

The Keap1-Nrf2 system and its role in disease



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Reactive oxygen species (ROS) play a major role in the pathogenesis of many age related degenerative diseases. Nuclear factor E2-related factor-2 (Nrf2) is a basic leucine zipper transcription factor orchestrating antioxidant and cytoprotective responses upon oxidative and electrophilic stress via binding to the antioxidant response element (ARE), a cis-acting sequence within the regulatory regions of a wide range of protective genes, thus defending against various stimuli relevant to disease pathologies. In addition to its role in the protection against oxidative stress, Nrf2 also influences genes involved in lipid and glucose metabolism that may impact on its role in cardiometabolic diseases and cancer.

Herein, the molecular mechanisms by which Nrf2 is activated upon endogenous and exogenous stimuli are portrayed, emphasizing the role of Nrf2 inhibiting protein Keap1. Specifically, Nrf2-activating properties of endogenous products of lipid oxidation and nitration as well as the cross-talk of Nrf2 signaling system with other stress signalling pathways are described. Furthermore, the role of Nrf2 in cardiovascular disease and cancer as well as the therapeutic potential of Nrf2 targeted therapies is discussed.

CURRICULUM VITAE

INSTITUTION AND LOCATION

University of Helsinki, Helsinki, Finland University of Helsinki, Helsinki, Finland University of Kuopio, Kuopio, Finland

DEGREES

MD	1994	Medicine
PhD	2000	Medicine
Docent	2005	Molecular medicine

Positions and Honors

1995-2000 Research Fellow, University of Helsinki, Department of Medicine
2000-2003 Postdoctoral Fellow, University of Alabama at Birmingham, Department of Pathology
2003-2004 Postdoctoral Researcher (Academy of Finland), University of Kuopio, A. I. Virtanen Institute, Department of Biotechnology and Molecular Medicine
2004-2011 Academy Research Fellow, University of Kuopio, A. I. Virtanen Institute for Molecular Sciences
2011- Research Director, University of Eastern Finland, A.I. Virtanen Institute for Molecular Sciences
2015- Director of the A. I. Virtanen Institute for Molecular Sciences
2001 Young Investigator Award, 8th Annual Meeting of the Oxygen Society, Research Triangle Park, NC
2002 Postdoctoral Career Enhancement Award, University of Alabama at Birmingham
2002 Young Investigator Award, 9th Annual Meeting of the Oxygen Society, San Antonio, TX

Professional Memberships

The Finnish Medical Association
The Finnish Medical Society Duodecim
The Finnish Atherosclerosis Society -Chair
The International Atherosclerosis Society
The Scandinavian Society for Atherosclerosis Research - Council Member

Selected Publications - from a total of 61 peer-reviewed publications, 3389 citations, h index 34, i10 index 48

1. **Levonen, A.-L.**, Dickinson, D.A., Moellering, D.R., Mulcahy, R.T., Forman, H.J., Darley-Usmar, V.M. Biphasic Effects of 15-Deoxy-delta^{12,14}-prostaglandin J₂ on Glutathione Induction and Apoptosis in Human Endothelial Cells. *Arterioscler. Thromb. Vasc. Biol.* 21:1846-1851, 2001.
2. **Levonen, A.L.**, Landar, A., Ramachandran, A., Ceaser, E.K., Dickinson, D.A., Zanoni, G., Morrow, J.D., and Darley-Usmar, V.M. Cellular mechanisms of redox cell signaling: the role of cysteine modification in controlling antioxidant defenses in response to electrophilic lipid oxidation products. *Biochem. J.* 378: 373-382, 2004.
3. **Levonen, A.-L.**, Inkala, M., Heikura, T., Jauhiainen, S., Jyrkkänen, H.-K., Kansanen, E., Määttä, K., Romppanen, E., Turunen, P., Rutanen, J., and Ylä-Herttua, S. Nrf2 gene transfer induces antioxidant enzymes and suppresses smooth muscle

cell growth in vitro and reduces oxidative stress in rabbit aorta in vivo. *Arterioscler. Thromb. Vasc. Biol.* 27: 741-747, 2007.

4. Hurttila, H., Koponen, J.K., Kansanen, E., Jyrkkänen, H-K, Kivelä, A., Kylätie, R., Ylä-Herttuala, S., **Levonen, A.-L.** Oxidative stress inducible lentiviral vectors for gene therapy. *Gene Ther.* 15: 1271-1279, 2008.
5. Jyrkkänen, H.-K., Kansanen, E., Inkala, M., Kivelä, A.M., Hurttila, H., Heinonen, S.E., Goldsteins, G., Jauhiainen, S., Tiainen, S., Makkonen, H., Oskolkova, O., Afonyushkin, T., Koistinaho, J., Yamamoto, M., Bochkov, V.N., Ylä-Herttuala, S., **Levonen, A.-L.** Nrf2 regulates antioxidant gene expression evoked by oxidized phospholipids in endothelial cells and murine arteries in vivo. *Circ. Res.* 103: e1-9, 2008.
6. **Levonen, A.-L.**, Vähäkangas, E., Koponen, J.K., Ylä-Herttuala, S. Antioxidant gene therapy for cardiovascular disease: current status and future perspectives. *Circulation* 117: 2142-2150, 2008.
7. Kansanen, E., Jyrkkänen, H.K., Volger O.L., Leinonen, H., Kivelä, A.M., Häkkinen, S.-K., Woodcock, S.R., Schopfer, F.J., Horrevoets, A.J, Ylä-Herttuala, S., Freeman, B.A., **Levonen, A.-L.** Nrf2-dependent and independent responses to nitro-fatty acids in human endothelial cells: identification of heat shock response as a major pathway activated by nitro-oleic acid. *J. Biol. Chem.* 284:33233-33241, 2009.
8. Kansanen, E., Bonacci, G., Schopfer, F.J., Linna, S., Tong, K.I., Leinonen, H., Woodcock, S.R., Yamamoto, M., Carlberg, C., Ylä-Herttuala, S., Freeman, B.A., **Levonen, A.-L.** Electrophilic nitro-fatty acids activate Nrf2 by a Keap1 cysteine 151-independent mechanism. *J. Biol. Chem.* 286:14019-14027, 2011.
9. Leinonen, H.M., Ruotsalainen, A.-K., Määttä, A.M., Laitinen, H.M., Kuosmanen, S.M., Kansanen, E., Pikkarainen, J.T., Lappalainen, J.P., Samaranayake, H., Lesch, H.P., Kaikkonen, M.U., Ylä-Herttuala, S., **Levonen, A.-L.** Oxidative stress-regulated lentiviral TK/GCV gene therapy for lung cancer treatment. *Cancer Res.* 72:6227-6235, 2012.
10. Leinonen, H.M., Kansanen, E., Pölönen, P., Heinäniemi, M., **Levonen, A.-L.** Role of the Keap1-Nrf2 Pathway in Cancer. *Adv. Cancer Res.* 122: 281-320, 2014.