Semin Immunopathol (2008) 30:193–194
DOI 10.1007/s00281-008-0127-2

INTRODUCTION

NOX enzymes in immuno-inflammatory pathologies

Karl-Heinz Krause · Karen Bedard

Published online: 17 June 2008

The field of NOX enzyme research has gone through amazing turns and twists. NOX enzymes are electron transporters that receive electrons from cytosolic nicotinamide adenine dinucleotide phosphate (NADPH) and transport them across the membrane. Electrons are then transferred to molecular oxygen leading to superoxide generation, either on the outside of the cell or within the lumen of an organelle. Superoxide is rapidly metabolized into different types of reactive oxygen species, ROS. It is often assumed that the only physiological role of ROS in the organism is the killing of microorganisms. However, the initial observation of the activity of a NOX enzyme was not even made in host-defense cells. To our knowledge, Otto Warburg first described NOX activity in the beginning of the twentieth century, while studying the respiratory burst observed during fertilization of sea urchin eggs. Whereas Otto Warburg did not know at the time that a NOX enzyme was the source of this respiratory burst, his observations already pointed towards the diverse biological roles of NOX enzymes, many of them still being discovered today. Indeed, the NOX-dependent generation of ROS during fertilization serves to harden the fertilization envelope, a first example of the intimate connection between NOX enzymes and the extracellular matrix (see article of Gabrielli).

It was not until about 30 years later that NOX-dependent "extrarespiration of phagocytosis" was detected by Baldridge and Gerard. This discovery led to the development of an intensely fruitful field, namely the research on the phagocyte NADPH oxidase, now referred to as NOX2, and chronic granulomatous disease, the genetic disease associated with NOX2 deficiency. It allowed major breakthroughs in the general understanding of the biochemistry of NOX enzymes (see contributions of Nauseef and El Benna), as well as in the definition of NOX2 as a crucial host defense enzyme (see contribution of Ligeti). The research on chronic granulomatous disease was also a breakthrough in the field of genetics, as for the first time a gene responsible for a human genetic disease was identified based on the information of its chromosomal location without knowledge of its product (see Stasia).

However, the focus on phagocytes and host defense led to the fact that until about a decade ago other aspects of NOX enzymes were largely ignored. It is now clear that NOX2 is not only a host-defense enzyme, but is also involved in the termination of inflammation, and NOX2 deficiency is therefore associated with hyperinflammation and autoimmune diseases (see Schaeppi). The complex pro- and anti-inflammatory role of NOX2 is well illustrated by its role in the oral cavity, where both an increase and a decrease in NOX2 activity is associated with gingival pathology (see Giannopoulou). A new twist to the NOX story came from the observation that the "phagocyte enzyme" NOX2 is not only expressed in phagocytes but also in other cells including lymphocytes, endothelium, and neurons. Thus, whereas phagocytes remain the major source for NOX2-dependent ROS generation, the enzyme may also contribute to ROS generation in other cell types.

And finally, at the turn of the millennium, the big bang of NOX research occurred with the discovery of the other members of the NOX family (NOX1, NOX3, NOX4, NOX5, DUOX1, and DUOX2). It became rapidly clear that NOX enzymes are involved in many different physiological functions and also in many disease processes, as for example vascular diabetic complications and gastrointestinal diseases (see Yabe-Nishimura and Rokutan). It also emerged that

K.-H. Krause (✉) · K. Bedard
Departments of Pathology, Immunology, and Clinical Pathology,
Centre Medical Universitaire,
1, rue Michel-Servet,
1211 Geneva 4, Switzerland
e-mail: Karl-Heinz.Krause@medecine.unige.ch

there is a close connection between NOX enzymes and Toll-like receptors (see Ogier-Denis). Given the increasing evidence for a role of overactive NOX enzymes in various disease processes, the concept that NOX inhibitors might become useful drugs is now increasingly discussed (see Lambeth).

Together, this collection of reviews provides up-to-date insights into the role of NOX enzymes in immunopathological processes. It should serve as a valuable resource as researchers continue to explore the complex role these enzymes play in development, cellular signalling, host defense, and disease processes.