IL-6 and type 1 diabetes mellitus: T cell responses and increase in IL-6 receptor surface expression

Karina Braga Gomes[1,2]

[1]Departament of Clinical and Toxicological Analysis, Pharmacy Faculty, [2]Departament of Geral Biology, Biological Sciences Institute, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

Correspondence to: Karina Braga Gomes. Pharmacy Faculty, Federal University of Minas Gerais, Antônio Carlos Avenue, 6627, Pampulha, Belo Horizonte, Minas Gerais, Brazil. Email: karinabgb@gmail.com.

Provenance: This is a Guest Commentary commissioned by Section Editor Mingzhu Gao, MD. (Department of Laboratory Medicine, Wuxi Second Hospital, Nanjing Medical University, Wuxi, Jiangsu, China).

Comment on: Hundhausen C, Roth A, Whalen E, *et al*. Enhanced T cell responses to IL-6 in type 1 diabetes are associated with early clinical disease and increased IL-6 receptor expression. Sci Transl Med 2016;8:356ra119.

Submitted Nov 17, 2016. Accepted for publication Nov 21, 2016.
doi: 10.21037/atm.2016.12.74
View this article at: http://dx.doi.org/10.21037/atm.2016.12.74

Type 1 diabetes mellitus (T1D) is an autoimmune disease characterized by beta cell destruction (1), associated with cellular infiltration and inflammatory responses in the islets of Langerhans (2). The cellular components of this infiltrate include monocytes, macrophages, CD4+ and CD8+ T cells (3), and the balance between Th1 and Th2 cells is crucial in the pathogenesis of this disease (4).

Cytokines play important role in the development and activation of immune cells, since they act as cell-signaling molecules, especially in autoimmune diseases, including T1D. Moreover, cytokines may serve as additional biomarkers of T1D. Cytokines may also provide valuable information about the pathways involved in the regulation of T1D processes (2). Interleukin-6 (IL-6), a multifunctional cytokine, is secreted by T cells and macrophages to stimulate immune response during inflammation and infection. Indeed, this cytokine is involved in the inflammatory response associated with insulin-resistant states (5).

IL-6/IL-6R (receptor) interaction leads to dimerization of gp130, which activates JAK family kinases. Subsequently, STAT proteins (STAT1 and STAT3) are phosphorylated, dimerize, and translocate to the nucleus, where they induce transcription of target genes (6,7). IL-6 signaling can occurs through engagement of gp130 with a complex of IL-6 and a soluble form of the IL-6R (sIL-6R), which is generated by translation of an IL-6R splice variant, or from proteolytic cleavage of the IL-6R from the cell surface (shedding). ADAM17 (or TACE) is the major protease that mediates IL-6R shedding (6,8,9). The effects of IL-6 in inflammation are associated with the IL-6R/gp130/STAT3 axis, which is important for T helper 17 (TH17) cell differentiation, inhibition of regulatory T (Treg) cell development and resistance of T effector (Teff) cells to suppression by Treg cells (6,10,11).

In a recent and important publication in *Science Translational Medicine*, Hundhausen *et al*. (6) investigated the relevance of IL-6 pathway in TD1. Peripheral blood mononuclear cells (PBMCs) and serum samples from 60 T1D and 58 controls were compared, matched for age and gender. They observed increased IL-6–induced pSTAT3 signals in CD4 and CD8 T cells from patients compared to controls. IL-6/pSTAT1 responses were increased in T cells from T1D subjects and were highly correlated with IL-6/pSTAT3. Interestingly, they also observed that diagnosis time from T1D negatively correlated with the frequency of pSTAT3+ CD4 and CD8 T cells, i.e., IL-6 signaling declined in patients with long-standing disease. These results suggest that T cells from T1D patients are hyperresponsive to IL-6 stimulation, although the authors did not find increased IL-6 production in T1D.

The results also showed that enhanced T cell responses to IL-6 in T1D are mainly determined by increased IL-6R surface levels, since there was no difference in IL-6 mRNA

between T1D and controls, and appear to be caused by altered posttranslational regulation of the receptor. Furthermore, ADAM17 mRNA was significantly reduced in CD4+ CD25– T cells from T1D patients. These data suggest that decreased ADAM17 expression, but not protease activity, in T cells from individuals with T1D contributes to higher IL-6R surface levels on T1D T cells.

