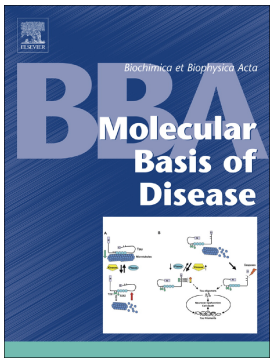

Metformin regulates mitochondrial biogenesis and senescence through AMPK mediated H3K79 methylation: Relevance in age-associated vascular dysfunction

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PII: S0925-4439(18)30029-2
DOI: https://doi.org/10.1016/j.bbadis.2018.01.018
Reference: BBADIS 65034

To appear in:

Received date: 15 November 2017
Revised date: 3 January 2018
Accepted date: 18 January 2018

Please cite this article as: Santosh Karnewar, Praveen Kumar Neeli, Devayani Panuganti, Sasikumar Kotagiri, Sreevidya Mallappa, Nishant Jain, Mahesh Kumar Jerald, Srigiridhar Kotamraju , Metformin regulates mitochondrial biogenesis and senescence through AMPK mediated H3K79 methylation: Relevance in age-associated vascular dysfunction. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Bbadis(2018), https://doi.org/10.1016/j.bbadis.2018.01.018

Metformin regulates mitochondrial biogenesis and senescence through AMPK mediated H3K79 methylation: Relevance in age-associated vascular dysfunction

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Keywords: Metformin, Mitochondrial function, endothelial dysfunction, cardiovascular diseases, atherosclerosis, aging.

ABSTRACT

Endothelial senescence in conjunction with mitochondrial dysfunction orchestrates age-associated cardiovascular disorders. In this study we investigated the causal link between these two processes and studied the molecular mechanisms by which metformin acts to coordinate the delay of endothelial senescence via enhancing mitochondrial biogenesis/function. AMPK activators metformin and AICAR delayed endothelial senescence via SIRT1-mediated upregulation of DOT1L, leading to increased trimethylation of H3K79 (H3K79me3). Treatment of cells with either siAMPK or siSIRT1 repressed DOT1L-mediated enhancement of H3K79me3. Moreover, the increase in SIRT3 expression and mitochondrial biogenesis/function by AMPK activators was H3K79me-dependent as H3K79N mutant or siDOT1L abrogated these effects. This was confirmed by the enrichment of H3K79me3 in the SIRT3 promoter with AMPK activation. Intriguingly, enhanced PGC-1α expression by SIRT3 via AMPK activation was responsible for increased hTERT expression and delayed endothelial senescence. In contrast, SIRT3 knockdown caused increased oxidative stress and premature senescence, possibly by depleting hTERT expression. Furthermore, a chronic low dose administration of metformin significantly attenuated vascular aging and inhibited age-associated atherosclerotic plaque formation in $ApoE^{-/-}$ mice. Overall, the results of this study show a novel regulation of mitochondrial biogenesis/function, and cellular senescence by H3K79me acting through SIRT3, thus providing a molecular basis for metformin-mediated age-delaying effects.