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Amyloid and the Macrophage: It's All About Local Production of IL-1β

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COMMENTARY

For the past 30 years, intense effort has been directed toward understanding the molecular pathways by which cytokines, such as interleukin (IL)-1, inhibit pancreatic β-cell function and cause β-cell death. The landmark findings of the Mandrup-Poulsen and colleagues (1,2) demonstrated that IL-1, derived from conditioned media, reduces glucose-stimulated insulin secretion and causes β-cell damage. IL-1 inhibits glucose-induced insulin secretion by attenuating mitochondrial glucose oxidation to CO_2 and thereby preventing the accumulation of ATP, which is necessary for ATP-sensitive K^+ channel closure, β-cell depolarization, and Ca^{2+}-dependent exocytosis of insulin granules (3−6). Nitric oxide has been identified as the molecular mediator of IL-1−induced inhibition of glucose-induced insulin secretion (5−7). The importance of IL-1−mediated β-cell damage has historically been placed in the context of autoimmune or type 1 diabetes; however, after 30 years of studies focused on the mechanisms by which IL-1 damages β-cells, the role of this cytokine in the development of type 1 diabetes remains to be fully elucidated. For example, administration of IL-1 to rodents results in an attenuation of insulin secretion, but these animals do not develop overt diabetes (8,9). Further, the administration of IL-1 to nonobese diabetic mice has been shown to attenuate disease development (10). In contrast to these studies, overexpression of the enzyme responsible for generating nitric oxide (inducible form of nitric oxide synthase) under the control of the rat insulin promoter results in the development of diabetes that occurs in a nitric oxide−dependent manner (11). These studies briefly illustrate the many complexities related to elucidating the role of IL-1 in the development of type 1 diabetes.

The local generation of IL-1 in islets has also been implicated in the development of β-cell dysfunction under conditions that are more closely associated with β-cell failure during the development of type 2 diabetes (12,13). Long-term culture of islets in the presence of elevated levels of glucose (20–30 mmol/L) results in the loss of β-cell function and mass that has been associated with the local production of IL-1 in islets (13). These studies suggested that IL-1, produced locally in islets, perhaps by β-cells themselves, could act in an autocrine/paracrine manner to mediate β-cell damage. In this issue, Westwell-Roper et al. (14) have examined the role of amyloid polypeptide in stimulating the local generation of IL-1 in islets. The authors show that treatment with human islet amyloid polypeptide (IAPP) results in the accumulation of IL-1β mRNA in islets in a manner dependent on the presence of resident macrophages. IL-1β, as well as the IL-1β−converting enzyme (ICE or caspase 1) responsible for the processing of IL-1β to its mature biologically active form, appears to be produced by resident islet macrophages following IAPP treatment. Other islet endocrine and nonendocrine cells do not express either IL-1β or ICE following this treatment, but they do express other inflammatory mediators such as chemokines. Using transgenic mice expressing human IAPP in β-cells, the authors show that high-fat diet feeding results in impaired glucose tolerance that is associated with the expression of IL-1β mRNA by macrophages. Liposome-mediated macrophage depletion restores normal glucose tolerance in these mice and decreases islet IL-1 mRNA accumulation. These findings support tissue macrophages as the cellular source of IL-1β in this model of islet inflammation. These studies are also consistent with the ability of amyloid to activate the NLRP3 inflammasome (15). Perhaps the most interesting finding in this study is that macrophage depletion, which normalizes glucose tolerance in high-fat diet−fed mice expressing human IAPP in β-cells, is also associated with an increase in islet amyloid accumulation in islets. This result begins to address questions regarding whether amyloid accumulation is a cause, consequence, or marker of β-cell failure. One potential interpretation is that resident macrophages function to remove amyloid from

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islets as it accumulates; however, a negative outcome of this process is that macrophages are activated and produce IL-1 locally in islets producing amyloid. By removing the resident macrophage population, local cytokine generation is attenuate; however, so is the removal of amyloid, thereby leading to elevated levels of amyloid accumulation in islets. While unknown, additional studies that examine the effects of prolonged fat feeding of macrophage-depleted human IAPP–expressing mice on macrophage-independent amyloid-mediated β-cell damage should address whether amyloid accumulation is toxic to β-cells independent of macrophage activation.

