Dokumenttyp: journal article

Autor(en) des Beitrags: Sun, X; Fratz, S; Sharma, S; Hou, Y; Rafikov, R; Kumar, S; Rehmani, I; Tian, J; Smith, A; Schreiber, C; Reiser, J; Naumann, S; Haag, S; Hess, J; Catravas, JD; Patterson, C; Fineman, JR; Black, SM

Titel des Beitrags: C-terminus of heat shock protein 70-interacting protein-dependent GTP cyclohydrolase I degradation in lambs with increased pulmonary blood flow.

Abstract: We showed that nitric oxide (NO) signaling is decreased in the pulmonary vasculature before the development of endothelial dysfunction in a lamb model of congenital heart disease and increased pulmonary blood flow (Shunt). The elucidation of the molecular mechanism by which this occurs was the purpose of this study. Here, we demonstrate that concentrations of the endogenous NO synthase (NOS) inhibitor, asymmetric dimethylarginine (ADMA), are elevated, whereas the NOS cofactor tetrahydrobiopterin (BH(4)) is decreased in Shunt lambs. Our previous studies demonstrated that ADMA decreases heat shock protein-90 (Hsp90) chaperone activity, whereas other studies suggest that guanosine-5’-triphosphate cyclohydrolase 1 (GCH1), the rate-limiting enzyme in the generation of BH(4), may be a client protein for Hsp90. Thus, we determined whether increases in ADMA could alter GCH1 protein and activity. Our data demonstrate that ADMA decreased GCH1 protein, but not mRNA concentrations, in pulmonary arterial endothelial cells (PAECs) because of the ubiquitination and proteosome-dependent degradation of GCH1. We also found that Hsp90-GCH1 interactions were
reduced, whereas the association of GCH1 with Hsp70 and the C-terminus of Hsp70-interacting protein (CHIP) increased in ADMA-exposed PAECs. The overexpression of CHIP potentiated, whereas a CHIP U-box domain mutant attenuated, ADMA-induced GCH1 degradation and reductions in cellular BH(4) concentrations. We also found in vivo that Hsp90/GCH1 interactions are decreased, whereas GCH1-Hsp70 and GCH1-CHIP interactions and GCH1 ubiquitination are increased. Finally, we found that supplementation with L-arginine restored Hsp90-GCH1 interactions and increased both BH(4) and NO(x) concentrations in Shunt lambs. In conclusion, increased concentrations of ADMA can indirectly alter NO signaling through decreased cellular BH(4) concentrations, secondary to the disruption of Hsp90-GCH1 interactions and the CHIP-dependent proteasomal degradation of GCH1.

Zeitschriftentitel / Abkürzung:
Am J Respir Cell Mol Biol

Jahr: 2011
Band: 45
Heft / Issue: 1
Seiten: 163-71
Sprache: eng
Print-ISSN: 1044-1549
TUM Einrichtung: r Kinderkardiologie und angeborene Herzfehler; chirurgie

Occurences:
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Lehr- und Forschungskooperationen mit den Kliniken und Instituten am Deutschen Herzzentrum > Klinik für Herz- und Gefäßchirurgie (Prof. Lange) > 2011
- Einrichtungen > Fakultäten > Fakultät für Medizin > Kliniken und Institute > Lehr- und Forschungskooperationen mit den Kliniken und Instituten am Deutschen Herzzentrum > Klinik für Kinderkardiologie und angeborene Herzfehler (Prof. Hess) > 2011

entries: