

NOX family NADPH oxidases: from pathophysiology to drug development



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NOX enzymes are reactive oxygen (ROS)- producing NADPH oxidases, which are found in most eukaryotic organisms and fulfill a large spectrum of physiological functions. Most mammals have 7 genes coding for NOX enzymes with different expression patterns and different activation mechanisms. The most relevant physiological functions of NOX enzymes cluster around i) host defense, ii) biosynthetic processes (e.g. thyroid hormone synthesis, crosslinking of extracellular matrix), and iii) cellular signaling (e.g. reversible inactivation of protein phosphatases). Thus, generation of ROS is not a pathological process in itself, however excessive ROS generation through overshooting and inappropriate NOX activation may contribute to pathophysiology. Such an involvement of NOX enzymes in disease processes is particularly well documented for cardiovascular diseases (in particular NOX1), fibrotic diseases (in particular NOX4), as well as for sensory impairments such as hearing loss (in particular NOX3) and loss of vision (various NOX isoforms involved). Given the importance of NOX overactivity in certain types of redox diseases, the concept of NOX inhibition as a novel therapeutic approach has been developed. At this point, there are no inhibitors with a specificity for a single NOX isoform, however recently developed molecules with NOX inhibitory activity have shown promising activities in animal models of fibrotic and in cardiovascular diseases. The most advanced NOX inhibitor (GKT137831) is presently investigated in a phase II trial on diabetic nephropathy, a fibrosing kidney disease.

Curriculum Vitae

PERSONAL DATA

Name Karl-Heinz KRAUSE

Birth date April 25, 1958

Nationality German

Professional Address: Centre Medical Universitaire, 1, rue Michel-Servet, CH-1211 Geneva 4, Switzerland

Present appointment: Professor of Medicine (*professeur ordinaire*)

EDUCATION

1968-1976 Wolfram-von-Eschenbach Gymnasium, Schwabach, Germany.

1976-1982 Medical School, University of München, Germany.

1982-1984 Thesis in Medicine, University of München, School of Medicine, Germany. Title of the thesis: "Tolerance development in long-acting nitrates".

1984 ECFMG, Visa Qualifying Examination, USA.

1993 Privat-Dozent, University of Geneva, School of Medicine, Switzerland. Title of the thesis: "Mechanisms and pharmacology of receptor-mediated Ca²⁺ influx in neutrophil granulocytes and other non-excitabile tissues".

1997 Board certification for Internal Medicine (Bavarian Chamber of Physicians, München, Germany).

PROFESSIONAL ACTIVITIES

1982-1984 Assistant physician, Medizinische Klinik Innenstadt der Universität München (Prof. E. Buchborn), Germany.

1984-1987 Assistant physician, Department of Internal Medicine, Clinique médicale et thérapeutique and Division of Infectious Diseases (Prof. F.A. Waldvogel), University Hospitals Geneva, Switzerland.

1987-1989 Fellow, Division of Infectious Diseases (Prof. R.A. Clark), Departments of Internal Medicine (Prof. M.J. Welsh) and Physiology (Prof. K.P. Campbell), University of Iowa Hospitals, Iowa City, Iowa, USA.

- 1989-1992 Chef de clinique scientifique (=junior faculty position), Department of Internal Medicine, Division of Infectious Diseases (Prof. D.P. Lew), University Hospitals Geneva, Switzerland.
- 1992-1998 Maître d'enseignement et de recherche (= tenured faculty position), Department of Internal Medicine, Division of Infectious Diseases (Prof. D.P. Lew), University Hospitals Geneva, Switzerland.
- 1998-2001 Associate Professor of Medicine (*Professeur clinique adjoint*), Department of Geriatrics, University Hospitals Geneva, Switzerland
- 2001-2005 Louis Jeantet Professor of Medicine (*Professeur ordinaire Louis Jeantet*), Department of Geriatrics, University Hospitals Geneva, Switzerland.
- Since 2005 Professor of Medicine (Professeur ordinaire), Department of Pathology and Immunology, University of Geneva, Switzerland.

