Protein Quality Control of NKCC2 in Bartter Syndrome and Blood Pressure Regulation

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Abstract

The kidney plays an essential role in blood pressure (BP) regulation by controlling fluid and sodium balance. Within the kidney, the thick ascending limb of the loop of Henle (TAL) is responsible for reabsorbing 25–30% of the filtered salt in a process mediated by the apical Na^+-K^+-$2Cl^-$ cotransporter NKCC2. Loss-of-function mutations in NKCC2 cause Bartter's syndrome and (type 1 BS), an inherited disorder featuring low BP due to renal NaCl wasting. Conversely, enhanced activity of NKCC2 has been linked to salt-sensitive hypertension. Given the importance of NKCC2 in renal function, studying the molecular regulation of this Na-K-2Cl cotransporter has attracted great interest. Therefore, several studies have addressed various aspects of NKCC2 regulation, such as phosphorylation and post-Golgi trafficking. However, the regulation of this cotransporter at the pre-Golgi level remained unknown for years. In this regard, we have provided evidence that export from the ER appears to be the rate-limiting step in the cotransporter's maturation and trafficking to the plasma membrane. The most compelling evidence comes from patients with type 5 BS, the most severe form of BS, in whom NKCC2 is not detectable in the apical membrane of TAL cells due to ER retention and ER-associated degradation (ERAD) mechanisms. In addition, type 1 BS is one of the diseases linked to ERAD pathways. Importantly, several molecular determinants of NKCC2 export from the ER and protein quality (QC) control have been identified by my group. A better understanding of the molecular mechanisms underlying the protein QC of NKCC2 could pave the way to the discovery of new and specific loop diuretics for the treatment of hypertension. Moreover, given that changes in NKCC2 expression occur with several chronic ER stress and hypertensive conditions, such as diabetes mellitus, obesity, and aging; changes in NKCC2-interacting proteins, in particular under ER stress conditions, could have an impact on the cotransporter's abundance and function, and thereby on chronic kidney adaptations, especially the regulation of BP.

Recent Publications

1: Laghmani K. Protein Quality Control of NKCC2 in Bartter Syndrome and Blood Pressure Regulation. Cells. 2024 May 10;13(10):818.

2 : Frachon N, Demaretz S, Seaayfan E, Chelbi L, Bakhos-Douaihy D, Laghmani K. AUP1 Regulates the Endoplasmic Reticulum-Associated Degradation and Polyubiquitination of NKCC2. Cells. 2024 Feb 24;13(5):389.

3: Bakhos-Douaihy D, Seaayfan E, Frachon N, Demaretz S, Kömhoff M, Laghmani K. Diacidic Motifs in the Carboxyl Terminus Are Required for ER Exit and Translocation to the Plasma Membrane of NKCC2. Int J Mol Sci. 2022 Oct 23;23(21):12761.

4: Demaretz S, Seaayfan E, Bakhos-Douaihy D, Frachon N, Kömhoff M, Laghmani K. Golgi Alpha1,2-Mannosidase IA Promotes Efficient Endoplasmic Reticulum- Associated Degradation of NKCC2. Cells. 2021 Dec 29;11(1):101.

5: Shaukat I, Bakhos-Douaihy D, Zhu Y, Seaayfan E, Demaretz S, Frachon N, Weber S, Kömhoff M, Vargas-Poussou R, Laghmani K. New insights into the role of endoplasmic reticulum-associated degradation in Bartter Syndrome Type 1. Hum Mutat. 2021 Aug;42(8):947-968.

6: Bakhos-Douaihy D, Seaayfan E, Demaretz S, Komhoff M, Laghmani K. Differential Effects of STCH and Stress-Inducible Hsp70 on the Stability and Maturation of NKCC2. Int J Mol Sci. 2021 Feb 23;22(4):2207.

7: Kömhoff M, Laghmani K. MAGED2: a novel form of antenatal Bartter's syndrome. Curr Opin Nephrol Hypertens. 2018 Jul;27(4):323-328.

8: Laghmani K, Beck BB, Yang SS, Seaayfan E et al. Polyhydramnios, Transient Antenatal Bartter's Syndrome, and MAGED2 Mutations. N Engl J Med. 2016 May 12;374(19):1853-63.



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Biography

Kamel Laghmani (K.L), director of research at CNRS and a group leader at the CRC (Paris, France), has recognized expertise in the field of molecular and cell biology of ion transport in the kidney, in particular in the biogenesis of renal salt transporters. His main interest is focused on the role of Endoplasmic Reticulum Stress in kidney function and disease. In recent years, his group has been focusing mainly on Bartter and Gitelman syndromes, two inherited salt-losing tubulopathies. In recognition of his expertise in the field, K.L has been invited to be involved in a large number of international collaborative research projects. K.L has published more than 25 papers in several reputable journals (with the majority as lead and/or last-author) related to salt transporters regulations, in particular in the context of ER stress conditions, salt salt-losing tubulopathy, and hypertension. Dr. Laghmani received in 2016, the award for excellence in research and training (PEDR 2016).

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