Type 1 diabetes and MIG

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Abstract

In Type 1 Diabetes (T1D), the monokine induced by interferon (IFN)-γ (MIG)/(C-X-C motif) receptor (CXCR)3 axis has a crucial role in β-cell destruction and in the autoimmune process of the disease, like many papers have reported. In fact, in T1D subjects the serum levels of the Type helper 1 chemokine MIG is increased, suggesting that this chemokine could be a predictive marker of T1D. Moreover, the pathophysiology of the disease course could be assessed by measuring MIG serum levels. A potential approach for T1D therapy could be the block of MIG expression at the beginning of the disease. Anyway, the chemokines-cytokines interactions in the T1D pathogenesis need to be further investigated.

Key words: MIG, type 1 diabetes

Introduction

Despite previous studies have identified many factors that take part to the beginning of Type 1 Diabetes (T1D) (environmental, genetic and immunological), leading to different hypotheses about its pathogenesis, this disease is still an important health issue, especially among western countries where the incidence in younger children has increased (1). In T1D the continuous and slow destruction of the pancreatic β-cells is determined by the autoimmune mechanisms. This causes a progressive shortage of β-cells and a final absence of endogenous insulin. Because of this deficiency, multiple hormonal abnormalities regarding glucagon and also incretin occur, causing the primary phenotype characterized by an extreme glycemic variability, as well as metabolic instability (2). T1D is caused both by autoantibodies and antigen-specific diabetogenic T cells against β-cells of the pancreas which produce insulin (3, 4). Unfortunately, either treatment and prevention of this disorder are thwarted because the debate about the key immunological mechanisms of its pathogenesis is still ongoing (5, 6). Islet-specific CD8+ T cytotoxic cells (CTL) are responsible for destroying β-cells in T1D in a cytokine microenvironment provided by diabetogenic CD4+ T cells [Type helper (Th)1]. Also at later stages of the disease islet-specific Th activity may be cytotoxic to islets, therefore a prior costimulation of CTL before killing β-cells could not be necessary (7, 8). Therefore, the potential strategies to prevent T1D includes targeting either CTL and Th which contribute to the pathogenesis of the disease. It has been found an association between T1D and the predominance of the Th1 response, which creates a derangement in the Th cell system, promoting the development of autoimmune diseases (9).

MIG, and CXCR3

Monokine induced by interferon (IFN)-γ (MIG) is a T-cell chemoattractant small cytokine also called chemokine (C-X-C motif) ligand (CXCL)9, and it is induced by IFN-γ. The genes of the Th1 dependent chemokines MIG, IFN-inducible T-cell α chemoattractant (I-TAC) and IFN-γ-inducible protein 10 (IP-10) are localised on human chromosome 4 (10, 11). Recruited Th1 lymphocytes increase either the production of IFN-γ and tumor necrosis factor (TNF)-α thus stimulating MIG secretion from several cells of the inflamed site, in this way creating an amplification feedback loop (12, 13). Higher levels of MIG in serum can be considered as a marker of the Th1 driven response and more in general of the host immune response, since many paper reported increased tissues expressions in the different organs specific of autoimmune diseases as well as augmented MIG serum levels (and also of other Th1 chemokines) (12, 13). For instance: systemic rheumatological disorders, like rheumatoid arthritis (14), systemic lupus erythematosus (15, 16), systemic sclerosis (17-21), psoriasis or psoriatic arthritis (22-24), autoimmune disorders such as autoimmune thyroiditis (25-32), Graves’ disease (33, 34) Graves’ ophthalmopathy (35-39), T1D (40-44), or sarcoidosis (45, 46), and also HCV-related cryoglobulinemia (47-53), other HCV immune mediated disorders (29, 54-61), other diseases, and furthermore in cancers (62-88).
CXCR receptor (CXCR)3 is a G protein-coupled receptor with two isoforms CXCR3-A and CXCR3-B, both binding IP-10, I-TAC and MIG (all Th1 dependent chemokines), while the -B isofom binds also CXCL4 (89). CXCR3 is expressed either on (C-C motif) receptor (CCR)5 and on Th1 cells which are recruited in the inflamed site by IP-10, MIG and I-TAC produced by the local cells of the inflamed site. Moreover, CXCR3 is expressed by other cells such as the endothelial and epithelial ones as well as Natural Killer and activated T lymphocytes. For the recruitment of inflammatory cells this receptor and its ligands are important (90). In this review, we report the role of MIG in T1D by presenting data in line with the International Narrative Systematic Assessment tool (91).

