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Shifting the paradigm of islet inflammation—good guy or bad guy?

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Islet Inflammation—The Focus of the 14th IGIS Symposium

The main theme for the Servier-IGIS Meetings, which have been held annually since 2000, is β-cell biology and insulin secretion. The 14th IGIS symposium in March 2013 focused on islet inflammation and its impact on islet function. It has been long known that type 1 diabetes (T1D) is associated with immune attacks on the β-cells and therefore that the immune system with its inflammatory components is a key player in this disease. In recent years, however, this knowledge has been widened so that metabolic disorders have now also been established as associated with both the innate and the adaptive immune system. This also includes the islet dysfunction in type 2 diabetes (T2D). This came about with the progressive characterization of the islet of Langerhans as a complex structure in which endocrine cells are interspersed with resident immune cells, and of β-cells as being able to express chemokines, cytokines and genes encoding innate immune receptors. Altogether this ensures close interactions with immune resident cells, and, more broadly, with the external environment of the islet of Langerhans. During the last decade it has also become apparent that the immune system plays a more subtle role in local and systemic metabolism, a topic now called immunometabolism. Immunometabolism is therefore highly relevant for obesity and T2D.

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Systemic Inflammation and Relation to Metabolism

Inflammatory processes are closely linked with glucotoxicity, lipotoxicity, oxidative stress and endoplasmic reticulum stress, as well as with physical inactivity and other factors associated with T2D, which is the basis for the hypothesis that low-grade inflammation is a potential pathway in the pathogenesis of the disease. An early suggestion in this context was that plasma levels of C-reactive protein (CRP) would predict the development of T2D in middle-aged males independently of established risk factors [1]. Another important finding was the association of elevated circulating levels of the proinflammatory IL-18 with increased risk of T2D [2]. Other proinflammatory markers are also associated with T2D [3]. However, proinflammatory stimuli also induce anti-inflammatory responses as a negative feedback mechanism, to prevent collateral tissue damage due to an excessive immune response.

Anti-inflammatory mechanisms may be potential targets for therapy. During the meeting, such anti-inflammatory markers associated with T2D were discussed. Adiponectin is an anti-inflammatory protein that may be involved in the pathophysiology of T2D. It is of interest that its circulating levels are decreased even before the onset of T2D. Other anti-inflammatory markers are increased in T2D, suggesting compensatory mechanisms, although these may be inefficient. Interleukin-1 receptor antagonist (IL-1RA), transforming growth factor-β1 (TGF-β1) and growth differentiation factor-15 (GDF-15) are examples of such factors that are reduced in T2D. Also other anti-inflammatory markers have also been studied in relation to T2D, such as omentin, interleukin-10 (IL-10) and secreted frizzled-related protein-5 (Sfrp5), although their potential role and function remain to be established.

Another systemic factor that may be of relevance is ApoCIII. This is an abundant apolipoprotein associated with chylomicrons and other lipoproteins in the circulation. It is largely produced in the liver, where it locally inhibits the activity of lipoprotein lipase. Elevated circulating ApoCIII is associated with cardiovascular disease. Elevated ApoCIII is also implicated in T1D and T2D, which may be due to combined action of the apolipoprotein and elevated circulating free fatty acids through the activation of cytokines such as STAT1 and NF-kB signalling. ApoCIII may also have direct negative effects on β-cell function by disrupting β-cell calcium handling, although it is unclear whether β-cells can sense ApoCIII produced in the liver.

Adipose Tissue Inflammation—A Concept for Metabolic Diseases

The concept of a link between inflammation in various tissues such as fat and metabolic diseases is not new, and several previous important observations laid the foundation for discussions during the meeting. Early evidence of linking diabetes with inflammation was the finding that high-dose sodium salicylate improves glycemic control in subjects with T2D [4]. Other earlier landmark discoveries include the demonstration of high expression of the proinflammatory cytokine TNF-α in adipose tissue in obesity and its contribution to insulin resistance [5], and the accumulation of proinflammatory macrophages in adipose tissue in obesity [6].

