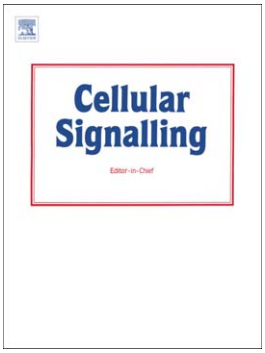

Extracellular heat shock protein 90 binding to TGFβ receptor I participates in TGFβ-mediated collagen production in myocardial fibroblasts

Raquel García, David Merino, Jenny M. Gómez, J. Francisco Nistal, María A. Hurlé, Aitziber L. Cortajarena, Ana V. Villar

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Authors

Raquel García[1] David Merino[2] Jenny M. Gómez[3] J. Francisco Nistal[4] María A. Hurlé[1] Aitziber L. Cortajarena[5] Ana V. Villar[1]

Afiliation

[1]Departamento de Fisiología y Farmacología, Universidad de Cantabria, Santander, Spain; Centro de Investigación Marqués de Valdecilla (IDIVAL), Santander, Spain

[2]Unidad de Inmunología, Centro de Investigación Marqués de Valdecilla (IDIVAL), Santander, Spain

[3]Servicio de Cardiología, Hospital Sierrallana, Santander, Spain

[4]Instituto de Investigación Marqués de Valdecilla (IDIVAL), Santander, Spain; Servicio de Cirugía Cardiovascular, Hospital Universitario Marqués de Valdecilla, Santander, Spain.

[5a]IMDEA-Nanociencia, Campus de Cantoblanco, 28049 Madrid, Spain, [b]CIC BiomaGUNE, Parque Tecnológico de San Sebastián, Paseo Miramón 182, Donostia-San Sebastián 20009, Spain.

Corresponding author

Ana V Villar e-mail, villarav@unican.es telephone +34942201961, and fax +34942201903

Tittle

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Abstract

The pathological remodeling heart shows an increase in left ventricular mass and an excess of extracellular matrix deposition that can over time cause heart failure. Transforming growth factor β (TGFβ) is the main cytokine controlling this process. The molecular chaperone heat shock protein 90 (Hsp90) has been shown to play a critical role in TGFβ signaling by stabilizing the TGFβ signaling cascade. We detected extracellular Hsp90 in complex with TGFβ receptor I (TGFβRI) in fibroblasts and determined a close proximity between both proteins suggesting a potential physical interaction between the two at the plasma membrane. This was supported by *in silico* studies predicting Hsp90 dimers and TGFβRI extracellular domain interaction. Both, Hsp90aa1 and Hsp90ab1 isoforms participate in TGFβRI complex. Extracellular Hsp90 inhibition lessened the yield of collagen production as well as the canonical TGFβ signaling cascade, and collagen protein synthesis was drastically reduced in Hsp90aa1 KO mice. These observations together with the significant increase in activity of Hsp90 at the plasma membrane pointed to a functional cooperative partnership between Hsp90 and TGFβRI in the fibrotic process. We propose that a surface population of Hsp90 extracellularly binds TGFβRI and this complex behaves as an active participant in collagen production in TGFβ-activated fibroblasts. We also offer an in vivo insight into the role of Hsp90 and its isoforms during cardiac remodeling in murine aortic banding model suffering from pathological cardiac remodeling and detect circulating Hsp90 overexpressed in remodeling mice.