# Letter by Neumann et al Regarding Article, "Myostatin Regulates Energy Homeostasis in the Heart and Prevents Heart Failure"

# Letter to the Editor

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## Letter by Neumann et al Regarding Article, "Myostatin Regulates Energy Homeostasis in the Heart and Prevents Heart Failure"

*To the Editor*:

We read with great interest the article by Biesemann et al[1] in which the authors uncovered an important role of myostatin and myostatin-dependent signaling pathways in the heart for maintaining cardiac energy homeostasis and preventing cardiac hypertrophy. The study is impressive because of the use of a mouse model that allows myostatin inactivation in adult cardiomyocytes and the amount and quality of collected data. The authors observed that inactivation of myostatin triggers both a metabolic switch toward an insulin-independent increase of glycolysis and the onset of cardiac hypertrophy. This metabolic switch is argued to occur via the increased activity of the energy sensor AMP-activated kinase (AMPK).

The supposed causal role of AMPK deregulation in cardiac hypertrophy is based mostly on the use of compound C. Compound C is a widely used pharmacological inhibitor of AMPK with known off-target effects, such as potent inhibition of several other kinases (ie, phosphorylase kinase and MAP-kinase–interacting kinase).[2] Therefore, caution should be taken in deducing AMPK involvement from such pharmacological approach. Moreover, through genetic models and the use of pharmacological activators, AMPK has been established as an inhibitor rather than a stimulator of cardiac hypertrophy, cell growth and proliferation, thus pointing to AMPK activation as a beneficial response mechanism and potential therapeutic strategy for cardiac hypertrophy and failure.[3,4] Accordingly, we suggest that AMPK, in its function as an energy sensor, is more likely to react to the metabolic alterations induced by myostatin ablation. Whether AMPK activation is a crucial step in mediating the observed metabolic changes and cardiac hypertrophy can be further questioned. In fact, stimulation of AMPK activity in cardiomyocytes simultaneously upregulates glucose and fatty acid uptake as well as their utilization.[5] Hence, a shift toward glucose if mediated by AMPK would require an unknown mechanism.

The reported increase of glycogen synthase phosphorylation, as an established AMPK substrate, turns out as inhibitory phosphorylation at Ser641 that is targeted by GSK3 (glycogen synthase kinase 3), another important player in cardiac hypertrophy.[6] The AMPK-dependent phosphorylation of glycogen synthase occurs at serine 7 and is likewise inhibitory to this enzyme.[7] Hence, the p-GS data do not add to the proposed involvement of AMPK.

The authors identified TAK1 (transforming growth factor β-activated kinase 1) as an inhibitory kinase of AMPK, which is opposite to previous published findings. In particular, cardiac-specific overexpression of a dominant negative mutant established TAK1 as an AMPK-activating kinase in heart and produced a phenotype reminiscent to human Wolff–Parkinson–White syndrome.[8] It is difficult to reconcile these data with the Biesemann study.

In the discussion section, one further link is made to PRKAG2 cardiomyopathy, which is mentioned as mimicking aspects of the myostatin phenotype (which refers to myostatin deletion). It should be noted that most of the described PRKAG2 mutations on the molecular level cause a loss of function rendering AMPK insensitive to AMP, which nevertheless results in increased AMPK activity, glycogen storage, and cardiac hypertrophy.[9] The reason for upregulated AMPK activity in PRKAG2 mutants, since occurring in conjunction with lack of stimulation, remains unclear at present.

Instead or besides AMPK there may be a role for protein kinase D signaling in cardiac hypertrophy caused by myostatin ablation, as the authors have shown that transphosphorylation, and presumably activity, of this kinase is increased. In this respect, protein kinase D1 activation is known to induce a hypertrophic programming in the heart via phosphorylation of HDAC5 (histone deacetylase 5) followed by deinhibition of the hypertrophic transcription factor MEF2 (myocyte enhancer factor 2).[10] Furthermore, protein kinase D1 activation might explain the reported increases in glucose uptake and utilization, as this kinase seems to play a crucial role in GLUT4 (glucose transporter type 4) translocation without having effects on myocardial fatty acid uptake and utilization.[11] Accordingly, cardiospecific constitutively active protein kinase D1 overexpression in mice stimulates GLUT4 translocation and thereby causes a myocardial substrate shift toward glucose.[12]

In conclusion, cardiac AMPK activation is the safeguard, not the culprit causing cardiac hypertrophy, in contrast to the authors' view. Despite disagreement over data interpretation, cardiac myostatin overexpression acutely affects AMPK activation, as the authors have convincingly shown. Therefore, future work should elucidate the changed cardiac energetics leading to suppressed AMPK activation (the T172 phosphorylation status), such as determining enzyme activities by kinase assay and measurements of AMP/ATP ratios backed up by in vivo PCr/Cr determinations. The alterations of heart metabolism that were observed on myostatin ablation, in particular the shift to glucose, enhanced glucose uptake, glycolysis, and the resulting cardiac hypertrophy, rather correspond to known effects of AMPK loss of function. Hence, the presented putative explanatory mechanisms at least deserve further scientific discussion.


## Acknowledgements

The authors thank the members of the Department of Molecular Genetics for helpful discussions.

## Sources of Funding

Current Research in the laboratory of D. Neumann is funded by The Netherlands Foundation for Scientific Research (NWO) (VIDI grant number 864.10.007).



(*Circ Res*. 2015;116:e95-e96. DOI: 10.1161/CIRCRESAHA.115.306463.)

## Disclosures

None.

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