Owing to a macrophage transcription signature of adipose tissue, the number of macrophages can be increased from 5% to as much as 50% of the cells in obesity; this is also associated with insulin resistance. Of particular importance for tissue inflammation in obesity is the accumulation of M1 macrophages. They accumulate in response to the local production of fatty acids and they, in turn, produce proinflammatory cytokines such as TNF-α and IL-1β that further aggravate the local inflammation. The importance of this process has been documented in studies showing that selective loss of M1 macrophages reduces local and systemic markers of inflammation and improves insulin sensitivity in high-fat diet (HFD) fed mice.

Not only macrophages, but also the density of mast cells and neutrophils as well as adaptive immune cells (CD3+ T-cells, NKT cells and B-cells) are increased in adipose tissue in obesity, whereas Treg cells drop in number. As Treg cells reduce immunologic responses, their reduction in adipose tissue in obesity may explain the increased inflammation. Thus, metabolic processes, especially related to obesity and insulin resistance, activate both the innate and adaptive arms of the immune system, although it is still unclear which antigen may regulate Tregs.

At the meeting, several novel and exciting findings were discussed which shed a new light on the mechanisms underlying the accumulation of inflammatory cells in adipose tissue in obesity. Increased lipolysis with formation of fatty acids, which in turn activate toll-like receptors, among others, is important, as this initiates accumulation of numerous types of immune cells in fat tissue, mainly M1 macrophages and T-cells. Hence, accumulation of immune cells in adipose tissue in obesity is intimately coupled to the local regulation of lipolysis, but has also consequences for metabolism in general. Thus, adipose tissue inflammatory cells talk with the pancreatic islets, resulting in both impaired β-cell function and recruitment of macrophages and T cells to the islets. Such local islet inflammation may be of particular importance in obesity and after intake of a fat-rich diet, may even be a cause of the β-cell dysfunction in T2D and thus a potential target for therapy. On the other hand, there is also accumulating evidence that recruitment of M2 macrophages to adipose tissue in obesity counteracts obesity, increases insulin sensitivity and might serve as a 'sink' for fatty acids to prevent their further release into the circulation. Therefore, inflammation may not be only associated with detrimental actions on metabolism but also be beneficial, thus being both a 'good guy' and a 'bad guy'.

Interaction Between Adipose Tissue and Pancreatic Islets

Since the discovery of increased production of the proin-flammatory cytokine TNF-α in adipose tissue of obese mice, various cytokines and chemokines such as leptin, IL-6 and MCP-1 were found to be produced by adipose tissue and over-produced during adiposity. This may have direct implication for islet function, and suggests an immunometabolic cross-talk between the fat tissue and the β-cells. While leptin and adiponectin are produced exclusively in adipocytes, TNF-α, IL-6 and MCP-1 are expressed at high levels in macrophages as well. Excess of nutrients such as glucose and free fatty acids induce local production of cyotokines and chemokines in adipocytes, and accumulation of macrophages in adipose tissue. These factors not only trigger an inflammatory response in adipose tissue

itself, but are also released into the circulation, eventually promoting inflammation in other tissues including pancreatic islets. IL-6 in particular is an interesting cytokine; whether IL-6 is deleterious or beneficial is currently a matter of debate. Increased circulating IL-6 concentrations have been found to be associated with the development of obesity and T2D, with adipose tissue being the major source of the cytokine. On the other hand, it has been reported that production and release of IL-6 from skeletal muscle in response to muscle contraction during exercise improves systemic insulin sensitivity. Very recently, elevated levels of circulating IL-6 were shown to increase the plasma concentrations of glucagon-like peptide 1 (GLP-1), an incretin hormone, improving insulin secretion and glucose intolerance. Intriguingly, IL-6 increased the production and secretion of GLP-1 not only from intestinal L-cells, but also from pancreatic α-cells through increased proglucagon and prohormone convertase 1/3 expression. Thus, IL-6 mediates the interaction between insulin-sensitive tissues such as adipose tissue and pancreatic islets, enabling adaption to changes in insulin demand. Leptin is another example. In addition to its role as a satiety factor, leptin is thought to act as a proinflammatory cytokine. It promotes autoimmune diseases including autoimmune diabetes in NOD mice, rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis. In human islets, leptin was shown to induce β-cell apoptosis by increasing release of IL-1β and decreasing IL-1RA. Thus, it has become apparent that cytokines released from insulin target tissues such as adipose tissue and mediate inflammation in the islets.

