PARAOXONASES: AN HISTORICAL PERSPECTIVE

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Abstract: This chapter provides a brief overview of the history of studies on human paraoxonases. It honors the memory of the late Dr. Bert La Du (1920–2005), who with his graduate students, postdoctoral fellows and collaborators made many contributions to our knowledge of this family of enzymes and the genes that encode them. Dr. La Du was honored for these contributions at the First International Conference on Paraoxonases (PONs) – “Paraoxonases: Basic and Clinical Directions of Current Research” held in Ann Arbor, Michigan in 2004. Many of the scientists who trained with and/or collaborated with the late Dr. La Du were present at this Second International Conference on Paraoxonases and have contributed to this volume. This chapter begins with a review of some of the early esterase enzymology and the discovery of plasma paraoxonase activity. The pioneering work of Dr. Norman Aldridge who differentiated the A- and B-esterases is described.

The studies that defined the polymorphic distribution of PON1 in human populations are discussed along with the many different biochemical assays that were developed to explore this interesting polymorphism. The experiments that led to the purification and cloning of human and rabbit PON1s are described along with the properties of this first enzyme known to retain its signal sequences for use in anchoring it into the HDL particle are discussed.

Recent advances by Tawfik and co-workers which include the generation of a PON1 sequence that could be expressed, crystallized and characterized are presented along with the characterization of the many different substrates of this promiscuous enzyme including physiological lactone and xenobiotic lactone substrates. The lactonase activities were characterized by both Tawfik’s team and Dr. La Du’s research group.

The expression and characterization of PON1, PON2 and PON3 by Dr. La Du’s research team is also discussed. This effort along with related work by other research groups has greatly expanded our knowledge of the many different activities of the PON family of enzymes. It is probably appropriate to include these proteins in the antioxidant family of proteins.

The history of the role of the PONs in lipid metabolism and the association of the genetic variability in the PON family of enzymes is discussed. The important take home lesson from understanding the relationship of genetic variability of PON1 and risk for vascular disease was often stressed by Dr. La Du as well as other leaders in PON1 research is that is both the quantity (plasma PON1 level) as well as the quality of PON1 (position 192 genotype) that need to be considered when evaluating risk of disease.

Experiments on the relationship of the genetic variability of PON1 and risk of exposure to organophosphorus compounds are also discussed. The take home message is...
the same, in some cases the quality of PON1 (Q192R) is important, but in all cases, the quantity of plasma PON1 is important. This consideration holds for all epidemiological studies that examine the relationship of PON genetic variability and disease.

Keywords: paraoxonase, PON1, organophosphate, organophosphorus compounds (OPs), chlorpyrifos, chlorpyrifos oxon, diazinon, diazoxon, regulation of gene expression, nerve agents, PON1 status, vascular disease, carotid artery disease, developmental regulation of PON1 level, quorum sensing, quorum sensing factors, anti-oxidants

This introductory chapter provides a brief overview of the history of studies on human paraoxonases. It honors the memory of the late Dr. Bert La Du (1920–2005), who made many contributions to our knowledge of this interesting family of enzymes, the genes that encode them, and who was honored for these contributions at the First International Conference on Paraoxonases (PONs) – “Paraoxonases: Basic and Clinical Directions of Current Research” held in Ann Arbor, Michigan in 2004. If we had to pick a single individual who contributed the most to our understanding of the paraoxonase family of enzymes and genes that encode them, it would be Dr. La Du. The reader is referred to excellent reviews for more extensive details of early PON1 research (Draganov and La Du, 2004; Geldmacher-von Mallinckrodt and Diepgen, 1988; La Du, 1992; Mackness et al., 1998) and to specialized reviews for the relationship of paraoxonase genetic variability and disease risk (e.g., Durrington et al., 2001; van Himbergen et al., 2006; Ng et al., 2005). The first book on paraoxonase (PON1) appeared in 2002 (Costa and Furlong, 2002). So many reviews on paraoxonase have appeared that it would be useful to have a “review of the paraoxonase reviews”, including reviews of genetic factors involved in cardiovascular and other diseases that include sections on PON genetic variability.

1. EARLY STUDIES

Dr Abraham Mazur, working at the Edgewood Arsenal, Maryland, is credited with the discovery that organophosphorus compounds can be hydrolyzed by enzymes (Table 1). Using manometric assays, he found that diisopropyl fluorophosphate was hydrolyzed by extracts of various tissues from human and rabbit, with the liver, kidney, small intestine and plasma having the highest activities (Mazur, 1946). Mazur’s studies were followed by an insightful series of studies by Norman Aldridge (1953a, b) who examined rates of paraoxon (E600) hydrolysis in different tissues of rats and rabbits (Figs. 1, 2). One of his interesting observations that proved to be useful for purifying paraoxonase 1 was that rabbits have very high PON1 levels in their plasma (Figs. 1, 3). Aldridge divided esterases into two categories, those that were inhibited by interaction with substrates (B-esterases) and those that could catalytically hydrolyze substrates (A-esterases). Paraoxonase falls into the A-esterase category (Aldridge, 1953b).