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Concise Review: New Insights Into the Role of Macrophages in β-Cell Proliferation

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ABSTRACT

Diabetes mellitus can potentially be treated with islet transplantation, but additional sources of β cells are necessary to overcome the short supply of donor pancreases. Although controversy still exists, it is generally believed that the postnatal expansion of the β-cell mass is mainly through pre-existing β-cell replication. Thus, understanding the molecular mechanisms underlying the regulation of β-cell proliferation might lead to clinical strategies for increasing β-cell numbers, both in vitro and in vivo. Macrophages have a well-recognized role in the development of insulitis as part of the pathogenesis of type 1 diabetes. However, a potential role for macrophage polarization, triggered by specific environmental stimuli, in promoting β-cell proliferation has only recently been appreciated. In the present review, we discuss several independent studies, using different regeneration models, that demonstrate a substantial inductive role for macrophages in β-cell proliferation. Additional dissection of the involved cell-cell crosstalk through specific signal transduction pathways is expected to improve our understanding of β-cell proliferation and might facilitate the current β-cell replacement therapy. STEM CELLS TRANSLATIONAL MEDICINE 2015;4:1–4

SIGNIFICANCE

New independent findings from different β-cell regeneration models, contributed by different research groups, have provided compelling evidence to highlight a previously unappreciated role for macrophages in β-cell proliferation. Additional dissection of the underlying mechanisms and cell-cell crosstalk might shed new light on strategies to increase the functional β-cell mass in vivo and on β-cell replacement therapies.

INTRODUCTION

Diabetes mellitus can potentially be treated with islet transplantation. Nevertheless, the short supply of donor pancreases constitutes a formidable obstacle to widespread clinical applications [1–5]. Although great efforts have been made to identify, isolate, and purify β-cell progenitors in the adult pancreas [6–13], mounting evidence suggests that β-cell neogenesis does not significantly contribute to the functional β-cell mass in the adult pancreas [14–28]. Most reports of β-cell transdifferentiation required genetic manipulations [29, 30].

Thus, increasing attention has been drawn to the induction of β-cell replication in vitro and in vivo, because mature β cells have a very slow proliferation rate [4] that declines further with age [31–36]. Macrophages have a well-recognized role in the development of insulitis as part of the pathogenesis of type 1 diabetes (T1D). However, a potential role for macrophage polarization, triggered by specific environmental stimuli, in promoting β-cell proliferation has only recently been appreciated [37–40]. In the present review, we discuss several independent studies using different regeneration models to demonstrate a substantial role for macrophages in β-cell proliferation. Additional dissection of the involved cell-cell crosstalk through specific signal transduction pathways is expected to improve our understanding of β-cell proliferation and might facilitate the current β-cell replacement therapy.

MACROPHAGE BIOLOGY

Macrophages are a type of white blood cell that engulf and digest cellular debris, foreign substances, microbes, and cancer cells in a process called phagocytosis. In addition to the macrophages that display this classic phenotype, designated M1 macrophages, another macrophage subtype, designated M2, is entirely different. The degree to which a given macrophage bears M1 or M2 characteristics is termed "polarization." The M1 macrophages are induced by T helper 1 (Th1)

cell-derived interferon-γ and microbial products and respond to microbial infection with an enhanced phagocytic capability through the expression of inducible nitric oxide synthase and the secretion of proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-12 (IL-12), IL-1β, and IL-23, and toxic mediators, such as reactive oxygen species and nitric oxide [41–44]. M2 macrophages are induced during Th2-type responses through stimulation with IL-4/IL-13 and are responsible for wound healing and tissue remodeling functions [41–44]. Specifically, M2 macrophages are known to secrete a wide range of chemokines,enzymes, and growth factors to promote neovascularization, fibrosis, and tissue repair [41–44]. The M1/M2 polarization of tissue-destructive versus tissue-reparative macrophages is now regarded as a simplified categorization of a complex cell lineage, and more and more macrophage phenotypes in between the two polar opposites are being described [41–44].

MACROPHAGES IN T1D AND TYPE 2 DIABETES

It has been shown that islets do contain resident macrophages [45, 46]. Macrophages play an essential role in the development of T1D. The inactivation of macrophages in nonobese diabetic (NOD) mice prevents the occurrence of diabetes [47], because an environment with macrophages is necessary for differentiation of anti-β cell-cytotoxic T cells [48]. M1 macrophages, along with a subpopulation of CD4+ T lymphocytes that secrete high levels of IL-17 (Th17 cells) and CD8+ cytotoxic T cells, are together considered to be the major cell types that promote the development of T1D [49–52].