Islet Inflammation

It is well established that islet inflammation (insulitis) associated with autoimmune processes, which eventually causes β-cell dysfunction and death, is a characteristic of T1D. Production of interferon-γ (IFN-γ) by diabetogenic T-cells has been thought to be an important contributor to the pathogenesis of T1D. In addition, the innate inflammatory cytokines TNF-α, and IL-1β also impact β-cells during the autoimmune process of the disease. An increased expression of class I major histocompatibility complex (MHC) molecules on β-cells, related with increased class I interferon gene expression in some models, is constantly observed as an early event in β-cell autoimmunity in experimental models and in humans. Evidence has also been given in the meeting linking the presentation of autoantigens by class I MHC molecules, their landmark function, to the islet metabolic environment, for example hyperglycaemia. In contrast to T1D, the concept of islet inflammation in T2D is relatively recent. Although obesity and T2D are associated with systemic and chronic inflammation(so-called low-grade inflammation), accumulating evidence indicates that local inflammation in the islets contributes to the pathogenesis of T2D. It was first reported that exposure to high glucose causes IL-1β secretion from β-cells, indicating that a non-autoimmune mechanism can induce proinflammatory cytokine production in the islet cells [7]. To date, two independent studies have shown increased macrophages in the islets of human T2D. In addition, morphological studies revealed that islets of various animal models of T2D, including HFD-fed mice, db/db mice, GK rats and Zucker rats, showed typical features of inflammation such as increased numbers of islet macrophages and expression of cytokines and chemokines. GK rats especially, in which impaired β-cell function rather than insulin resistance is the primary defect in the

pathogenesis of diabetes, show increased expressions of cytokines such as IL-1β, IL-6, and TNF-α, and increased chemokines such as CXCL1, MCP-1 and MIP-1α. This suggests that inflammation likely occurs specifically in the islets of T2D. Macrophages are comprised of two subsets, M1 (proinflammatory) and M2 (anti-inflammatory). In the normal state, islet-resident macrophages are largely of the M2 phenotype, whereas in T2D animal models macrophages with M1 phenotype are relatively increased. This suggests that macrophage polarity is shifted towards M1 in the islets of T2D.

Nutrients such as glucose and free fatty acids induce various cytokines and chemokines from human and rodent islets, which promote migration of monocytes and neutrophils. An attractive model has been proposed [8], according to which free fatty acids and AGE (advanced glycation end-products) bind their receptors (i.e., toll-like receptor [TLR]2 or TLR4 and RAGE, respectively), leading to NF-κB activation and the production of various proinflammatory cytokines and chemokines. In addition, high concentrations of glucose induce NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasomes in both β-cells and macrophages. Human islet amyloid polypeptide (IAPP) also appears to contribute to the induction of IL-β production in the islets through the NLRP3 inflammasome. Interestingly, relatively high concentrations of IL-1β suppress both β-cell proliferation and insulin secretion, whereas relatively low concentrations exert beneficial effects including stimulation of β-cell proliferation and insulin secretion, suggesting that IL-1β plays a dual role in a concentration-dependent manner.

Autophagy in the β-cells is another emerging field. Autophagy is the major intracellular degradation system by which cytosolic materials are delivered to and degraded in the lysosome. Chronic suppression of β-cell autophagy activity causes reduction in both β-cell mass and insulin secretion, suggesting that basal autophagy is important for maintenance of β-cell well-being. As autophagy deficiency is a proinflammatory condition, dysregulation of autophagy in pancreatic islets likely contributes to the development of islet dysfunction by inducing recruitment of inflammatory cells and promoting inflammatory changes.

