Chronic Granulomatous Disease

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KEYWORDS

• Chronic granulomatous disease • Gene defects • NADPH oxidase • Immune defect • Inflammatory bowel disease

KEY POINTS

- Chronic granulomatous disease (CGD) is a single gene defect that can be reconstituted in vitro and does not require complete correction to be effective, as proven by the normal lives of many X-linked carriers, and by the stable chimeras generated in some transplant protocols.
- Unlike the case with severe combined immunodeficiency, corrected CGD cells do not have a growth or survival advantage in the marrow or tissue. Therefore, selection and augmentation of those cells is difficult.
- Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is active outside the neutrophil, such as in nuclear factor κβ signaling, liver damage from carcinogens, and the arterial vasculature.
- NADPH oxidase somatic and hematopoietic activity is involved in strokes and pulmonary vascular permeability. NADPH contributes to long-term potentiation of memory and may be related to IQ.
- NADPH oxidase is clearly active in many more sites than just phagocytes, suggesting that CGD is more complex and can teach about more than just infections and bone marrow transplants alone.

Chronic granulomatous disease (CGD) was first described in 1954[1] and 1957[2] as recurrent infections occurring in the setting of hypergammaglobulinemia, as opposed to the disease then recently recognized by Bruton,[3] in which infections were associated with hypogammaglobulinemia. The disease was not well characterized until 1959,[4] when it was initially termed *fatal granulomatous disease of childhood*, but it is now simply referred to as *chronic granulomatous disease*. Originally thought to be only an X-linked disease, its recognition in girls in 1968 also led to the determination of autosomal recessive forms.[5] Over almost 60 years, CGD has evolved from a disease of early fatality to one of effective management with high survival.[6] CGD is a paradigm

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for nonlymphoid primary immune defects, and has guided elucidation of oxygen metabolism in the phagocyte, vasculature, and brain.[7] It has been in the forefront of the development of antimicrobial prophylaxis before the advent of advanced HIV and before its routine use in neutropenia.[8] It has been an attractive target for gene therapy and bone marrow transplantation for nonmalignant diseases. Therefore, CGD is worthy of attention for its historical interest and because it is a disease for which expert management is imperative.

Multiple separate proteins contribute to the intact nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mutations in 5 of which lead to the single syndrome of CGD. NADPH oxidase catalyzes the transfer of an electron from cytoplasmic NADPH to molecular oxygen (6; OMIM# 306400, 233690, 233700, 233710, 601488), thereby oxidizing NADPH and leading to the name *NADPH oxidase*. Although impairments of the NADPH oxidase typically present as phagocyte defects, in fact only gp91^{phox} is relatively phagocyte-specific, whereas the other autosomal components are also expressed elsewhere.[7] The components are broken into membrane-bound (cytochrome b558, composed of gp91^{phox} and p22^{phox}) and cytosolic (p47^{phox}, p67^{phox}, and p40^{phox}) structures. The subunits gp91^{phox} and p22^{phox} require each other for expression in the phagocyte; however, because p22^{phox} is expressed in other tissues and gp91^{phox} is not, p22^{phox} and the other members of the NADPH oxidase join with other partners in the other tissues, which are other members of the *Nox* family of proteins. Therefore, individuals who have autosomal recessive forms of CGD may also have other subtle abnormalities, such as vascular disease and diabetes in p47^{phox}-deficient CGD or perhaps inflammatory bowel disease in p40^{phox}-deficient CGD.[9]

Activation of the NADPH oxidase is a carefully choreographed process.[6] On cellular activation, such as ingestion of bacteria of fungi, the cytosolic components p47^{phox} and p67^{phox} are phosphorylated and bind tightly together. The secondary (specific) granules, which contain the cytochrome complex (gp91^{phox} and p22^{phox}) fuse with the phagolysosome, followed by the primary (azurophilic) granules, which contain the antibacterial peptides neutrophil elastase and cathepsin G. This process embeds the cytochrome in the wall of the phagolysosome and the antibacterial peptides inside it. The cytoplasmic complex of p47^{phox} and p67^{phox} in association with p40^{phox} and RAC2 combine with the cytochrome to form the intact NADPH oxidase, which is oriented into the internal aspect of the phagolysosome (this process can also occur on the plasma membrane focused outside the cell). An electron is then taken from cytoplasmic NADPH and donated to molecular oxygen inside the phagolysosome, leading to the formation of superoxide. In the presence of superoxide dismutase, this is converted to hydrogen peroxide, which, in the presence of myeloperoxidase and chlorine in the phagolysosome, is converted to bleach. Although the metabolites of superoxide themselves can contribute to bacterial killing, the generation of superoxide has broader implications.[10] With the generation of superoxide, a charge is imparted to the phagolysosome that is rectified by the rapid influx of potassium ions.[11] This potassium influx leads to activation of the now-intraphagosomal peptides, which mediate microbial killing.[10,11] Therefore, reactive oxidants are working more as intracellular signaling molecules, leading to activation of other nonoxidative pathways in addition to causing killing directly. Thus, a spectrum of microbicidal activity can be regulated by NADPH oxidase activity, rather than distinct oxidative and nonoxidative pathways and mechanisms.

In addition to activation of intracellular antimicrobial peptides, the NADPH oxidase is required to activate neutrophil extracellular traps (NETs), complex assemblies of DNA and antimicrobial peptides released from apoptotic neutrophils.[12] Repair of the NADPH oxidase system with gene therapy in a patient with X-linked CGD led to