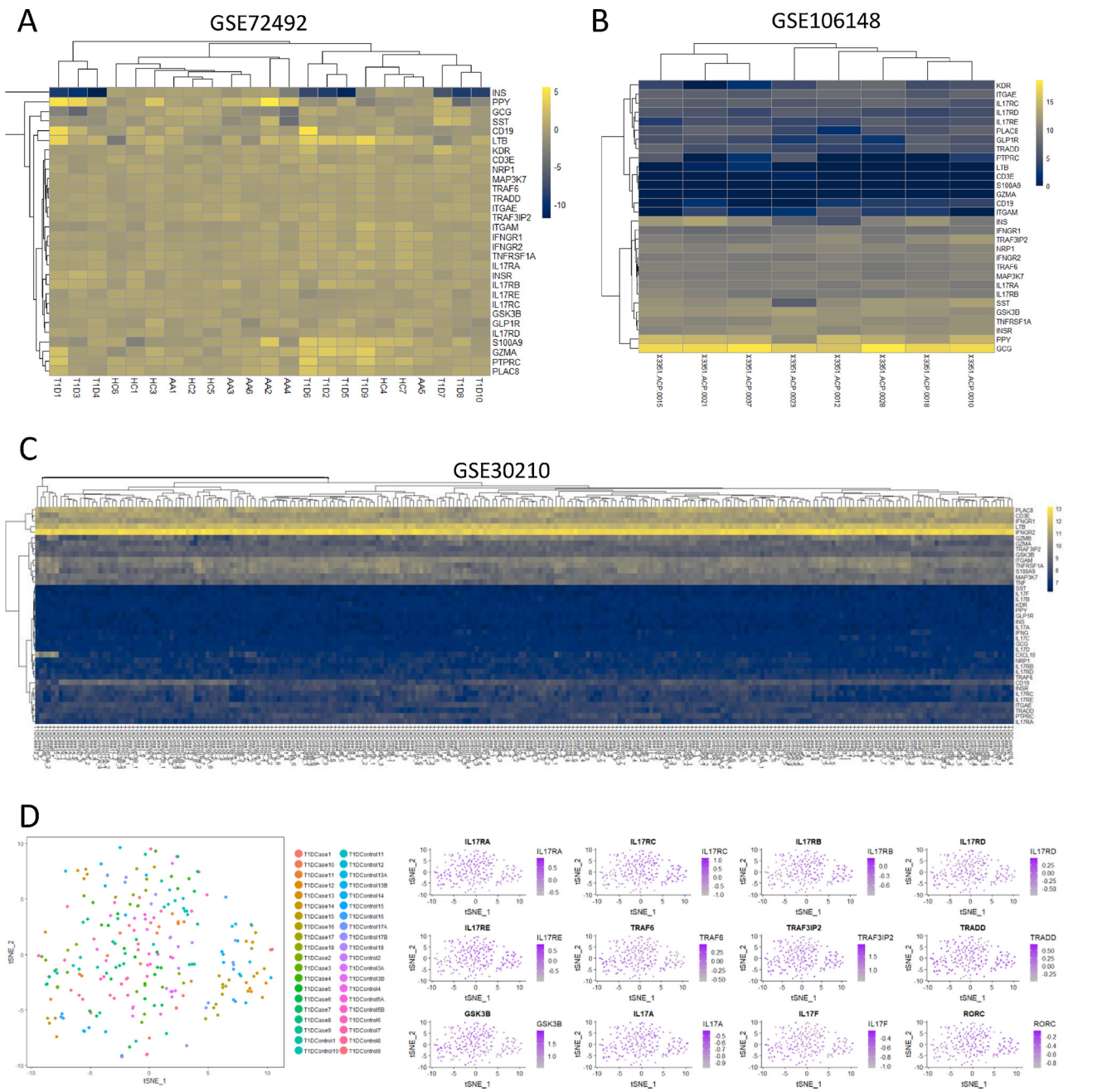

Fig. 4. Expression profile studies of samples from T1D patients.
Expression profile studies from T1D patients shows little noticeable change in the expression of IL17 receptors with respect to disease. A) A whole-pancreas microarray study comparing expression differences between healthy controls, autoantibody –positive subjects, and established T1D patients. B) A RNAseq study of alpha cells sorted out from the islets of 5 healthy controls and 3 T1D patients. C) A large case-control microarray study of the peripheral blood of children with T1D also does not show obvious differences in expression of these receptors (or of IL17 A/F itself), although there is clear positive expression of these receptors. D) tSNE clustering and visualization of C based on global gene expression confirms the lack of noticeable differences, as the cases and controls do not appear to separate based on the initial dimensions.