Novel Techniques and Approaches

Various new methodologies have recently been developed to study inflammation, and were discussed during the meeting. For example, non-invasive imaging of the microvasculature provides a powerful means to monitor inflammation, as alterations in vascular parameters, such as vasoconstriction, vasodilatation and vascular leakage accompany inflammation. In fact, changes in vasculature, vascular swelling, and/or endothelial cell modifications precede insulitis within the islets and in the peri-islet region in streptozotocin-diabetic mice and NOD mice. High-resolution MRI, which utilizes long-circulating magnetic-fluorescent nanoparticles, has recently been developed to image microvascular leakage as an indicator of inflammation, and applied to monitor the initiation and progression of insulitis in NOD mice in real time. An intriguing method for monitoring inflammatory and immune responses in pancreatic islets *in vivo* has been introduced. In this method, pancreatic islets are transplanted into the anterior chamber of the eye, where they engraft on the iris and become vascularized and innervated. As the cornea represents a body-window, this method permits monitoring of the islets at the single-cell level with high-resolution non-invasively and

longitudinally in diabetic as well as normal states. These new techniques are valuable tools for the long-term study of islet inflammation and its chronic effects on islet function.

Recently, it has been proposed that the antigen at the onset of metabolic inflammation might be derived from the environment. In this respect, the intestinal microbiota has drawn particular attention. The human gastrointestinal tract is inhabited by 10^{13-14} microorganisms, more than 10 times the number of cells in the human body. With the advent of the next-generation sequencing technique, a catalogue of genes that belong to the intestinal microbiota has been established. To date, more than 4-5 million non-redundant bacterial genes (metagenome) have been sequenced from the intestinal microbiota of patients. In addition, the discovery of bacterial DNA within host tissues such as liver, adipose tissue and blood, permits the establishment of a tissue microbiota. Metagenome analysis by use of next-generation sequencing should be an important approach to clarification of the relationship between inflammation and metabolic disorders such as obesity and diabetes.

Inflammation as a Potential Therapeutic Target

Interfering With Macrophage Polarization

The complex process of macrophage recruitment in obesity may be a potential therapeutic target. Thus, the M1 macrophages in adipose tissue appear of major importance for the local inflammation. However, macrophages may be polarized to the M2 phenotype, which in contrast to M1 macrophages, reduce inflammation and improve insulin sensitivity. Directing polarization may therefore be a potential target for therapy. During the meeting, it was shown that Trib1, which is an adaptor protein involved in protein degradation of immune-related transcription factors, controls the differentiation of tissue-resident M2-like macrophages and is of key importance for maintenance of adipose tissue and suppression of metabolic disorders. The evidence was based on findings in mice lacking Trib1 in haematopoietic cells, which show severe lipodystrophy with increased lipolysis in response to a HFD. These mice develop high triglyceride levels and insulin resistance, together with increased proinflammatory cytokine production. The mechanisms promoting the M1 phenotype involve PPARγ, IKKβ and JNK. Therefore, inhibition of these signals or directly promoting M2 phenotype could be an interesting therapeutic approach.

Immunostrategies to Treat Insulitis in T1D

The β-cells are targets in autoimmune T1D and insulin is the major autoantigen recognized by T-lymphocytes during progression of the disease. During the meeting it was reviewed that infectious agents, such as enteroviruses, may be triggering this response, although this concept is still awaiting proof. It was furthermore discussed that several novel genes encode T-lymphocytic coactivation molecules involved in cross-talk with β-cells and islet resident immune cells, besides the previously well-described class I and class II MHC molecules. These genes include ICOS and ICOS ligand (B7RP1). The basis for this assumption was revealed in studies in which NOD mice devoid of these molecules deviate their autoimmunity from the islets towards muscles. However, many other genes and molecules are involved as well, for example insulin, proinsulin and GAD. These are important to establish as they may form the basis both for diagnostics and immunotherapy of T1D. Many

strategies have been applied for immunotherapy; unfortunately, although they have been promising in preventing diabetes in the NOD mouse, they have failed to act in human T1D. This is explained by the NOD mouse expressing different MHC molecules than humans and, therefore, that peptides that are potential T-cell targets in humans cannot be tested in mice. This enforces the need for more proper preclinical models to develop such strategies before applying to humans, and during the meeting a novel humanized mouse model for T1D was described. This model (YES) was developed following the generation of mice that are deficient for endogenous class I and/or class II MHC molecules, instead expressing human HLA class I and class II alleles. These mice developed insulitis following a single immunization against a human β-cell line in complete Freund's adjuvant. With the use of this model, there may be a hope to develop immune strategies to treat T1D in humans.