Obesity induces insulin resistance, which is a predisposing factor for the development of type 2 diabetes (T2D). Insulin resistance is promoted by a transition in macrophage polarization from the M2 activation state, maintained by STAT6 and peroxisome proliferator-activated receptors, to a classic M1 activation state driven by nuclear factor-κB (NF-κB), activator protein 1, and other related factors [53–56]. Previous studies in T2D have shown that M1 macrophages are associated with increasing inflammation, obesity, and insulin resistance, and M2 macrophages are associated with a reduction in both obesity and insulin resistance [49, 50]. Thus, macrophages play a nonredundant role in the pathogenesis of both T1D and T2D [57].

Very recently, epigenetic modifications in spontaneous autoimmune diseases have been identified. In line with this concept, a small-molecule inhibitor of a family of bromodomain-containing transcriptional regulators was recently shown to induce macrophages to adopt an anti-inflammatory phenotype, which suppressed the development of T1D in NOD mice in an NF-κB-dependent manner [58]. In this model, islet inflammation was inhibited, and β cell regeneration occurred [58].

MACROPHAGES IN β-CELL PROLIFERATION

Macrophages, especially M2 macrophages, have been shown to secret a variety of trophic factors, including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor-β (TGF-β), angiopoietins, and Wnts, to regulate development, tissue remodeling, and tissue repair. However, evidence of their role in promoting β-cell proliferation has only been reported recently [37–40].
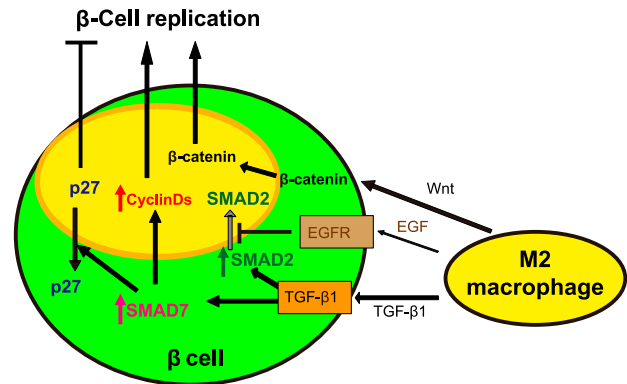

Figure 1. Signaling pathways through which macrophages regulate β-cell replication. M2 macrophages, not only release TGF-β1 to directly induce upregulation of SMAD7 in β cells, but also release EGF to activate EGFR signaling that inhibits TGF-β1-activated SMAD2 nuclear translocation, resulting in inhibition of TGF-β receptor signaling. SMAD7 promotes β-cell proliferation by increasing CyclinD1 and CyclinD2 and by inducing nuclear exclusion of p27. M2 macrophages also secrete Wnt ligands to activate the Wnt signaling pathway, which induces nuclear translocation and retention of β-catenin to promote β-cell replication. Abbreviations: EGF, epidermal growth factor; EGFR, EGF receptor; TGF-β1, transforming growth factor-β1.

First, in a regulatable β cell-specific VEGF overexpression mouse model, which results in significant β cell loss, withdrawal of VEGF overexpression led to β-cell proliferation, replenishing the reduced β-cell mass [39]. In this model, β-cell proliferation was found to depend on the recruitment of bone marrow-derived macrophages and their subsequent crosstalk with islet endothelial cells. Trophic factors released locally by recruited macrophages were proposed as a trigger for β-cell proliferation [39].

In another β cell regeneration model, in which mesenchymal stem cells were transplanted into the streptozotocin-treated mouse pancreas, significant β-cell proliferation was detected, contributing to the regeneration of functional β-cell mass [40]. In this model, recruited macrophages were found to be required for the β-cell proliferation to occur. In addition, Wnt signaling was proposed to be responsible for the cross-talk between M2 macrophages and β cells to induce β-cell proliferation [40] (Fig. 1).

In a β−cell injury/regeneration model, triggered by diphtheria toxin receptor-mediated conditional targeted cell death [59], β-cell regeneration was found to be attributable to the proliferation of surviving β cells, which was dependent on recruited M2 macrophages, involving the Wnt signaling pathway [38] (Fig. 1).

