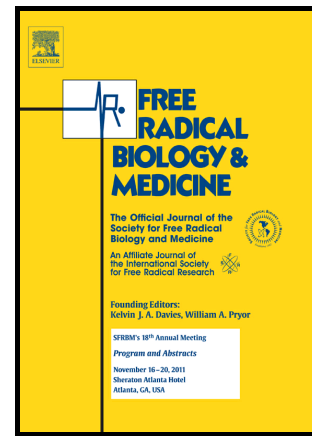


# Author's Accepted Manuscript

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Yichi Yu, Lei Wang, Florian Delguste, Arthur Durand, Axel Guilbaud, Clementine Rousselin, Ann Marie Schmidt, Frédéric Tessier, Eric Boulanger, Remi Neviere



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**Advanced glycation end products receptor RAGE controls myocardial dysfunction and oxidative stress in high-fat fed mice by sustaining mitochondrial dynamics and autophagy-lysosome pathway**

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**ABSTRACT**

Oxidative stress and mitochondrial dysfunction are recognized as major contributors of cardiovascular damage in diabetes and high fat diet (HFD) fed mice. Blockade of receptor for advanced glycation end products (RAGE) attenuates vascular oxidative stress and development of atherosclerosis. We tested whether HFD-induced myocardial dysfunction would be reversed in RAGE deficiency mice, in association with changes in oxidative stress damage, mitochondrial respiration, mitochondrial fission and autophagy-lysosomal pathway. Cardiac antioxidant capacity was upregulated in RAGE<sup>-/-</sup> mice under normal diet as evidenced by increased superoxide dismutase and sirtuin mRNA expressions. Mitochondrial fragmentation and mitochondrial fission protein Drp1 and Fis1 expressions were increased in RAGE<sup>-/-</sup> mice. Autophagy-related protein expressions and cathepsin-L activity were increased in RAGE<sup>-/-</sup> mice suggesting sustained autophagy-lysosomal flux. HFD induced mitochondrial respiration defects, cardiac contractile dysfunction, disrupted mitochondrial dynamics and autophagy inhibition, which were partially prevented in RAGE<sup>-/-</sup> mice. Our results suggest that cardioprotection against HFD in RAGE<sup>-/-</sup> mice include reactivation of autophagy, as inhibition of autophagic flux by chloroquine fully abrogated beneficial myocardial effects and its

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<sup>1</sup> Equally contribute to this work

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