Interfering With Islet Inflammation by Rosiglitazone

During the last decade it has also become evident that there is an islet inflammation component in T2D [9]. Thus, there may exist pathogenic similarities between T1D and T2D. Indeed, using a T-cell immunoblotting assay, it was shown that islet-reactive T-cells occur in T2D, and that this is associated with a more severe β-cell dysfunction compared to other patients with T2D, including antibody-positive patients. This has led to the hypothesis that environmental factors, mainly related to obesity and high-fat feeding, initiate an islet T-cell activation which results in β-cell dysfunction as background for T2D. The overall relative contribution to the T2D β-cell dysfunction of this mechanism vs. mechanisms related to detrimental islet lipid actions and/or amyloid infiltration was discussed at the meeting. The proposed islet inflammation with T-cell activity as an important pathogenic factor has also prompted a study comparing the glucose-lowering actions of rosiglitazone vs. glyburide in patients with 'autoimmune' T2D. It was found that rosiglitazone, which has anti-inflammatory effects, was associated with improved β-cell function along with a significant reduction in circulating levels of the proinflammatory cytokines IL-12 and INF-γ and an increase in adiponectin. Whether the improvement is causally related to suppression of islet inflammation is a provocative hypothesis that needs further studies.

Targeting NLRP3 Inflammasomes

Caspase-1 is known to be activated by NLRP3 inflammasomes, and as caspase-1 in turn activates inflammatory cytokines, such as IL-1β, it has been proposed that the NLRP3 inflammasome may be of importance for initiating inflammation in metabolic diseases, as was reviewed during the meeting. This may also be a novel target for reducing inflammation and is supported by the beneficial effects of IL-1 antagonism by anakinra in T2D. However, novel approaches may also involve this target, such as glyceride, which suppresses IAPP-mediated NLRP3 activation and IL-1β production [10], and interestingly metformin, which induces same effects. Palmitate and ceramide also activate NLRP3 and may be novel targets.

Target Inflammation With the IL-1β —NF-κB Pathway and TNF-α

IL-1β has been shown to be involved in islet glucose toxicity [7]. During the meeting it was also discussed that activated caspase-1 cleaves pro-IL-1β into active IL-1β, which in turn activates NF-κB, resulting in the release of a broad array of cytokines, including IL-1β itself

(vicious cycle of autoinduction), and chemokines such as IL-8. This has suggested that this pathway may be a therapeutic target, and previous proof-of-principle studies targeting IL-1β and its downstream signalling have shown to have beneficial metabolic effects and improve glycaemia in patients with T2D [11]. A large phase III study of IL-1 antagonism with 17 200 patients using an IL-1β antibody is currently ongoing (ClinicalTrials.gov NCT01327846). Also TNF-α has been suggested to be a target, owing to its role in insulin resistance [5]. Several studies using TNF-α antagonism have been performed but as reviewed during the meeting, these have not had optimal design and therefore a state-of-the art clinical study with a TNF-α antagonist is still warranted in T2D.

