Francesca Pacifici,[1] Roberto Arriga,[1] Gian Pio Sorice,[2,3] Barbara Capuani,[1] Maria Giovanna Scioli,[4] Donatella Pastore,[1] Giulia Donadel,[1] Alfonso Bellia,[1] Sara Caratelli,[1,5] Andrea Coppola,[1] Francesca Ferrelli,[1] Massimo Federici,[1] Giuseppe Sconocchia,[1,5] Manfredi Tesauro,[1] Paolo Sbraccia,[1] David Della-Morte,[1,6] Andrea Giaccari,[2,7] Augusto Orlandi,[4] and Davide Lauro[1]

Peroxiredoxin 6, a Novel Player in the Pathogenesis of Diabetes

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Enhanced oxidative stress contributes to the pathogenesis of diabetes and its complications. Peroxiredoxin 6 (PRDX6) is a key regulator of cellular redox balance, with the peculiar ability to neutralize peroxides, peroxynitrite, and phospholipid hydroperoxides. In the current study, we aimed to define the role of PRDX6 in the pathophysiology of type 2 diabetes (T2D) using PRDX6 knockout (−/−) mice. Glucose and insulin responses were evaluated respectively by intraperitoneal glucose and insulin tolerance tests. Peripheral insulin sensitivity was analyzed by euglycemic-hyperinsulinemic clamp, and molecular tools were used to investigate insulin signaling. Moreover, inflammatory and lipid parameters were evaluated. We demonstrated that PRDX6$^{-/-}$ mice developed a phenotype similar to early-stage T2D caused by both reduced glucose-dependent insulin secretion and increased insulin resistance. Impaired insulin signaling was present in PRDX6$^{-/-}$ mice, leading to reduction of muscle glucose uptake. Morphological and ultrastructural changes were observed in islets of Langerhans and livers of mutant animals, as well as altered plasma lipid profiles and inflammatory parameters. In conclusion, we demonstrated that PRDX6 is a key mediator of overt hyperglycemia in T2D glucose metabolism, opening new perspectives for targeted therapeutic strategies in diabetes care.

A large body of evidence supports a pivotal role for oxidative stress in the etiopathogenesis of insulin resistance (IR) and diabetes (1). Oxidative stress is characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defense systems. Among all body tissues, pancreatic β-cells are very sensitive to oxidative stress because of their low expression of antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (2). Moreover, hyperglycemia by itself induces IR, increasing oxidative stress injuries, which lead to overt type 2 diabetes (T2D) (3). Interestingly, a relatively new family of antioxidant proteins, the peroxiredoxins (PRDXs), is more highly expressed in pancreatic β-cells (4). Among the six members of this non-seleno peroxidase family, PRDX6 is present in the cytoplasm and is unique because it has peroxidase and also phospholipase A_2 activity (5). Several findings demonstrate the importance of PRDX6 in maintaining redox homeostasis, as follows: lack of PRDX6, in fact, increases the susceptibility to oxidative stress in different tissues (6,7). Nevertheless, data on the relationship between PRDX6 and the pathogenesis of IR and T2D are not available (8). Therefore, we hypothesized that, in terms of physiological status, PRDX6 may play a role in the etiology of IR and diabetes conditions through tissue redox levels. In the current study, we tested our hypothesis in a model of PRDX6 knockout mice (PRDX6$^{-/-}$).

RESEARCH DESIGN AND METHODS

Animal Models

C57BL/6J wild-type (WT) mice weighing 18–20 g were obtained from The Jackson Laboratory (Bar Harbor, ME), while PRDX6$^{-/-}$ mice of mixed background (C57BL6/129SvJ) were provided by Professor Xiaosong Wang (The Jackson

[1]Department of System Medicine, University of Rome Tor Vergata, Rome, Italy
[2]Division of Endocrinology and Metabolic Diseases, Università Cattolica del Sacro Cuore, Rome, Italy
[3]Diabetic Care Clinics, Associazione dei Cavalieri Italiani Sovrano Militare Ordine di Malta, Rome, Italy
[4]Anatomic Pathology, Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[5]Institute of Translational Pharmacology, National Research Council, Rome, Italy
[6]Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Pisana, Rome, Italy
[7]Fondazione Don Carlo Gnocchi, Milan, Italy

Corresponding author: Davide Lauro, d.lauro@med.uniroma2.it.

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