HONORS, AWARDS and SPECIAL ACADEMIC TASKS

Thesis in Medicine: Magna cum Laude (University of Munich), 1984;
Recipient of several scholarships (Martini-Stiftung, Germany; Holderbank-Stiftung, Switzerland; Deutsche Forschungsgemeinschaft, Germany), "1984-89; Young investigators award of the International Immunocompromised Host Society. 1992.
Honorary Professor, Beijing Hospital, Beijing, China, 2000.
Scientific Councillor for the Swiss National Science Foundation (2001-2009)
Friendship award of the Chinese government, Beijing, China, 2003
Elected as an individual member of the Swiss Academy of Medical Sciences
Elected as an individual member of the American Society for Clinical Investigation
Ernst Klenk-Lecturer, University of Cologne, 2010
Founder and first chairman of the Gordon Research conference NOX NADPH oxidases

FOUNDER OF UNIVERSITY SPIN-OFF COMPANIES

Genkyotex (<http://www.genkyotex.com/>)
Transcure Bioservices (<http://www.transcurebiosciences.com/>)
Neurix (<http://www.neurix.ch/>)

10 SELECTED PUBLICATIONS:

1. Cosset E, Martinez Y, Preynat-Seauve O, Lobrinus JA, Tapparel C, Cordey S, Peterson H, Petty TJ, Colaianna M, Tieng V, Tirefort D, Dinnyes D, Dubois-Dauphin M, Kaiser L, Karl-Heinz Krause: Human three-dimensional engineered neural tissue reveals cellular and molecular events following cytomegalovirus infection, *Biomaterials*, Volume 53, June 2015, Pages 296-308
2. Brault J, Goutagny E, Telugu N, Shao K, Baquié M, Satre V, Coutton C, Grunwald D, Brion JP, Barlogis V, Stephan JL, Plantaz D, Hescheler J, Krause KH, Sarić T, Stasia MJ. Optimized Generation of Functional Neutrophils and Macrophages from Patient-Specific Induced Pluripotent Stem Cells: Ex Vivo Models of X(0)-Linked, AR22(0)- and AR47(0)-Chronic Granulomatous Diseases. *Biores Open Access*. 2014 Dec 1;3(6):311-326.
3. Deffert C, Schäppi MG, Pache JC, Cachat J, Vesin D, Bisig R, Ma Mulone X, Kelkka T, Holmdahl R, Garcia I, Olleros ML, Krause KH. *Bacillus calmette-guerin* infection in NADPH oxidase deficiency: defective mycobacterial sequestration and granuloma formation. *PLoS Pathog*. 2014 Sep 4;10(9):e1004325.
4. Myburgh R, Cherpin O, Schlaepfer E, Rehrauer H, Speck RF, Krause KH, Salmon P. Optimization of Critical Hairpin Features Allows miRNA-based Gene Knockdown Upon Single-copy Transduction. *Mol Ther Nucleic Acids*. 2014 Oct 28;3:e207.
5. Xu R, Feyeux M, Julien S, Nemes C, Albrechtsen M, Dinnyés A, Krause KH. Screening of Bioactive Peptides Using an Embryonic Stem Cell-Based Neurodifferentiation Assay. *AAPS J*. 2014 May;16(3):400-12.
6. Tieng V, Stoppini L, Villy S, Fathi M, Dubois-Dauphin M, Krause KH. Engineering of midbrain organoids containing long-lived dopaminergic neurons. *Stem Cells Dev*. 2014 Jul 1;23(13):1535-47.
7. Kern I, Xu R, Julien S, Suter DM, Preynat-Seauve O, Baquié M, Poncet A, Combescure C, Stoppini L, van Thriel C, Krause KH. Embryonic stem cell-based screen for small molecules: cluster analysis reveals four response patterns in developing neural cells. *Curr Med Chem*. 2013;20(5):710-23.
8. Carnesecchi S, Deffert C, Donati Y, Basset O, Hinz B, Preynat-Seauve O, Guichard C, Arbiser JL, Banfi B, Pache JC, Barazzzone C, Krause KH. A key role for NOX4 in epithelial cell death during development of lung fibrosis. *Antioxid Redox Signal*. 2011 Aug 1;15(3):607-19.
9. Bonnefont J, Laforge T, Plastre O, Beck B, Sorce S, Dehay C, Krause KH. Primate-specific RFPL1 gene controls cell-cycle progression through cyclin B1/Cdc2 degradation. *Cell Death Differ*. 2011 Feb;18(2):293-303.
10. Preynat-Seauve O, Suter DM, Tirefort D, Turchi L, Virolle T, Chneiweiss H, Foti M, Lobrinus JA, Stoppini L, Feki A, Dubois-Dauphin M, Krause KH. Development of human nervous tissue upon differentiation of embryonic stem cells in three-dimensional culture. *Stem Cells*. 2009 Mar 5;27(3):509-520.