8. Possible alternate sources of IL-17

It is also important to remark here that IL-17 is not necessarily exclusively produced by T cells. While the endocrine cells are not expected to produce the cytokine intrinsically regardless of disease, and T cells are the most ready circulating source for IL-17, it is also possible that some cells in the acinar and exocrine pancreas may also be a source. After all, it is now appreciated that innate lymphoid cells dot a number of non-immune organs to act as local sensors of pathogen/damage (Eberl et al., 2015). Recently, work done in the gut has shown that a number of these ILCs express high levels of the transcription factor RORγt, and that this expression enables them to also produce IL-17 (Xu et al., 2012). It is unknown if such a population also exists in the pancreas; thus far, scRNAseq results do not appear to have detected such a population in healthy or T2D subjects, though it is possible that deeper sampling may be able to uncover such a population during T1D. Given the proximity of the pancreas to the intestine, it is also possible that IL-17 secreted in the lamina propia by ILCs there, or released elsewhere into circulation, may also influence pancreas behavior. One recent paper has reported that ILC secretions may protect the endocrine pancreas through defensing signaling, and it is likely that distal cytokine signaling could mediate a similar effect (Miani et al., 2018). More

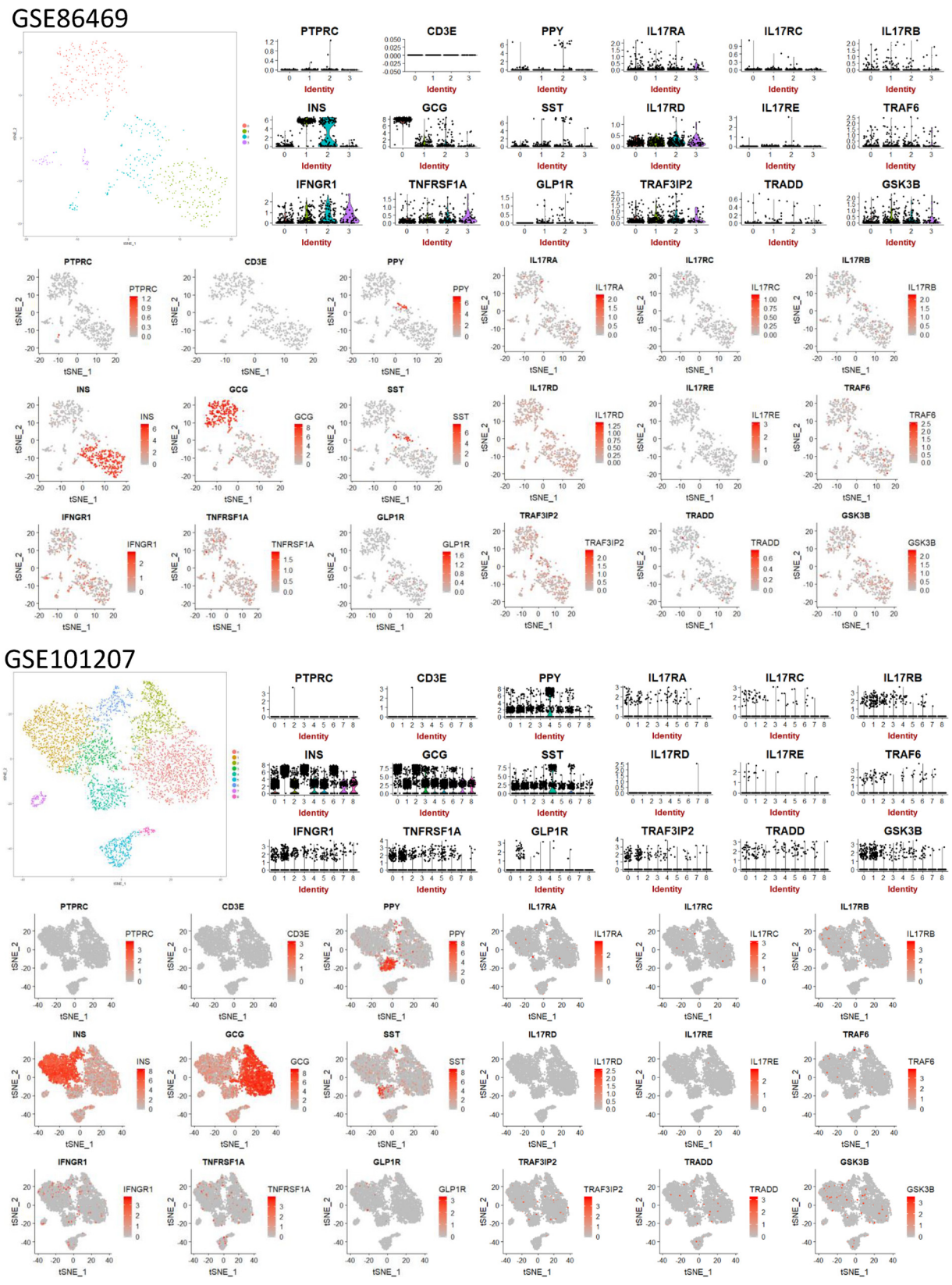

Fig. 5. Single cell sequencing studies of human islet transcriptomes. In each study panel, the initial tSNE plot was generated with the Seurat to show the clusters identified based on expression differences of genes with high dispersion and expression. In order to generate an informative mapping of these datsets, we selected 18 genes for visualization; 4 to match with known endocrine cell types (GCG, INS, SST, PPY), 2 for possible immune infiltration (PTPRC, CD3E), 3 key signaling components (TRAF3IP2, TRADD, GSK3B), and 3 receptors of known expression. The violin plots shown mark the quantified expression level of each individual gene with the clustered numbered as per the tSNE plot. tSNE visualizations of 18 chosen genes are shown to give an identification of the major clusters and highlight the distribution profile of IL17 receptors and downstream signaling elements within each endocrine cell type.