In order to address the mechanistic IL-6 function, the authors conducted a transcriptome analysis of IL-6-treated CD4 cells and observed a cluster of chemokines and chemokine receptors up-regulated, including 40 genes. The highest up-regulated receptors were CCR5 and CXCR6, followed by CCR1, CCR2, and CCR7. Indeed, six genes implicated in T cell migration were also up-regulated. Consequently, the data suggest that IL-6 significantly improves expression of cell migration- and inflammation-associated genes in CD4 T cells from patients with T1D. Corroborating with this data, they observed increased migration of CD4 cells treated with IL-6 toward CCL5 and CCL19 compared to unstimulated cells. These findings suggest a link between IL-6 and T cell migration that strengthens the possibility that T cell responses to IL-6 in T1D may contribute to disease pathogenesis by changing homing of T cells to the sites of islet inflammation.

Together, the results obtained by Hundhausen *et al*. (6) indicate that IL-6 reactivity could predict disease progression, as well as the IL-6 pathway and IL-6R may assist as therapeutic procedures based in IL-6 or IL-6R inhibition.

Several studies investigated the IL-6 levels in T1D. Alnek *et al*. (2) observed that IL-6 decreased with age and tended to be lower in spring compared to summer, but no difference was observed between T1D and control groups. IL-6 levels was also similar in young T1D patients when compared to controls (12). However, another study including young subjects observed significant higher IL-6 levels in T1D group (4). Bradshaw *et al*. (13) also found marked increase IL-6 secreted by monocytes isolated from the blood cells of recent-onset T1D patients as compared to healthy subjects.

Pestana *et al*. (3) observed higher urinary IL-6 levels in T1D with micro- and macroalbuminuria when compared to T1D with normoalbuminuria or controls, but no difference was observed in plasma levels between the groups. Domingueti *et al*. (14) showed higher IL-6 plasma levels in T1D with chronic kidney disease (CKD) when compared to patients without this complication. These results suggest that IL-6 may vary with the progression of nephropathy in T1D patients, and intrinsic renal cells are able to synthesize pro-inflammatory cytokines, but Hundhausen *et al*. (6) did not consider the status of kidney disease, a limitation of this study.

Hundhausen *et al*. (6) observed no difference in IL-6 mRNA between T1D and controls. Contrary, Ururahy *et al*. (15) observed higher IL-6 mRNA levels in peripheral blood leukocytes from T1D when compared to control. In the former study, the authors also showed higher IL-6 expression in T1D patients with poor glycemic control (according to the values of glycated hemoglobin—HBA1c) when compared to control group. However, Hundhausen *et al*. (6) did not observed correlation between IL6-induced pSTAT3 signaling and HBA1c or blood glucose levels in T1D patients.

Kiec-Wilk *et al*. (16) in a multiple linear regression analysis observed that the number of hypoglycemic episodes per 7 days was an independent predictor of high levels of IL-6. In another study, Gogitidze Joy *et al*. (17) evaluated T1D patients during either a 2-h hyperinsulinemic euglycemic or hypoglycemic clamp, where it was observed that IL-6 plasma levels were significantly increased during the 2 h of hyperinsulinemic hypoglycemia as compared with euglycemia subjects. These results suggest that acute hypoglycemia can result in activation of proinflammatory IL-6 in T1D patients, but this variable was not considered by Hundhausen *et al*. (6), which could affect their results.

This study showed that dysregulation of IL-6 may be a marker of early disease. However, another work where biomarkers were measured at four time points over 20 years in 886 DCCT/EDIC participants with T1D (18) showed that IL-6 levels increased across the time, contrary observed by Hundhausen *et al*. (6). Together, these data suggest that IL-6 signaling can change with the disease progression in T1D subjects and can be a bias in the studies.

The last aspect is that Hundhausen *et al*. (6) study falls in investigating the IL-6 role in peripheral blood, but not in islet-specific T cells or pancreatic lymph nodes. However, we consider important results, which show that immune dysfunction play key role in the pathogenesis of T1D and open new perspectives in order to consider the IL-6 as a therapeutic target in the disease intervention.

