Mussbacher *et al.: Intrinsic Activity*, 2015; **3**(Suppl. 2):A1.12
http://www.intrinsicactivity.org/2015/3/S2/A1.12
published online: 9 September 2015

21st Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the British Pharmacological Society and the Pharmacological Societies of Croatia, Serbia and Slovenia

Graz, 16–18 September 2015

MEETING ABSTRACT

A1.12

Cardiac dysfunction in adipose triglyceride-deficient mice: role of the ubiquitin–proteasome system

Marion MUSSBACHER[1,*], Heike STESSEL[1], Gerald WÖLKART[1], Guenther HAEMMERLE[2], Rudolf ZECHNER[2], Bernd MAYER[1] and Astrid SCHRAMMEL[1]

[1]*Institute of Pharmaceutical Sciences, Department of Pharmacology and Toxicology, University of Graz, Austria;* [2]*Department of Molecular Biosciences, University of Graz, Austria*

Background: Adipose triglyceride lipase (ATGL) represents a key enzyme of the lipolytic cascade. Global ATGL deficiency in mice leads to massive accumulation of neutral lipids in adipose and multiple non-adipose tissues [1]. In hearts of ATGL knockout mice, ectopic storage of triglycerides results in progressive development of lethal cardiomyopathy [1]. Recently it was demonstrated that ATGL knockout mice suffer from pronounced cardiac oxidative inflammatory stress and defective PPARα signaling [2, 3]. Since dysfunction of the ubiquitin–proteasome system (UPS) has been closely linked to various cardiac pathologies, we investigated if disturbances in cellular protein degradation might contribute to the observed cardiac phenotype.

Methods: Western-blot analysis and quantitative PCR were used to compare protein ubiquitination and markers of inflammatory oxidative stress between cardiac tissue of wild-type and ATGL knockout mice. Furthermore, mice were treated with the PPARα agonist Wy14,643 to test for the role of defective PPARα signaling in this scenario.

Results: Western-blot analysis revealed significantly increased amounts of ubiquitinated cardiac proteins in ATGL-deficient hearts. In parallel, protein expression of the ubiquitin-activating enzyme E1a, which initiates protein ubiquitination, was significantly upregulated in cardiac ATGL deficiency. Both effects were reversed upon cardiomyocyte-directed overexpression of ATGL in ATGL knockout mice. In parallel, we observed activation of cardiac NF-κB signaling in these hearts. Chronic treatment of ATGL knockout mice with the PPARα agonist Wy14,643 (which substantially improves cardiac performance) reversed accumulation of ubiquitinated proteins, prevented activation of NF-κB, and decreased oxidative stress.

Discussion: In summary, our data suggest a hitherto unrecognized link between proteasomal function, PPARα signaling and cardiovascular disease.

Acknowledgements: This work was supported by the Austrian Science Fund (P24005, F3003 and W901 DK Molecular Enzymology to B.M.).

References

1. Haemmerle G, Lass A, Zimmermann R, Gorkiewicz G, Meyer C, Rozman J, Heldmaier G, Maier R, Theussl C, Eder S, Kratky D, Wagner EF, Klingenspor M, Hoefler G, Zechner R: **Defective lipolysis and altered energy metabolism in mice lacking adipose triglyceride lipase.** *Science,* 2006; 312(5774):734–737. doi:10.1126/science.1123965
2. Schrammel A, Mussbacher M, Winkler S, Haemmerle G, Stessel H, Wölkart G, Zechner R, Mayer B: **Cardiac oxidative stress in a mouse model of neutral lipid storage disease.** *Biochim Biophys Acta,* 2013; 1831(11):1600–1680. doi:10.1016/j.bbalip.2013.07.004
3. Haemmerle G, Moustafa T, Woelkart G, Büttner S, Schmidt A, van de Weijer T, Hesselink M, Jaeger D, Kienesberger PC, Zierler K, Schreiber R, Eichmann T, Kolb D, Kotzbeck P, Schweiger M, Kumari M, Eder S, Schoiswohl G, Wongsiriroj N, Pollak NM, Radner FP, Preiss-Landl K, Kolbe T, Rülicke T, Pieske B, Trauner M, Lass A, Zimmermann R, Hoefler G, Cinti S, Kershaw EE, Schrauwen P, Madeo F, Mayer B, Zechner R: **ATGL-mediated fat catabolism regulates cardiac mitochondrial function via PPAR-α and PGC-1.** *Nat Med,* 2011; 17(9):1076–1085. doi:10.1038/nm.2439

*Corresponding author e-mail: *marion.mussbacher@uni-graz.at*