Interactome Screening Identifies the ER Luminal Chaperone Hsp47 as a Regulator of the Unfolded Protein Response Transducer IRE1 alpha

Por: Sepulveda, D (Sepulveda, Denisse)[1,2,3] ; Rojas-Rivera, D (Rojas-Rivera, Diego)[1,2,3] ; Rodriguez, DA(Rodriguez, Diego A.)[1,3,4] ; Groenendyk, J (Groenendyk, Jody)[5] ; Kohler, A (Kohler, Andres)[1,16] ; Lebeaupin, C (Lebeaupin, Cynthia)[6] ; Ito, S (Ito, Shinya)[7] ; Urra, H (Urra, Hery)[1,2,3] ; Carreras-Sureda, A(Carreras-Sureda, Amado)[1,2,3] ; Hazari, Y (Hazari, Younis)[1,2,3] ...Más
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Resumen

Maintenance of endoplasmic reticulum (ER) proteostasis is controlled by a dynamic signaling network known as the unfolded protein response (UPR). IRE1a is a major UPR transducer, determining cell fate under ER stress. We used an interactome screening to unveil several regulators of the UPR, highlighting the ER chaperone Hsp47 as the major hit. Cellular and biochemical analysis indicated that Hsp47 instigates IRE1 alpha signaling through a physical interaction. Hsp47 directly binds to the ER luminal domain of IRE1 alpha with high affinity, displacing the negative regulator BiP from the complex to facilitate IRE1 alpha oligomerization. The regulation of IRE1 alpha signaling by Hsp47 is evolutionarily conserved as validated using fly and mouse models of ER stress. Hsp47 deficiency sensitized cells and animals to experimental ER stress, revealing the significance of Hsp47 to global proteostasis maintenance. We conclude that Hsp47 adjusts IRE1 alpha signaling by fine-tuning the threshold to engage an adaptive UPR.

Palabras clave

KeyWords Plus:ENDOPLASMIC-RETICULUM STRESS; MOLECULAR CHAPERONE; CELL FATE; EXTRACELLULAR-MATRIX; SENSOR IRE1-ALPHA; MAMMALIAN-CELLS; BAX INHIBITOR-1; MESSENGER-RNAS; IV COLLAGEN; DROSOPHILA

Información del autor

Dirección para petición de copias: Hetz, C (autor para petición de copias)

+ Univ Chile, BNI, Fac Med, Santiago 8380453, Chile.

Dirección para petición de copias: Hetz, C (autor para petición de copias)

Ctr Gerosci Brain Hlth & Metab GERO, Santiago, Chile.

Dirección para petición de copias: Hetz, C (autor para petición de copias)

+ Univ Chile, Program Cellular & Mol Biol, Inst Biomed Sci, Santiago 8380453, Chile.

Dirección para petición de copias: Hetz, C (autor para petición de copias)

+ Buck Inst Res Aging, Novato, CA 94945 USA.

Dirección para petición de copias: Hetz, C (autor para petición de copias)

+ Harvard Sch Publ Hlth, Dept Immunol & Infect Dis, Boston, MA 02115 USA.

Direcciones:

+ [1] Univ Chile, BNI, Fac Med, Santiago 8380453, Chile

[2] Ctr Gerosci Brain Hlth & Metab GERO, Santiago, Chile

+ [3] Univ Chile, Program Cellular & Mol Biol, Inst Biomed Sci, Santiago 8380453, Chile

+ [4] St Jude Childrens Res Hosp, Dept Immunol, 332 N Lauderdale St, Memphis, TN 38105 USA

+ [5] Univ Alberta, Dept Biochem, Edmonton, AB T6G 2S7, Canada

+ [6] Inserm, Team 8, C3M, F-06204 Nice, France

+ [7] Kyoto & Sangyo Univ, Dept Mol Biosci, Fac Life Sci, Kita Ku, Kyoto 6038555, Japan

[8] Inst Ecol & Sci Environm Paris, Bondy, France

[9] Sorbonne Univ, F-7113 Paris, France

+ [10] INSERM, F-7113 Paris, France

+ [11] Imperial Coll London, Dept Life Sci, London SW7 2AZ, England

+ [12] Univ Rennes 1, Inserm U1242, Chem Oncogenesis Stress & Signaling, F-35000 Rennes, France

+ [13] Ctr Lutte Canc Eugene Marquis, F-35000 Rennes, France

+ [14] Tech Univ Dortmund, IfADo Leibniz Res Ctr Working Environm & Human Fa, D-44139 Dortmund, Germany

+ [15] Univ Washington, Div Metab Endocrinol & Nutr, Sch Med, Seattle, WA 98195 USA

+ [16] Univ Chile, Program Physiol & Biophys, Inst Biomed Sci, Santiago 8380453, Chile

+ [17] Buck Inst Res Aging, Novato, CA 94945 USA

+ [18] Harvard Sch Publ Hlth, Dept Immunol & Infect Dis, Boston, MA 02115 USA

Direcciones de correo electrónico:chetz@hsph.harvard.edu

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