**MIG in T1D** (Tab. 1)

A first in vitro study evaluated the inducible and constitutive expression of the chemokines and their receptors by pancreatic islets, showing that stimulation of islets by inflammatory cytokines caused de novo expression of MIG, Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES), CC ligand (CCL)2, IP-10 and an increased of macrophage-inflammatory protein-2 (MIP-2) (92).

In a further study to better analyze in T1D the role and interaction between human leucocyte antigen (HLA) high-risk haplotypes DQ2(DQA*0501-DQB*0201)-DQ8(DQA*0501-DQB*0302) and the IP-10 (rs8878, rs35795399 and rs3921) and MIG (rs3733236, rs10336) polymorphisms, a combination of family (n=221) and case-control (n=447 cases and n=300 controls) analysis was performed. Some interesting results were obtained in the family group analysis regarding an overtransmission of the alleles G and T of the polymorphisms rs8878 and rs35795399 in the entire group as well as in combination with the HLA-high risk haplotypes. Moreover, to the affected offspring was less often transmitted the haplotype rs8878A-rs35795399C while the more often transmitted was the rs8878G-rs35795399T ones. However, these results didn’t turn out significant when corrected for multiple testing and the Authors didn’t find associations between T1D and MIG/IP-10 polymorphisms in the German population. Otherwise, they did not exclude their possible role in other populations (93).

Further studies aimed to found inside the chemokine/receptor family, potential therapeutic targets. To reach this goal they integrated murine models of virus-induced and spontaneous T1D, histopathological examination of pancreas received from diabetic organ donors, and a human islet culture system. In vivo, in the islet environment of T1D patients and prediabetic animals, the proteins MIG, monocyte chemoattractant protein 2, chemokine (C-X-C motif) ligand (CX3CL)1 and RANTES were present at lower levels; while in the islets of both species IP-10 was identified as the dominant chemokine expressed (94).

In another study were measured sera cytokines [interleukin (IL)-12, IL-6, IL-1β, TNF-α, IL-10] and chemokines (IP-10, CXCL8, MIG, CCL2) both in newly diagnosed T1AD patients and healthy controls; significantly higher levels of both chemokines and cytokines were found in the first group. No association has been shown between HLA DR3, DR4 or DR3/DR4 and PTPN22 polymorphism and pancreatic islet cell antibodies or the abovementioned cytokines (95).

A paper verified the capacity of the 1,25-dihydroxyvitamin D(3) [1,25(OH)(2)D(3)] [vitamin D receptor (VDR) naural ligand] to interfere in inflammatory and T cell stimulatory ability of macrophages, within a chronic inflammatory disease features of experimental T1D. It was found that 1,25(OH)(2)D(3) is able to induce VDR and its downstream targets expression, and that macrophages constitutively expressed VDR. In control mice, the expression of IL-12p40,
TNF-α and inducible Nitric Oxide Synthase (iNOS) caused by the macrophages activation as well as their effect in T cell-recruiting (by MIG, IP-10 and I-TAC), were in part blocked if they were programmed with 1,25(OH)(2)D(3). This compound was able to reduce the functions mediated by macrophages also in non-obese diabetic (NOD) mice, where macrophages/monocytes had a raised responsiveness against danger signals and a major T cell stimulatory capacity. Therefore, a possible therapeutic applicability of this natural immunomodulator thanks to its capacity to neutralize macrophage inflammatory and T cell-activating pathways, arose from this study (96).

A subsequent study was aimed to examine if duration and complications of T1D in Iranian patients were associated with the pro-angiogenic chemokines, such as CXCL1, and anti-angiogenic chemokines, such as MIG, expression. The serum levels of these chemokines were measured by ELISA, in the blood samples of 209 T1D patients and 189 healthy controls. They found increased plasma levels of both chemokines in T1D patients with respect to the controls. The Authors demonstrated a strictly association between chemokines and T1D complications, and a highly chemokines levels in those subjects who reported complications (97).