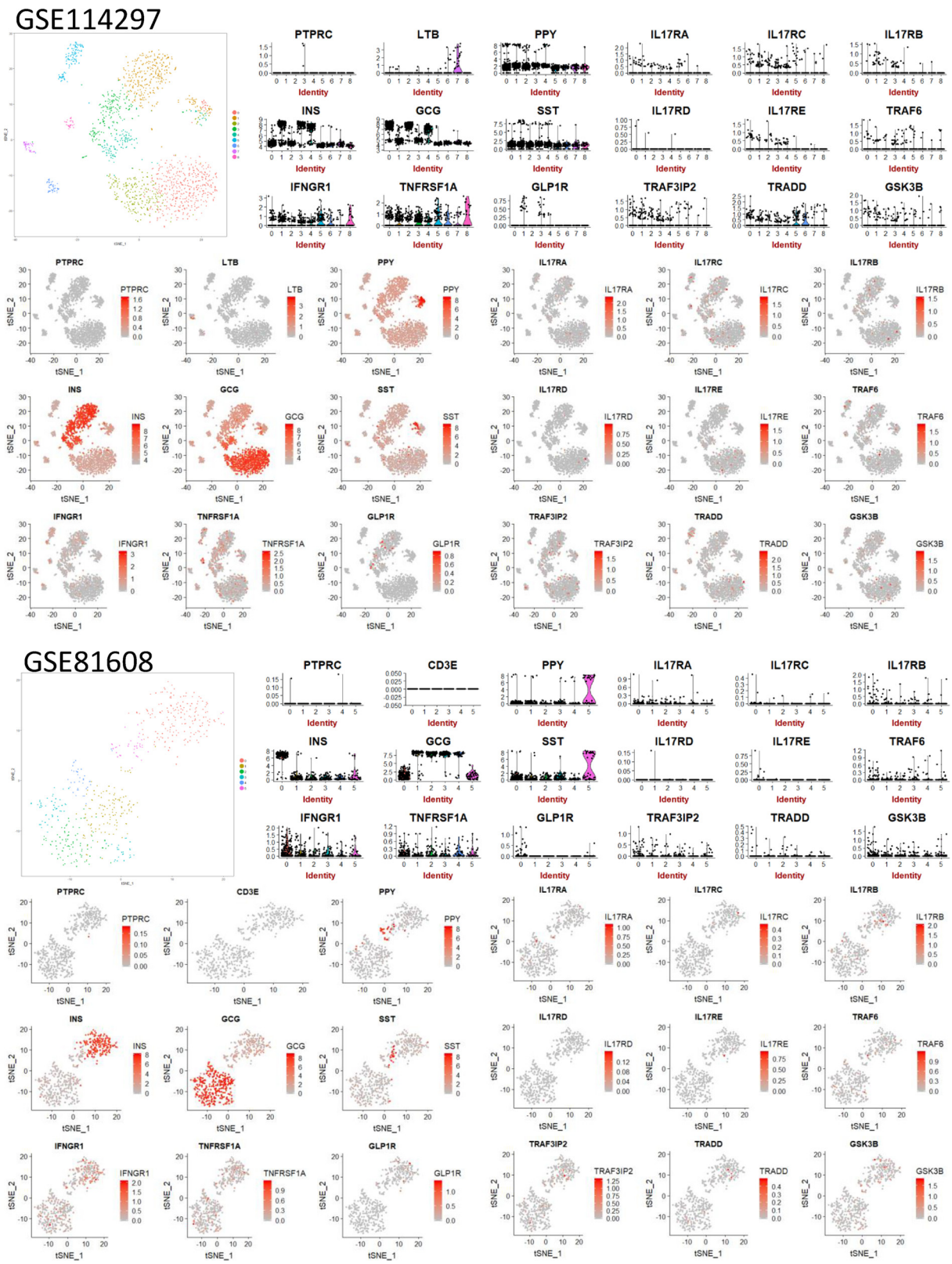

Fig. 5. (*continued*)

detailed signaling and sequencing studies of different cell types in the islet periphery will be necessary to definitively establish the relevant source(s) of IL-17.

9. IL-17 and the gut

Beyond the potential direct effects of IL-17 in beta cells, a general increase in circulating IL-17 levels will likely have important effects in a number of other tissues that regulate blood glucose and insulin signaling. For instance, an increase in IL-17 will almost certainly have

