

Insulin Micro-secretion in Patients with Long Duration Type 1 Diabetes: Implications of Interferon- γ ?

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Rec date: Apr 03, 2014, Acc date: May 13, 2014, Pub date: May 16, 2014

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Type 1 diabetes (T1D) is a T-cell mediated autoimmune disease characterized by the destruction of pancreatic β -cells leading to absolute insulin deficiency [1]. Exogenous insulin represents the core of therapy for T1D that is fatal unless treated [2]. Several years of progressive autoimmune β -cells damage generally precede the clinical onset of diabetes [2]. Moreover, it has been found that the decline in insulin production in patients with T1D is variable [2]. The majority of patients with long-duration T1D has been demonstrated to be insulin microsecretors and to have residual functioning β -cells [2,3]. On this regard, it has been speculated that the small still functional β -cells could have escaped immune attack or have undergone a regeneration process known to be so far extremely limited in human adult [2,4]. Multiple immunological mechanisms have been proposed to contribute to β -cell destruction [5]. Although cytotoxic T lymphocytes directly attack β -cell in T1D, cytokines produced by immune system cells infiltrating pancreatic islets are candidate mediators of islet β -cell dysfunction and death [2-7]. Apoptosis represents the main form of cytokine-induced pancreatic β -cell death [5]. Different pro-inflammatory cytokines, such as Tumor necrosis factor- α (TNF- α), Interleukin-1 (IL-1) and Interferon- γ (IFN- γ), have been involved in T1D pathogenesis [1]. Among these cytokines, IFN- γ has been conventionally described as responsible for driving pancreatic islets autoimmune damage, leading to β -cell apoptosis and the initial destruction of pancreatic β -cells in the onset of diabetes [1,2,4-8]. IFN- γ has been reported to influence immune and autoimmune responses by supporting the homing of diabetogenic activated T cells [8]. The development of diabetes has been linked to the accumulation of IFN- γ producing T-cells in the islets [6]. Furthermore, an association between IFN- γ polymorphism and T1D onset has been corroborated [7]. On the contrary, it has been provided evidence that IFN- γ receptor deficiency prevents diabetes [9]. What is more, reduced diabetes incidence was observed by neutralizing endogenous IFN- γ with anti IFN- γ antibodies [9,10]. Interestingly, IFN- γ has also been shown to play a major role in β -cell dysfunction associated with chronic pancreatitis [11]. The different biological effects of IFN- γ have been connected with its action in regulating gene transcription [5,7,12].

On this regard, it has been found that β -cells under attack are characterized by changes in their gene/protein expression that render them more vulnerable to the deadly effects of cytokines [5]. Janus family kinase 1 (JAK1)- signal transducer and activator of transcription 1 (STAT1) signaling pathway are considered crucial transcription factors mediating the IFN- γ effects on β -cell apoptosis and the subsequent development of T1D [3,5,12-14]. The JAK/STAT signaling cascade is an essential inflammatory signaling pathway that controls the immune responses [14]. It is a critical intracellular

machinery of cytokines involved in gene expression and cellular activation, proliferation and differentiation [12,13]. IFN- γ has been found to activate the expression of target genes through binding of activated STAT1 proteins on a consensus element termed the IFN- γ -activated site (GAS) [15,16]. It has been shown that upon stimulation of IFN- γ , JAKs are activated and phosphorylate STAT1 that shapes a homodimer and moves into the nucleus binding to GASs within promoters of target gene [5,15,16]. Intriguingly, it has been reported that IFN- γ is a transcriptional inducer of survivin gene in an autocrine manner through STAT1 pathway [16]. It has been detected that IFN- γ -activated STAT1 binds directly to a GAS element in the survivin promoter region to trigger survivin expression [16]. Survivin is the smallest member of the inhibitor of apoptosis protein gene family [15-18]. It is an established cancer gene that is over-expressed in almost all human tumors and during embryonic and fetal development, whereas it is hardly detectable or minimally expressed in normal mature tissues [15,17,18]. It has been demonstrated that survivin orchestrates integrated cellular networks that are essential for tumour cell proliferation and viability [18]. Survivin has been implicated in cell death, cell division and cellular adaptation [15,17-19]. Initially, survivin has been shown to be expressed in β -cells of fetal human pancreas, but not in adult islets [17]. Recently, it has also been discovered in the β -cells in areas of pancreatitis and within lobular areas of surviving islets of pancreata of patients with presumed T1 childhood-onset diabetes [17-19]. Survivin has been involved in both the normal expansion of the β -cell mass after birth and in the survival of β -cells following stress-induced apoptosis [18-20]. Thus, survivin has been connected with the maintenance of β -cell mass via replication and anti-apoptotic mechanisms [17,19,21]. Concordantly, exogenous expression of survivin in a streptozotocin-induced model of diabetes has been correlated with protection of pancreatic β -cells from programmed cell death [22].

All these contentions led us to hypothesize that small still functional β -cells in long duration T1D undergo IFN- γ -mediated regeneration. We suggest that IFN- γ , via STAT1, has a dual and paradoxical role of inhibiting apoptosis preserving survival and expansion of islet β -cells through upregulation of survivin and concomitantly to promote apoptosis through JAK1 leading to β -cell death. Proteomic analysis should be directed toward increasing the understanding of the interplay among IFN- γ , JAK1/STAT1 and surviving in order to disclose novel molecules providing new therapeutic strategies employed to halt or even prevent T1D. Accurate evaluation of potential GAS sites in the survivin gene promoter able to bind STAT1 dimers is needed. Furthermore, clinical investigations are required to test the possibility to utilize selective JAK1 inhibitors to keep remaining β -cells from dying in children and young adults recently diagnosed with T1D.

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