

Sex Differences in Age-Related AMPK-Sirt1 Axis Alteration in Human Heart

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Abstract : Introduction: Aging is associated with deterioration of the physiological function, leading to systemic inflammation and mitochondrial dysfunction that promote the development of cardiovascular diseases. Sex differences in aging-related cardiovascular diseases have been postulated. However, their precise mechanisms remain unclear. In the current study, we aimed to investigate the sex difference in the age-related alteration in Sirt1-AMPK signaling and its relation to the mitochondrial biogenesis and inflammation. Methods: Male and female human non-disease lateral left ventricular wall tissue (young (17-40 years; n= 7 male and 7 female) and old (50-68 years; n= 9 male and 8 female)) were used. qRT-PCR, western blot and immunohistochemistry assays were performed for expression analyses of Sirt1, AMPK, pAMPK, ac-Ku70, TFAM, PGC-1 α , Sirt3, SOD2 and catalase. CD68 was used as a marker for macrophages and the ratio of IL-12:IL10 (pro-inflammatory phenotype (high IL-12/low IL-10) and anti-inflammatory phenotype (low IL-12/high IL-10) was used to examine the inflammatory stage in the heart. Results: Sirt1 expression was significantly higher in young females compared to young males, whereas in aged hearts Sirt1 expression was significantly downregulated in females, but not in males. In line with the Sirt1 downregulation in aged females, acetylation of nuclear Ku70, a direct target of Sirt1, in aged female hearts was significantly elevated. The activity of AMPK was significantly decreased in aged individuals, however no sex differences in the AMPK expression or activity were found in young or old individuals. The expression of mitochondrial proteins TOM40, SOD2 and Sirt3 was significantly higher in young females compared to young males, while in aged female hearts SOD2 and TOM40 were downregulated. In addition, the expression of catalase, a key cytosolic and mitochondrial anti-oxidative enzyme was significantly higher in young females and this female sex benefit was lost in aged hearts. In addition, the number of cardiac macrophages was significantly increased in old female, but not in male hearts. Consistently, the pro-inflammatory shift in old females was further confirmed by differences in the IL12/IL10 ratio in young female cardiac tissue in a favour of the anti-inflammatory mediator IL-10 (ratio 1:4) compared to young males (ratio 1:1). The anti-inflammatory environment in the heart was lost in aged females (ratio 1:1). Conclusion: Aging leads to the significant downregulation of Sirt1 expression and elevated acetylation of Ku70 in female, but not in male hearts. Furthermore, a beneficial upregulation of mitochondrial and anti-oxidative proteins in young females is lost with aging. Moreover, the malfunctions in the expression of Sirt1 and mitochondrial proteins in aged female hearts is accompanied by a significant pro-inflammatory shift. The study provides a molecular basis for the increased incidence of cardiovascular diseases in old women.

Keywords : inflammation, mitochondrial dysfunction, aging, Sirt1-AMPK axis

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