The CD38-Cyclic ADP-Ribose Signal System in Pancreatic β-Cells
The Discovery and Biological Significance of a Novel Signal System in Mammalian Cells

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HISTORICAL BACKGROUND

In the early 1980's, we showed that maintenance of the cellular NAD⁺ level in β-cells of the islets of Langerhans is essential for the synthesis and secretion of insulin, and proposed a unifying model for the action of the diabetogenic agents alloxan and streptozotocin on pancreatic β-cells (Figure 1) [1-10]. Central to the model are breaks in the nuclear DNA of β-cells, resulting from either an accumulation of free radicals or from the alkylation of DNA. These breaks induce DNA repair involving the activation of poly(ADP-ribose) synthetase/polymerase (PARP), which uses cellular NAD⁺ as a substrate. As a result, the intracellular levels of NAD⁺ fall dramatically, which leads to energy depletion and the inhibition of cellular functions including insulin synthesis and secretion, and thus the β-cell ultimately dies.

If alloxan- and streptozotocin-induced β-cell damage is provoked by the mechanism shown in Figure 1, then, theoretically, it can be prevented by inhibiting the serial reactions that originate from the DNA strand breaks. One possibility would be by scavenging the radicals with such radical scavengers as superoxide dismutase and desferrioxamine. Another would be by inhibiting PARP with specific inhibitors such as nicotinamide and 3-aminobenzamide. In fact, the alloxan-induced and streptozotocin-induced NAD⁺ depletions were prevented by PARP inhibitors such as nicotinamide and picolinamide [11-14]. The alloxan-induced and streptozotocin-induced decreases in insulin synthesis and secretion were also prevented by...
superoxide dismutase and catalase as well as by PARP inhibitors in a dose-dependent manner [13, 15].

**Figure 1.** A unifying model for β-cell damage and its prevention in toxin- or virus-induced and immune diabetes (The OKAMOTO model) (adapted from [3-10]). The β-cell damage is theoretically preventable through inhibition of the serial reactions, as indicated by shaded arrows. One method is by inhibiting abnormal immune reactions with immunomodulators such as cyclosporin, linomide, and OK-432. Others include scavenging the radicals, which break DNA, by superoxide dismutase and other radical scavengers, and inhibiting the PARP by specific inhibitors such as nicotinamide, 3-aminobenzamide and picolinamide to prevent the decrease in the NAD⁺ level. IL-1β, interleukin-1β. NO⁺, nitric oxide. O₂⁺, superoxide.

Interest in the model for the mechanism of action of alloxan and streptozotocin has been heightened by its possible extension to the effects of viruses and inflammation, especially immune-mediated events, on β-cells [1-10]. Thus, since the early 1980s, we have proposed that, although type I (insulin-dependent) diabetes can be caused by many different agents such as immunologic abnormalities, inflammatory tissue damage, and β-cytotoxic chemical substances, the final pathway for the toxic agents is the same (Figure 1). Therefore, type I (insulin-dependent) diabetes is theoretically preventable by suppressing immune reactions, scavenging free radicals, and inhibiting PARP.

Concerning nitric oxide (see Figure 1), we produced transgenic mice expressing nitric oxide synthase constitutively in pancreatic β-cells and found that the β-cell mass was markedly reduced and that the transgenic mice developed severe diabetes [16]. In 1999, using PARP deficient mice, three independent groups in Germany, Japan, and the U.S. provided irrefutable support for the model shown in Figure 1: PARP deficient mice