

β -Cells Step Up in Controlling the Autoimmune Response

Paolo Fiorina

During the autoimmune response, when autoantigens are presented in addition to signals induced upon T-cell receptor engagement, T-cell activation requires the engagement of their costimulatory receptors by ligands on antigen-presenting cells (APCs) (1–3). The number of known costimulatory receptor/ligand pairs has grown significantly over the last decade (2,3), and it is now clear that costimulatory receptors can deliver signals either enhancing or inhibiting T-cell activation, thus determining the fate of the immune response (4). Classically, costimulatory molecule ligands were found on major histocompatibility complex (MHC) class II-expressing cells (so-called “professional APCs”), yet new data have demonstrated parenchymal expression of costimulatory ligands (e.g., in pancreatic islets) (5), thus providing a second level of immune response regulation in situ (6).

Many players appear to have a role in the interaction between the immune system and β -cells: the classical costimulatory molecule B7.1 (or CD80), a receptor expressed by APCs and parenchymal cells that engages the T-cell ligand CD28 and thus activates the immune system (9); programmed death receptor-1 (PD-1), an inhibitory receptor induced on activated T-, B-, and myeloid cells; and finally, the ligand for PD-1 (PD-L1 or B7-H1), which is constitutively expressed in parenchymal organs (10–12). Triggering negative signals through the interaction of PD-1 and PD-L1 could inhibit T-cell activation as well as the migration of T-cells into peripheral tissues (10–13). In NOD mice, islet PD-L1 expression has been shown to protect syngeneic transplanted islets (NOD.SCID into hyperglycemic NOD) against recurrence of diabetes (5). While PD-L1 inhibits pathogenic self-reactive CD4 T-cell-mediated tissue destruction and effector cytokine production in NOD mice, no data are available thus far in the context of nonautoimmune strains (e.g., C57BL/6). Moreover, no data are currently available on the inhibitory effect of PD-L1 on CD8 T-cells, which ostensibly are more sensitive than CD4 T-cells to the inhibition induced by PD-1/PD-L1 engagement (14).

In this issue of *Diabetes*, Rajasalu et al. (15) investigate the interaction of costimulatory molecules (on β -cells) and their ligands (on CD8 T-cells) in a relatively new model of experimental autoimmune diabetes (EAD). The authors immunized C57BL/6 RIP-B7.1 mice (which constitutively

expressed B7.1 under the control of the insulin promoter) with a plasmid-based DNA vaccine expressing an autoantigen (preproinsulin [ppins]) to prime insulin-specific CD8 T-cells (16), inducing EAD in 90% of mice. Anti-CD8, but not anti-CD4, antibody inhibited diabetes progression, establishing that the effector phase of EAD depends on diabetogenic CD8 T-cells. The role of CD8 T-cells was then confirmed by pathological analysis, which revealed a large number of infiltrating CD8 T-cells in the pancreatic islets, as well as by *ex vivo* assays, which demonstrate marked production of γ -interferon (IFN- γ) from CD8 T-cells isolated from ppins-primed mice when rechallenged with autoantigen (17). When immunizing WT-B6 mice, EAD incidence was relatively low, indicating the necessary role of costimulatory/inhibitory signals in sensitizing β -cells for CD8 T-cell-mediated destruction.

To strengthen their hypothesis, a series of adoptive transfer experiments were then performed. The authors show that CD8 T-cells primed in WT-B6 mice can efficiently destroy β -cells *in vivo* in an IFN- γ -dependent manner, as suggested by the onset of diabetes in sublethally irradiated RIP-B7.1 mice once splenic CD8 T-cells were adoptively transferred from primed WT-B6 mice. Since B7.1 is not expressed normally on islet β -cells and PD-1/PD-L1 ligation can inhibit the B7.1/CD28 costimulatory pathway, the authors then investigated whether loss of the inhibitory PD-1/PD-L1 signal has similar effects to B7.1 constitutive knock-in. The authors thus abrogated PD-L1 signaling either using a blocking monoclonal antibody or through gene targeting (by using PD-L1^{-/-} mice), rendering β -cells susceptible to CD8 T-cell-mediated destruction and resulting in severe hyperglycemia.

By multiple bone marrow transplantation and chimeric generation, the authors discovered that either the selective deficiency of PD-L1 on β -cells or the deficiency of PD-1 on CD8 T-cells triggered CD8 T-cell-mediated EAD, suggesting the importance of signal balance between the B7.1/CD28 and PD-1/PD-L1 pathways in maintaining tolerance toward β -cells in the periphery.