The effects of the extract of Hypericum perforatum [St. John’s wort (SJW)] and its components hyperforin (HPF) in inhibiting the activation of signal transducer and activator of transcription (STAT)-1 and the nuclear factor κB (that were induced by cytokines) and in preventing apoptosis in a cultured β-cell line were already shown. An in vitro study was conducted to investigate the protection exerted by SJW and HPF on isolated rat and human islets after the exposition to cytokines. Both compounds were able, either in rat and human islets to: 1) downregulate the mRNA expression of pro-inflammatory genes, such as iNOS, MIG, IP-10, COX2; 2) hamper the functional impairment induced by cytokines; 3) reduce the cytokines-induced NO production; 4) prevent the increase of apoptosis and necrosis, mainly with SJW, obtained after 48 h of exposure to cytokines; 5) avoid early β-cell damage (such as mitochondrial alterations and loss of insulin granules) induced by an incubation with cytokines for 20 h (98).

A study, on the base of the RNA sequencing dataset obtained from SRA database, profiled the transcriptome in human islets of Langerhans under control conditions or after the exposure to pro-inflammatory cytokines. They identified 63 differentially expressed genes of whom 60 upregulated and 3 downregulated. In the samples treated with cytokines, the two most upregulated genes were MIG and GBP5 with the log2 fold change of 10.901 and 12.208, respectively (99).

Another paper proposed a mechanism for Treg cell homing to the β-islets in the NOD model during pre-diabetes, by inducible costimulator (ICOS) through the upregulation of the CXCR3. A CXCR3 expression occurred in the islet-specific ICOS+ Treg cell subset in the pancreatic lymph nodes (pLN); this expression correlated with the IFN-γ production by T effector (T$_{eff}$) cells in pancreatic sites which mediate the pancreatic inflammation. The Authors also observed a ICOS+ CXCR3+ Treg cell chemotaxis in vitro mediated by the chemokines MIG, IP-10 and I-TAC that were released by intra-pancreatic APC populations and by islet β-cells (but not α nor δ). A Th1-like profile characterized the ICOS+ Treg cells, which maintained their suppressive capacity that consists in the T-bet and CXCR3 expression and the IFN-γ production in the draining pLNs. In vivo studies showed a block of the Treg cell CXCR3 upregulation by neutralizing IFN-γ; thus underline the role covered by this cytokine in the regulation of the CXCR3 expression by Treg cells (100).

Both fragments of glucagon-like peptide-1 (GLP1), GLP1$_{7-36}$ and GLP1$_{9-36}$, could modulate the response of lymphocytes to cytokine stimuli. In 34 patients with T1D and in 35 healthy controls were assessed hematologic parameters, the incretin axis and CXCR3 (receptor of DPP4 ligand cytokines CXCL9-11) expression on Tregs. Flow cytometry revealed a higher CXCR3 expression on the CD25(-)(low)Foxp3(+) with respect to CD25(+)Foxp3(+) Tregs independently from T1D, thus suggested that CD25(-)(low) Foxp3(+) Tregs were in a “standby” mode possibly waiting for orientational chemotactic stimuli (101).

A further study demonstrated that: 1) genes encoding the chemokines MIG, IP-10, and I-TAC were primary response genes in pancreatic β-cells and raised in rat, mouse, and human islets, as part of the inflammatory response; 2) STAT-1 took part in the transcription control of these genes in response to the pro-inflammatory cytokines IL-1β and IFN-γ; 3) circulating levels of chemokines activating CXCR3 were elevated in NOD mice, in accordance with clinical findings in human diabetes; 4) mice having genetic deletion of CXCR3 reported a delay in diabetes development after the injection of multiple low doses of streptozotocin. Accordingly, these abovementioned chemokines, released by islet β-cells, are able to control leukocytes migration and activity into pancreatic tissues, that eventually influenced the mass and function of islet β-cells (102).

In vitro and in vivo studies were carried out in a last paper to test the damage induced by H1N1 virus in human β cells/pancreatic islets and on glucose metabolism. The in vitro studies showed the ability of the Human H1N1 A/California/2009-derived viruses to infect human pancreatic β-cells, are able to control leukocytes migration and activity into pancreatic islets, followed by an increase of the release of MIG and IP-10. In the infected mice, a clear susceptibility to the virus was observed, the virus was also found in extrapulmonary organs, such as pancreas (103).

Conclusion

In T1D, the MIG/CXCR3 axis has a crucial role in β-cell destruction and in the autoimmune process of the disease, as reported by the above studies. In fact, in T1D subjects the serum levels of the Th1 chemokine MIG is increased, suggesting that this chemokine could possibly be a predictive marker of T1D. Moreover, the pathophysiology of the disease course could be assessed by measuring MIG serum levels. A potential approach for T1D therapy could be the block of MIG expression at the beginning of the disease. Additional studies are needed to investigate the chemokines-cytokines
interactions in the T1D pathogenesis.

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