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Poly(ADP-ribose)polymerase inhibition as a novel therapeutic approach against intraepidermal nerve fiber loss and neuropathic pain associated with advanced diabetic neuropathy:

A commentary on PARP INHIBITION OR GENE DEFICIENCY COUNTERACT INTRAEPIDERMAL NERVE FIBER LOSS AND NEUROPATHIC PAIN IN ADVANCED DIABETIC NEUROPATHY

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Diabetes mellitus is the most common cause of neuropathy which is estimated to affect 20-30 million people worldwide [1]. Clinical trials in subjects with Type 1 and Type 2 diabetes indicate that intensive therapy and improved blood glucose control reduce incidence and slow progression of diabetic neuropathy, thus implicating hyperglycemia as a leading causative factor [1]. Numerous mechanisms have been proposed to link chronic hyperglycemia to diabetic cardiovascular complications, nephropathy, and impairments in motor and sensory nerve functions among other manifestations of peripheral diabetic neuropathy (PDN, reviewed in [2-4]). It has been hypothesized, that hyperglycemia-induced overproduction of superoxide by mitochondrial electron-transport chain activates multiple pathways of cell injury (e.g. protein kinase C (PKC), advanced glycosylation end product formation (AGE), hexosamine and polyol pathway fluxes, and nuclear factor-κB signaling, among many others) by inhibiting glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity in endothelial cells [3]. The hyperglycemia-induced enhanced mitochondrial superoxide and iNOS-derived nitric oxide (NO) formation favor the generation of reactive oxidant peroxynitrite through diffusion-controlled reaction in the vascular endothelium and smooth muscle [4]. Peroxynitrite interacts with lipids, DNA, and proteins via direct oxidative reactions or via indirect, radical-mediated mechanisms, triggering cellular responses ranging from subtle modulations of cell signaling to overwhelming oxidative injury [4]. Oxidative DNA damage also leads to the over-activation of the nuclear enzyme poly(ADP-ribose) polymerase-1 (PARP; the most abundant isoform of the PARP enzyme family), which depletes its substrate NAD(+), slowing the rate of glycolysis, electron transport and ATP formation on one hand [5]. On the other hand, it inhibits GAPDH by poly-ADP-ribosylation and may also be involved in the regulation of various important inflammatory pathways [5]. These processes lead to acute endothelial dysfunction in diabetic vessels both in experimental animals [6-10] and in humans [11], a concept pioneered by Dr. Szabo's group (reviewed in [5]). According to the vascular concept of diabetic neuropathy [12], endothelial dysfunction in *vasa nervorum* (small vessels supplying nerves) results in decrease in nerve blood flow and endoneurial hypoxia, eventually culminating into functional and morphological changes in the diabetic nerves. The neurochemical concept of PDN suggests the importance of similar mechanisms in the *neural* elements (e.g. Schwann cells and neurons).

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Indeed, numerous recent studies established that oxidative-nitrosative stress and interrelated downstream pathways play an important role in the pathogenesis of various diabetic complications, including cardiovascular complications, retinopathy, nephropathy, and PDN (reviewed in [2-5]). However, the role of oxidative damage in diabetic sensory neuropathy, especially in its advanced stage, is remarkably understudied. One of the strengths of the paper by Obrosova et al. [13] is that, using a comprehensive approach with assessment of multiple variables of sensory function (thermal algesia by paw withdrawal and tail flick tests, mechanical algesia by rigid von Frey filament and Randall-Selitto tests, tactile allodynia) as well as spontaneous diabetic neuropathic pain (formalin pain test), the authors were able to clearly dissect the key role of PARP activation in neuropathic pain and sensory loss characteristic for advanced diabetic neuropathy. To achieve their goal they have utilized dual approach of PARP-1 suppression by genetic deletion in mice or pharmacological inhibition with the PARP inhibitor GPI-15427 in rats [13]. Another attractive feature of the current study is that it is not limited by functional measurements, but extends beyond that i.e. to evaluation of the role for PARP activation in small sensory nerve fiber degeneration [13]. Until recently, small-caliber nerve fiber degeneration has not been evaluated in either human subjects with diabetes mellitus or in animal models due to a lack of objective measures. Novel techniques such as corneal confocal microscopy (a rapid, reiterative, non-invasive in vivo imaging technique for quantitative evaluation of degeneration and regeneration of corneal nerve fibers [14] and skin biopsy with visualization and quantitation of epidermal nerve fibers [15], hold enormous potential for a better understanding of the mechanisms underlying small nerve fiber degeneration, a phenomenon which may ultimately lead to a complete loss of sensory function and is a major cause of foot amputation. Recent studies revealed that subjects with both Type 1 and Type 2 diabetes, but not those with metabolic syndrome, display epidermal nerve fiber loss [15,16]. Dr. Obrosova's lab was one of the pioneers in evaluation of the effects of pharmacological interventions on this variable of small sensory nerve fiber degeneration in rat and mouse models of Type 1 and Type 2 diabetes. She and co-authors [17,18] have shown that epidermal nerve fiber loss is clearly manifest in streptozotocin-diabetic mice with Type 1 diabetes and leptin-deficient ob/ob mice with Type 2 diabetes, and that small sensory nerve fiber degeneration can be prevented by pathogenetic treatments in these animal models. The current study provides evidence of small sensory nerve fiber degeneration in STZ-diabetic rats with advanced diabetic neuropathy, consistent with previous report by Toth et al [19]. Furthermore, the data in both STZ-diabetic rats treated with a PARP inhibitor and STZ-diabetic PARP-deficient mice clearly and for the first time dissect a key role of PARP activation in this phenomenon present in both experimental and clinical diabetic neuropathy. The findings promote a better understanding of the role for PARP activation in peripheral diabetic neuropathy, and provide rationale for development of orally active and potent PARP inhibitors and PARP inhibitor containing combination therapies for prevention and treatment of this devastating complication of diabetes mellitus.

Since the role for the enzyme of poly(ADP-ribose) catabolism, poly (ADP-ribose) glycohydrolase (PARG), in diabetic complications and, in particular, diabetic neuropathy, has not been studied, the authors may consider this direction in the future. Studies with PARG inhibitors and PARG-deficient mice would dissect the role of poly(ADP-ribosyl)ation vs. other phenomena resulting from PARP activation i.e., NAD depletion, energy failure and resultant inhibition of glucose utilization, in functional, metabolic and morphological manifestation of peripheral diabetic neuropathy. It would also be interesting to study the possible role of other minor isoforms of PARP in the development and progression of diabetic complications.

Collectively, the study by Obrosova et al. [13] supports the concept that PARP activation plays an important role in the development and progression of various interrelated aspects of diabetic complications, suggesting that pharmacological inhibition of the enzyme may also provide significant benefits in patients suffering from diabetic and possible other forms of neuropathy.

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