In addition to these three independent studies, we used another model of enhanced β-cell proliferation, partial pancreatic ductal ligation (PDL) [37]. We have previously compared two experimental models of β-cell proliferation, partial pancreatectomy (PPX) and PDL [19, 20, 60]. β-Cell proliferation after PPX is robust, presumably resulting from an increased workload demand on the residual β cells after surgical removal of a significant amount of the functional β-cell mass. In contrast, inflammation appears to be the major trigger for β-cell proliferation after PDL [20]. In line with this view, tissue injury in the PDL pancreas is accompanied by substantial infiltration of inflammatory cells, which appears to create a proliferation niche for β cells, such as has been seen in other regeneration models [38–40]. With the help of a recently

developed intraductal infusion system [18, 61, 62], we found that M2 macrophages, not only release TGF-β1 to directly induce upregulation of SMAD7 in β-cells, but also release EGF to activate EGF receptor signaling, which inhibits TGF-β1-stimulated SMAD2 nuclear translocation, resulting in inhibition of TGF-β receptor signaling. SMAD7 promotes β-cell proliferation by increasing CyclinD1 and CyclinD2 and by inducing nuclear exclusion of p27 [37] (Fig. 1).

FUTURE DIRECTIONS

From these recent studies, we hypothesize that a proliferation niche is needed for efficient β-cell proliferation and that macrophages might play a pivotal role in establishing this niche [37–40, 63]. β-Cell proliferation might involve the coordination of multiple processes, such as the detachment of cell-cell contacts, modulation of extracellular matrix, and release of growth factors, both locally and systemically [64]. Macrophages, with their high plasticity and phenotypic diversity, appear to play a critical role in β-cell proliferation by creating crosstalk among different cell types, including β cells, non-β endocrine cells, endothelial cells, mesenchymal cells, and other circulation-derived blood cells (Fig. 2). Additional elucidation of this crosstalk might substantially enhance our understanding of β-cell proliferation.

Because acinar cells have been shown to reprogram into insulin-producing cells by soluble growth factors [13] or genetic alterations [29, 30], it would be interesting to examine the role of macrophages in these models. Moreover, although a role for M2 macrophages in promoting β-cell proliferation in mice has been well described, any similar role for M2 macrophages in human β-cell proliferation has not been examined. A coculture experiment could potentially be applied to address this point.

CONCLUSION

Taken together, new independent findings from different β-cell regeneration models, contributed by different research groups, have provided compelling evidence to highlight a previously unappreciated role for macrophages in β-cell proliferation. Additional dissection of the underlying mechanisms and cell-cell crosstalk could shed new light on strategies to increase the functional β-cell mass in vivo and on β-cell replacement therapies.
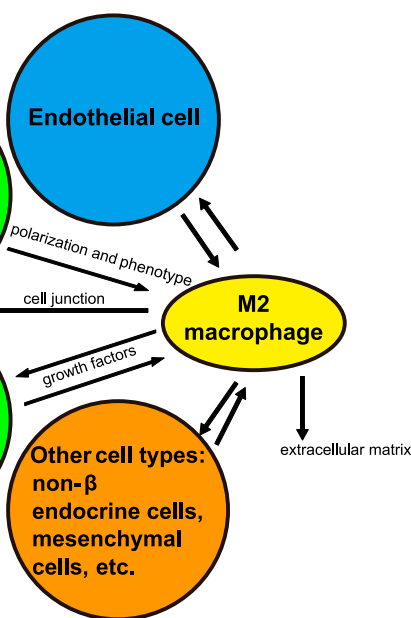

Figure 2. M2 macrophages play an essential role in creating a proliferation niche for β-cell proliferation. β-Cell proliferation could involve the coordination of multiple processes, such as detachment of cell-cell contacts, modulation of extracellular matrix, and release of growth factors, both locally and systemically. Macrophages, with their high plasticity and phenotypic diversity, appear to be play a critical role in β-cell proliferation by creating crosstalk among different cell types, including β cells, non-β endocrine cells, endothelial cells, mesenchymal cells, and other circulation-derived blood cells.

AUTHOR CONTRIBUTIONS

X.X. and G.K.G: manuscript writing, final approval of manuscript.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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