Acknowledgements

KBG is grateful to CNPq grant and Research Fellowship (PQ).

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Ferreira-Hermosillo A, Molina-Ayala M, Ramírez-Rentería C, et al. Inflammatory Cytokine Profile Associated with Metabolic Syndrome in Adult Patients with Type 1 Diabetes. J Diabetes Res 2015;2015:972073.
2. Alnek K, Kisand K, Heilman K, et al. Increased Blood Levels of Growth Factors, Proinflammatory Cytokines, and Th17 Cytokines in Patients with Newly Diagnosed Type 1 Diabetes. PLoS One 2015;10:e0142976.
3. Pestana RM, Domingueti CP, Duarte RC, et al. Cytokines profile and its correlation with endothelial damage and oxidative stress in patients with type 1 diabetes mellitus and nephropathy. Immunol Res 2016;64:951-60.
4. Talaat IM, Nasr A, Alsulaimani AA, et al. Association between type 1, type 2 cytokines, diabetic autoantibodies and 25-hydroxyvitamin D in children with type 1 diabetes. J Endocrinol Invest 2016;39:1425-1434.
5. Yin YW, Sun QQ, Zhang BB, et al. The lack of association between interleukin-6 gene -174 G/C polymorphism and the risk of type 1 diabetes mellitus: a meta-analysis of 18,152 subjects. Gene 2013;515:461-5.
6. Hundhausen C, Roth A, Whalen E, et al. Enhanced T cell responses to IL-6 in type 1 diabetes are associated with early clinical disease and increased IL-6 receptor expression. Sci Transl Med 2016;8:356ra119.
7. Heinrich PC, Behrmann I, Haan S, et al. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J 2003;374:1-20.
8. Matthews V, Schuster B, Schütze S, et al. Cellular cholesterol depletion triggers shedding of the human interleukin-6 receptor by ADAM10 and ADAM17 (TACE). J Biol Chem 2003;278:38829-39.
9. Althoff K, Reddy P, Voltz N, et al. Shedding of interleukin-6 receptor and tumor necrosis factor alpha. Contribution of the stalk sequence to the cleavage pattern of transmembrane proteins. Eur J Biochem 2000;267:2624-31.
10. Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature 2006;441:235-8.
11. Veldhoen M, Hocking RJ, Atkins CJ, et al. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. Immunity 2006;24:179-89.
12. Heier M, Margeirsdottir HD, Brunborg C, et al. Inflammation in childhood type 1 diabetes; influence of glycemic control. Atherosclerosis 2015;238:33-7.
13. Bradshaw EM, Raddassi K, Elyaman W, et al. Monocytes from patients with type 1 diabetes spontaneously secrete proinflammatory cytokines inducing Th17 cells. J Immunol 2009;183:4432-9.
14. Domingueti CP, Fóscolo RB, Reis JS, et al. Association of Haemostatic and Inflammatory Biomarkers with Nephropathy in Type 1 Diabetes Mellitus. J Diabetes Res 2016;2016:2315260.
15. Ururahy MA, Loureiro MB, Freire-Neto FP, et al. Increased TLR2 expression in patients with type 1 diabetes: evidenced risk of microalbuminuria. Pediatr Diabetes 2012;13:147-54.
16. Kiec-Wilk B, Matejko B, Razny U, et al. Hypoglycemic episodes are associated with inflammatory status in patients with type 1 diabetes mellitus. Atherosclerosis 2016;251:334-8.
17. Gogitidze Joy N, Hedrington MS, Briscoe VJ, et al. Effects of acute hypoglycemia on inflammatory and pro-atherothrombotic biomarkers in individuals with type 1 diabetes and healthy individuals. Diabetes Care 2010;33:1529-35.
18. Hunt KJ, Baker NL, Cleary PA, et al. Longitudinal Association Between Endothelial Dysfunction, Inflammation, and Clotting Biomarkers With Subclinical Atherosclerosis in Type 1 Diabetes: An Evaluation of the DCCT/EDIC Cohort. Diabetes Care 2015;38:1281-9.

Cite this article as: Gomes KB. IL-6 and type 1 diabetes mellitus: T cell responses and increase in IL-6 receptor surface expression. Ann Transl Med 2017;5(1):16. doi: 10.21037/atm.2016.12.74