The important take-home message and the article's strength is the description of how β -cell inhibitory signals and T-cells are attuned to maintain tolerance toward autoantigen and the number of events that can interfere with costimulatory cascades to actually break this tolerance. For instance, the priming of the immune system, the upregulation of costimulatory molecules on β -cells, or the disruption of inhibitory signals on β -cells or in the immune system may all precipitate diabetes. Few weaknesses can be highlighted in this research; however: 1) β -cells do not normally express B7.1, but events leading to B7.1 upregulation (e.g., viruses, stresses, IFN- γ production, etc.) may trigger autoimmune diabetes; 2) the proposed model is not yet fully studied, and NOD mice remain the gold standard for studies on autoimmune diabetes; and 3) other factors have been shown to expand autoreactive T-cells once transgenically overexpressed on β -cells (e.g., heat shock

From the Transplantation Research Center, Nephrology Division, Children's Hospital of Boston, Harvard Medical School, Boston, Massachusetts, and the San Raffaele Scientific Institute, Milan, Italy.

Corresponding author: Paolo Fiorina, paolo.fiorina@childrens.harvard.edu.

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See accompanying article, p. 1966.

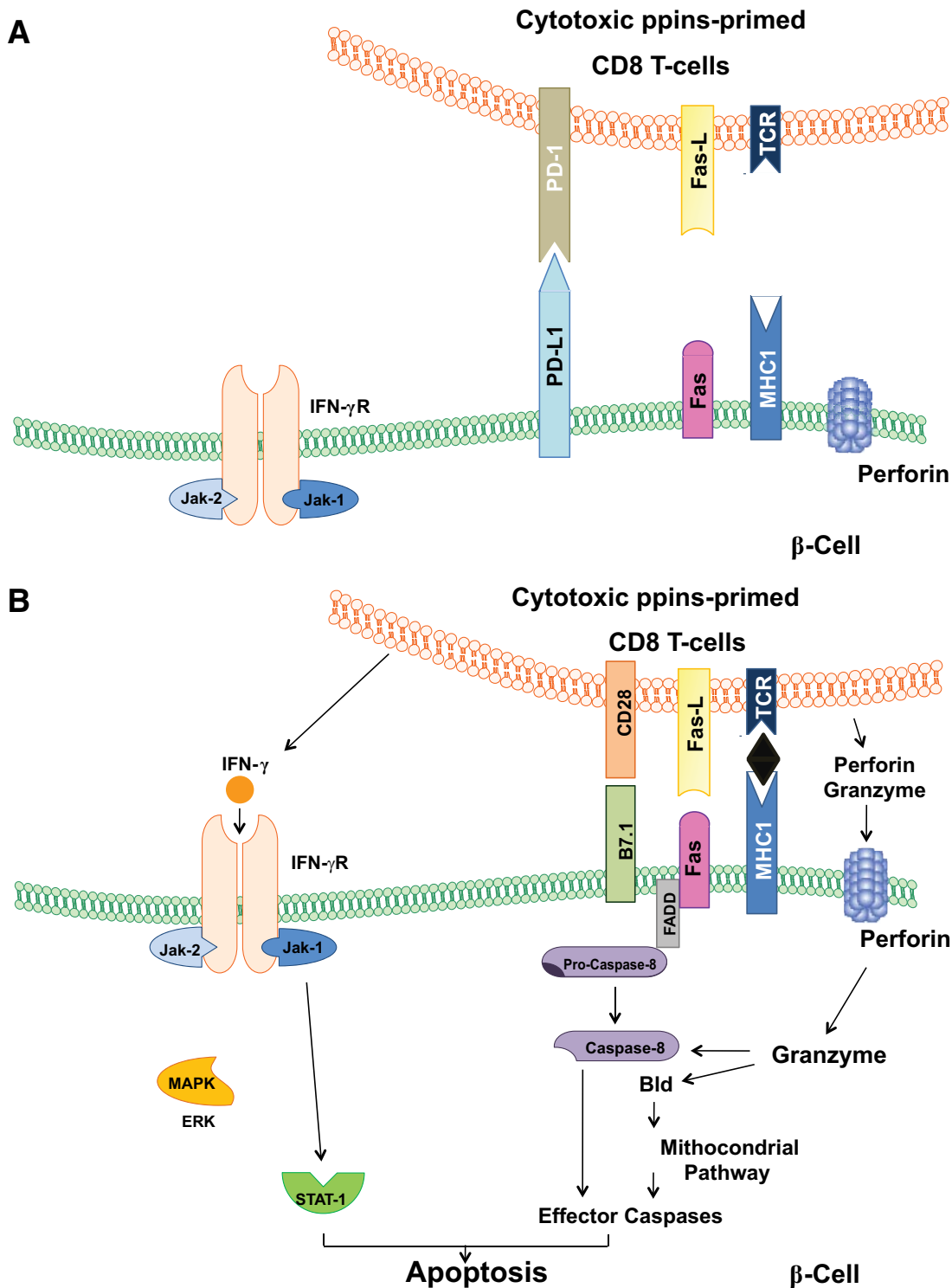


FIG. 1. Model proposal of a more proactive β-cell role in autoimmune response. A resting immune system is maintained by the delivery of inhibitory signals to T-cells through negative costimulatory molecules expressed on β-cells (A). B7.1 up-regulation promotes engagement of CD8 T-cells with β-cells, thus triggering experimental autoimmune diabetes (B). In the absence of B7.1 on β-cells, the deletion (or downregulation) of PD-1 on CD8 T-cells or of PD-L1 on β-cells may trigger experimental autoimmune diabetes (C). (A high-quality digital representation of this figure is available in the online issue.)