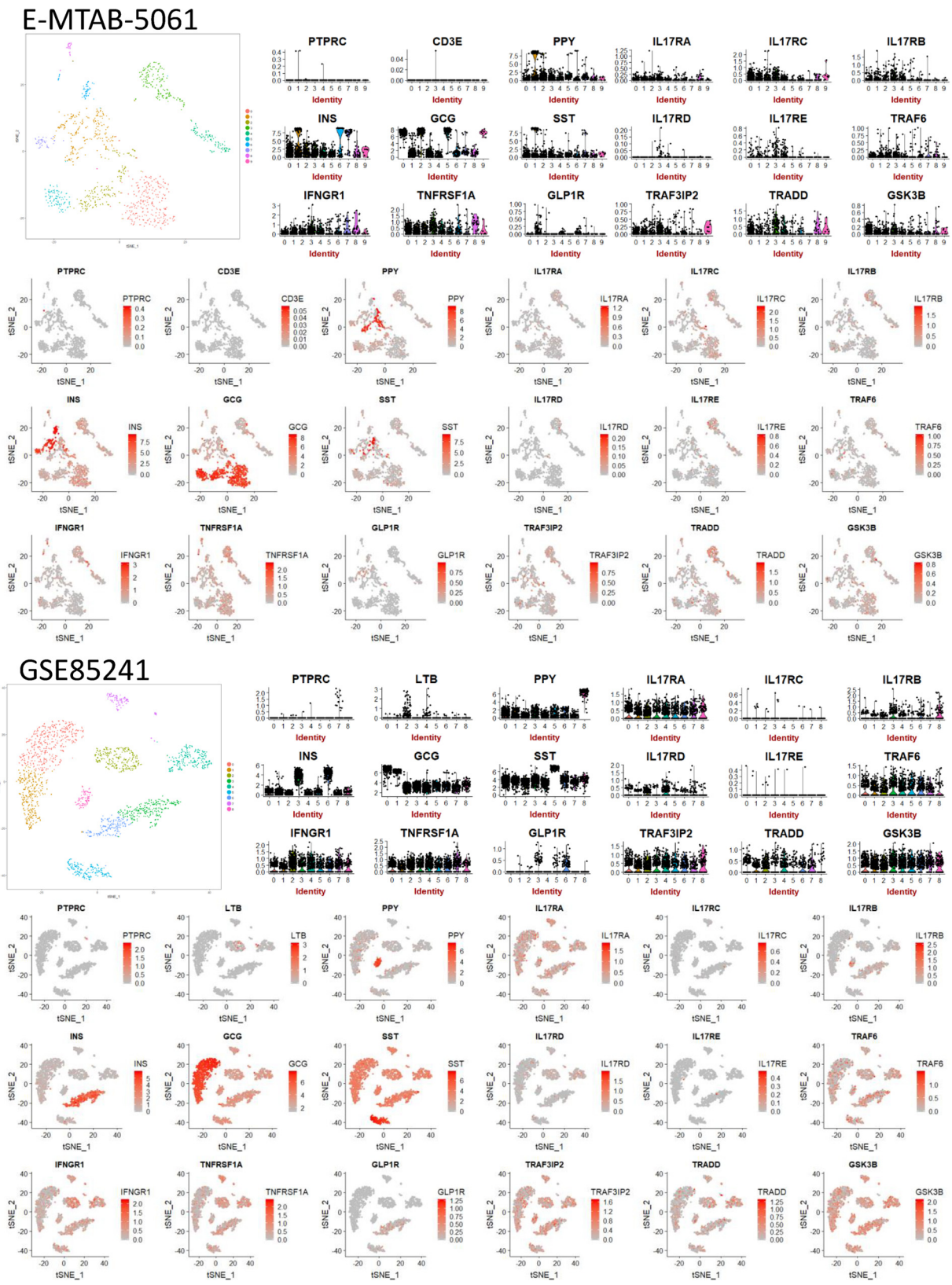

Fig. 5. (*continued*)

significant effects on the gut, where substantial populations of IL-17 producing cells exist under the control of residential APCs (Schlitzer et al., 2013). Changes in the levels of IL-17 in the gut have been shown to lead to alteration in microbiota content and metabolic capacity in a number of other autoimmune diseases, and such a pattern would likely extend to T1D (Blander et al., 2017; Palm et al., 2015). Importantly, these can be influenced by dietary consumption, and include production of fatty acids, a key secondary signal for insulin secretion, as well as glucose uptake in general (Garidou et al., 2015; Patrick et al., 2013; Yedulla et al., 2018). These effects have been shown to also modulate

neuronal activity as part of the gut-brain axis, which may also lead to indirect effects on the islets (Tsui et al., 2008). Indeed, a number of studies have already shown that significant changes occur in the microbial diversity of patients with T1D. Reductions in Firmicutes and increases in Bacteriodetes have been reported in a number of different cohorts of T1D patients, as has increased gut epithelial permeability (de Groot et al., 2017; Wen et al., 2008; Kostic et al., 2015). Since IL-17 is well known to play a key role in regulating epithelial permeability, a function demonstrated during inflammatory bowel diseases, it is possible that changes are partly influenced by dysregulated IL-17 activity (Lee et al., 2015). From animal models, it has already been observed that early antibiotic treatment can accelerate disease onset (Zhang et al., 2018b; Livanos et al., 2016). Interestingly, lower amounts of lactate and butyrate producers have also been reported to be present in seropositive patients, suggesting that T1D may lead to the favoring of increased Th17 cells over Tregs in the gut (since butyrate is known to promote Treg differentiation, while lactate represses effector T cell functions) (Dutta et al., 2012). However, it has also been reported that an increase in IL-17 in the gut can actually be protective against diabetic incidence in rodents (Nikoopour et al., 2010; Lau et al., 2011). Metabolic studies are still needed to characterize the exact nature of the correlation between microbiota composition changes and consequent alterations in IL-17 secretion and Th17 function within the context of T1D development.