The local generation of cytokines in islets was originally proposed by Dr. Paul Lacy (16,17) as a mechanism that could lead to β-cell damage and potentially the induction of autoimmunity directed against β-cells. In support of this proposal, we showed using rat, mouse, and human islets that antibody neutralization of IL-1β and the inhibition of IL-1 signaling using the IL-1 receptor antagonist protein attenuates the damage induced by treating islets with tumor necrosis factor (TNF) + LPS (rat) and TNF + LPS + interferon-γ (IFN-γ) (mouse and human) (18–20). In addition, macrophage depletion using low temperature culture of islets for 7 days at 24°C (conditions established by Lacy and Finke [17]) was used to demonstrate that the 10–15 resident macrophages found in an islet could produce IL-1β to levels sufficient to cause β-cell damage. In these previous studies, signaling pathways activated by IL-1 were used as an index of the local generation of IL-1 in islets, as reagents lack the sensitivity to detect or directly quantify IL-1. Consistent with these previous studies, Westwell-Roper et al. were also not able to directly measure IL-1 in human IAPP-treated islets.

In conclusion, the findings by Westwell-Roper et al. (14) provide evidence using a third model system that it is possible to produce IL-1β locally in islets to levels that cause β-cell damage. We first showed that classical inflammatory activators of macrophages, TNF, IFN-γ, and LPS are capable of activating resident islet macrophages to produce IL-1β in rodent and human islets (18–20). Westwell-Roper et al. now report that human IAPP stimulates macrophages to produce IL-1β and provide evidence that macrophage IL-1β production in islets mediate the toxic effects of human IAPP on β-cell function (Fig. 1). Elevated levels of glucose have also been shown to impair β-cell function by a mechanism associated with the intraislet production of IL-1, and β-cell may be the source of this cytokine (12,13). These studies suggest that the local production of IL-1 in islets may be a common mechanism associated with the loss of β-cell function in the context of type 1 and 2 diabetes. With new hypotheses come new questions. At the molecular level, how does IAPP and high glucose stimulate IL-1β expression? Specifically, what are the transcription factors and signaling cascades required for the transcriptional activation of IL-1β in macrophages? How is ICE/caspase 1 activated or regulated? Does glucose activate the inflammasome in β-cells and or macrophages? Perhaps the most relevant question is whether the local generation of IL-1 in islets by resident macrophages is the mechanism by which amyloid accumulation causes the loss of functional β-cell mass? The evidence presented in the study by Westwell-Roper et al. (14) supports this hypothesis, as macrophage depletion attenuates the glucose intolerance observed in high-fat diet–fed mice expressing human IAPP in β-cells. This improvement in glucose intolerance is also associated with the enhanced accumulation of amyloid in islets, suggesting that the accumulation of amyloid may not be toxic, but that toxicity is due to macrophage activation as these phagocytes attempt to remove this accumulated protein from the islet.

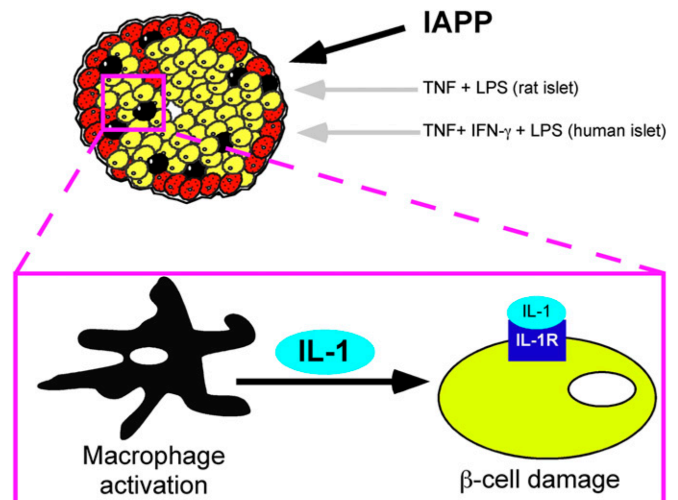

Figure 1—Intraislet macrophage activation and β-cell damage. Westwell-Roper et al. (14) provide evidence that IAPP damages β-cells (yellow) by a mechanism that is associated with resident islet macrophage (black) activation and the local release of IL-1β within islets to levels sufficient to damage β-cells. This pathway is consistent with previous studies showing that macrophage activators (TNF + LPS, rat; TNF + LPS + IFN-γ, mouse and human) cause β-cell damage through the local generation of IL-1 in islets (18–20). Overall, these studies begin to define general mechanisms by which tissue macrophage activation may contribute to the loss of β-cell function under conditions associated with type 1 and 2 diabetes.

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