protein 70), so that this expansion may not be exclusive to the proposed pathway (18).

This new acquired knowledge may change the view of how β-cells and the immune system interact in autoimmune diabetes (Fig. 1A–C). Therefore, it is certainly time to revisit examination of β-cell function during the autoimmune response, thereby assigning β-cells a more proactive

role in controlling autoimmunity rather than viewing them as bystanders waiting to be destroyed by autoreactive CD4/CD8 T-cells (Fig. 1A–C) (7,8). Future directions of this work may lead us to rethink β-cells as active players and as potential immunomodulatory tools in the onset and therapy of autoimmune diabetes, respectively. Possible therapeutic applications to halt the autoimmune

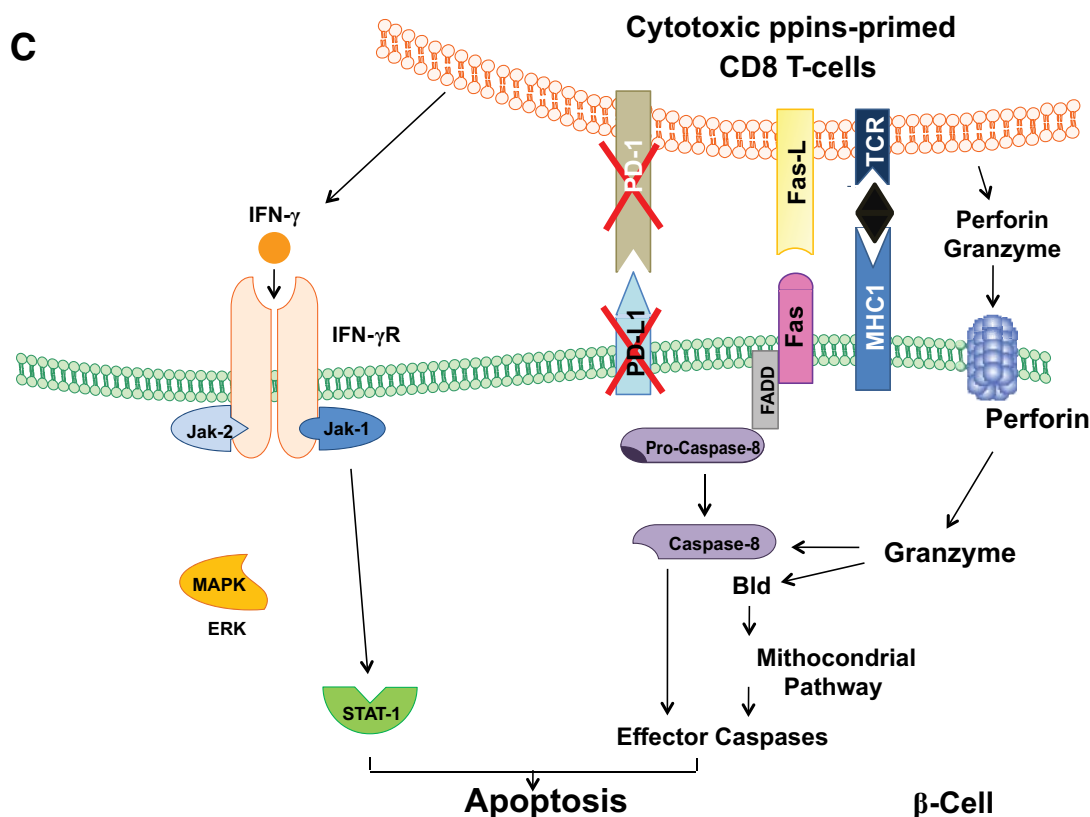


FIG. 1. Continued.

response include the engineering of β -cells overexpressing inhibitory costimulatory signals (PD-L1) in the islet transplantation setting, the use of small molecules able to signal through inhibitory costimulatory receptors, or the discovery of new agents capable of downregulating β -cell sensitization (in the type 1 diabetes prevention setting). β -Cells appear to step up and control the autoimmune response, thus being more responsible for their fate and acting as gatekeepers of the insulinitic process, and this proposed model may be used to cure or prevent type 1 diabetes.

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