Beyond these metabolic influences, it is also possible that changes in the microbiota composition may have even more direct effects on immune responses. Gut bacteria have been shown to permeate into the pancreatic lymph nodes and influence immune responses there, and antigens from microbes may also nonspecifically activate immune cells in mice (Costa et al., 2016; Tai et al., 2016).These direct effects are likely predominantly channeled through innate immune responses, which would also be sensitive to IL-17 levels. Additional animal and human studies may be able to clarify if IL-17 levels indeed change in the gut during T1D, as well as the possible timing for such changes during disease progression.

10. IL-17 and diabetic kidney disease

While early onset T1D is understood to manifest as a pancreatic disease, prolonged progression can give rise to a number of diabetic complications. Similar to the case in T2D patients, many of these complications are linked to hyperglycemia and poor blood glucose control. One of the most prominent and severe of these complications is diabetic kidney disease (DKD), in which the kidneys progressively lose function (Thomas et al., 2015). Although DKD at early stages appears to be mediated mostly by hyperglycemia-related metabolic dysregulation and hemodynamic abnormalities, immune activation and infiltration contribute significantly to the progression of the disease. While the kidneys are not known to contain a residential population of IL-17 producing cells under physiological conditions, significant upregulation of the cytokine may occur during chronic disease (Chan et al., 2014a). In addition, Th17 cells may infiltrate into the kidneys during inflammation (Krebs and Panzer, 2018). Importantly, a wide range of cells in the kidneys are expected to express receptors for IL-17, including stromal, endothelial, tubule, and collecting duct cells, as well as residential APCs (Han et al., 2018; Park et al., 2018). In the general context of autoimmunity, increased IL-17 in the kidneys has been shown to increase levels of fibrosis and complement deposition into the glomeruli (Krohn et al., 2018; Koga et al., 2017; Chan et al., 2014b). These effects lead to worsened proteinuria/albuminuria and elevated blood urea nitrogen, and may be further exacerbated by additional leukocyte recruitment (Peng et al., 2015). Since Th17 cells have been shown to have relative high tolerance for hypoxia due to high expression of HIF1 A, they might also be resistant to the nutrient-deprivation induced brake on inflammation in the kidneys (Dang et al., 2011). Damage promoted by elevated IL-17 in the kidneys may also lead to dysregulation of glucose re-uptake in the kidneys, which is predominantly driven by the SGLT2-expressing cells in the proximal tubule. While pharmacological targeting of these cells is currently being used as a treatment modality for T2D (with drugs in the –flozin class), it is unclear how effective of a management strategy this would be in T1D when there is inefficient glucose uptake.

At the same time however, total ablation of IL-17 has also been shown to actually lead to worsened kidney damage, while injections of IL-17 may actually serve to reverse DKD in mice (Mohamed et al., 2016). Furthermore, it has been observed that patients with severe DKD may have lower levels of circulating IL17 than healthy controls (Vasanthakumar et al., 2015). The underlying mechanisms that shunt IL-17 towards potentially being protective in DKD and damaging in almost all other forms of kidney disease are unclear. Part of the discrepancy may be the result of species differences between mice and humans in renal function. More detailed spatiotemporal studies of the distribution and function of IL-17 signaling receptors in the kidney during DKD development may clarify matters.

11. IL-17 and other diabetic complications

Diabetic retinopathy can also be a serious complication in T1D patients with poor blood glucose management. While the eye is usually an immune-privileged site, (hence enabling experiments that graft islets into the eyes of immunocompetent mice) the integrity of the blood-retinal barrier may dissolve during the inflammation that drives retinopathy (Antonetti et al., 2012). How significant a role T cells play in diabetic retinopathy is not well understood, with much of the focus being on the vascularization and retinal thinning that occurs. There is some evidence that IL-17 is elevated in the aqueous humor of patients with retinopathy, and that IL-17 might lead to dysfunction of the Muller cells that support retinal neurons (Qiu et al., 2016; Xu et al., 2015). However, the absolute percentages of IL-17 positive cells in the eye is likely low, and would likely need to be supported by significant amounts of other pro-inflammatory cells for there to be phenotypic effects. Based on results from models of age-related macular degeneration and uveitis, it seems likely that IL-17 can have significant importance during retinal inflammation, some of which may be protective (Liu et al., 2011; Hasegawa et al., 2013; Ke et al., 2009). Additional signaling studies are required to characterize the extent of IL-17 signaling networks in the diabetic eye.