Interleukin-6

Blocking IL-6 has been examined as therapy in inflammatory disorders like rheumatoid arthritis (tocilizumab). Could IL-6 blockade be a potential therapy also of obesity and T2D? While plausible, this may be problematic considering that IL-6, in addition to being pro-inflammatory, is also potentially beneficial for metabolic diseases. This duality paradox of IL-6 was discussed at the meeting. The hypothesis was put forward that IL-6 on one hand activates the IL-6 receptor, with signalling through gp130 receptors and AMPK activation which stimulates insulin sensitivity, whereas on the other hand as a circulating factor it may form a complex with the soluble form of IL-6 receptor, which in a trans-signalling manner may stimulate the gp130-complex in other cells where insulin resistance is induced. This hypothesis of dual IL-6 action explains the previous confusions in the field: on one hand global IL-6 knock out in mice results in obesity and insulin resistance and infusion of IL-6 in humans increases insulin sensitivity, whereas on the other hand IL-6 from the adipose tissue can induce insulin resistance in the liver. Therefore, blocking IL-6 cannot constitute a simple treatment for metabolic diseases. Indeed, as expected from this perspective, tcoilizumab has resulted in increased body weight and hypertriglyceridaemia in several clinical trials for various inflammatory disorders, mainly rheumatoid arthritis. Studies are now ongoing to dissect the IL-6 mechanisms of action, in view of improving metabolic disorders by selective stimulation of the cell-signalling of IL-6, avoiding its trans-signalling.

Lipoxygenases

During the meeting, dysregulation of the path-ways for two oxidoreductases of arachidonic acid (AA) and other fatty acids (12- and 15-lipoxygenases (LO), 12-LO and 15-LO) was also discussed. Dysregulation of the 12- and 15-LO pathways were shown to play an active role in the inflammatory processes associated with diabetes. An important pathway is the production of 12(S)-hydroxyeicosatetraenoic acids (HETEs), which in obesity are mainly generated by 12/15-LO. As 12(S)-HETE is associated with increased inflammation both systemically and within adipose tissue, cross-talk with the 12- and 15-LO pathways may contribute to the development of diabetes. These pathways are also operative in islets and may be involved in islet dysfunction during cytokine stress in both T1D and T2D, as 12- and 15-LO pathways increase the production of proinflammatory cytokines in islets. Thus, this pathway may be a target for treating the islet dysfunction in diabetes, which is supported by findings of improved glucose homeostasis in mice with genetic deletion of 12- and 15-LO. Furthermore, targeting genetic deletion in adipose tissue and in islets results both in improved glycaemia, suggesting that 12-HETE may be involved in the insulin resistance, as

well as in islet dysfunction in T2D. Generation of specific pharmacologic inhibitors for each of the LO isoforms in humans would now be of great interest; studies are underway to identify effective, small molecular inhibitors [12].

Physical Activity

The relation between physical activity and low-grade inflammation was also discussed. It was thus emphasized that exercise performed at higher intensities with combined aerobic and resistance exercise training is associated with improvements in the inflammatory profile, as evident by changes in key mediators of inflammation, most notably increased circulating levels of IL-6. This has enforced IL-6 as an energy sensor, possibly to preserve fuel availability during exertion by activating hepatic glucose production and fatty acid mobilization from fat, possibly mediated by AMPK. IL-6 may also, in association with exercise, inhibit release of proinflammatory mediators such as TNF-α, and stimulate release of anti-inflammatory mediators such as IL-8 and MIP-1α. Of importance is that IL-6 induces hepatic glucose release only when muscles are activated, which has supported the hypothesis that a circulating factor, probably related to IL-6 receptor, needs to be released together with IL-6 to achieve this effect, reinforcing the trans-signalling mechanism discussed above. The release of IL-6 is dependent on the intensity and duration of exercise; these findings provide a novel mechanism underlying the public health benefits of exercise.

Conclusions and Future Challenges

The 14th IGIS meeting provided an exciting update of the current edge knowledge of inflammatory pathways of relevance for β-cell biology and diabetes pathophysiology and treatment. It was also obvious that there are still many unknown areas within the context of islet inflammation. These need to be understood to further delineate the impact of islet inflammation for the pathophysiology of diabetes, and the potential of targeting inflammation in its treatment. We need to understand both the potential beneficial impact of islet inflammation on β-cell function and the mechanisms behind the destructive impact of inflammation for islet function—we need to understand both the good guy and the bad guy. Novel techniques would thereby be of importance. This IGIS symposium indeed illuminated key aspects for future studies which will enhance our understanding of β-cell function under normal conditions and in diabetes.

Acknowledgments

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