Recent microscopy-driven studies have demonstrated that the islets are heavily innervated by sympathetic neurons, and as such, any change to the ability of the brain to mount sympathetic responses will also impact the ability of beta cells to receive additional signals promoting the secretion of insulin (Borden et al., 2013; Chiu et al., 2012). It is thus far unknown if the increase in Th17 cells seen in circulation during early onset would have an impact on nerve function, but more detailed cell characterization technologies like scRNAseq and mass cytometry may clarify the picture. While it is unlikely that Th17 cells could directly attack the CNS, given the lack of neurological symptoms reported to be associated with T1D onset, it is possible that low levels of IL-17 permeating into the brain may sculpt sympathetic peripheral responses and contribute to local activation of microglia/macrophages closer to the islets. Damage to these peripheral neurons may lead to the development of diabetic neuropathy. While IL-17 has been suggested to directly modulate neuronal cell behaviors in vitro, it is unclear if these effects also extend to T1D in vivo (Habash et al., 2015). Of particular interest may be the influence IL-17 can have on neuronal interactions with macrophages in the islets. A full appreciation of the importance of any particular cytokine in these complications is impossible without much more investigation into their development.

12. Conclusions

T1D is a complex autoimmune disease involving contributions from

a large number of cell types across different organs that leads to beta cell dysfunction and ultimate death. As a commonly expressed and broadly functional cytokine with known increases close to the time of disease onset, IL-17 has been the recent focus of study as a potential treatment target. While the independent ability of IL-17 to drive beta cell damage is likely low, its influence on other immune cells in the inflammatory environment may allow for it to have an additive effect on damage driven by other cell types. At the same time, it may be able to modulate distal effects in the gut, CNS, and kidneys to influence disease progression and complications. Given the insufficiency of genetic ablation of IL-17 to prevent diabetes onset in mouse models, it is unlikely that monotherapy targeting IL-17 would fare much better in clinical cases. The current evidence does not suggest that IL-17 might be an initial cause that sparks T1D disease onset, or that it is essential for T1D onset. Rather, IL-17 might be considered to serve as a key support platform upon which the complex machinery of inflammation may then be constructed and maintained. While it may be somewhat dispensable to disease incidence when missing, it can be expected to buttress existing immune programmes when it arises normally. As such, a lowering of IL-17 as part of a broader therapeutic regimen would likely lead to favorable outcomes and amelioration of diabetic complications by reducing the bystander impacts that chronic increases in IL-17 can induce. Much more work using direct provision of IL-17 and IL-17 receptor conditional knockout systems will be necessary to clarify its true importance, but the emergence of new high-throughput technologies may significantly hasten the process.

The advent of scRNAseq and other single-cell technologies has the potential to greatly improve understandings of signaling pathways in different tissues. While pathways with low expression in bulk transcriptomics tended to be somewhat neglected previously, a re-evaluation in light of emerging single cell data may be necessary as smaller subsets of cells may still express the elements necessary for pathway function and be sensitive to the stimulus. From an exploration of a number of datasets, it seems apparent that a significant portion of islet cells express the component necessary for IL-17 signaling. This expression does not appear to be highly condition-dependent, as a number of different treatment methods and analysis protocols used did not lead to any substantial alterations (a summary of the datasets analyzed is included as supplementary Table 1). These results have also been confirmed on a single-cell level in datasets generated of islets taken from healthy donors. However, the relatively low expression of these signaling elements renders them susceptible to dropout in single-cell analysis, and all of the datasets generated thus far have been somewhat static (being restricted to one time point). And while imputation-driven approaches do offer valuable insights into the workings of the system, further improvements in sequencing technology in the future are still necessary to truly capture the realities of its expression. Furthermore, the true biological impact of the expression of this signaling pathway during T1D remains unclear, and further experimental validation using different approaches on both RNA and protein levels will be necessary.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.molimm.2018.11.007.

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