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Klotho expression in cardiomyocytes in patients at a higher atherosclerotic cardiovascular disease risk

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Klotho proteins (α- and β-Klotho) are transmembrane proteins whose extracellular domain is secreted into blood and urine by ectodomain shedding. As such they behave as circulating proteins that regulate cell metabolism, endothelial function and calcium homeostasis, as well as modulating the lifespan connected activity of Fibroblast Growth Factors (FGFs, mainly 21 and 23) and other molecules (1). Recent data have shown that highest levels of plasma circulating Klotho are associated with a lower cardiovascular risk, thereby suggesting a possible role for Klotho in cardiovascular diseases (2). However, although Klotho has been identified in various organs, including kidney, brain, adipose tissue and intestine, it is unknown whether cardiomyocytes express Klotho and FGFs and, if so, whether high cardiovascular risk can be associated with cardiac expression of Klotho, FGFs and other related molecules.

We examined myocardial biopsies from 20 patients with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk in the range of 5% to 7.5% and 10 age-matched control subjects with an estimated 10-year ASCVD risk of <5% (3) undergoing cardiac surgery other than coronary artery by-pass. Both groups of patients were statin naive, had normal hemoglobin A1c, normal coronary arteries on left heart catheterization, and had LDL cholesterol levels between 70 and 189 mg/DL. Using immunohistochemistry methods, we evaluated Klotho and FGFs expression in human cardiomyocytes, and whether higher ASCVD risk influenced the expression of other molecules involved in endoplasmic reticulum stress (GRP78), oxidative stress (SOD1, NFkB) and inflammation (iNOS, eNOS).

Cardiomyocytes of patients with a higher ASCVD risk exhibited lower expression of Klotho, but also higher expression of FGFs, as compared to cardiomyocytes of patients with a reduced ASCVD risk. Furthermore, higher ASCVD risk was associated with significantly increased expression of GRP78, SOD1, NFkB and iNOS (all $p<0.05$). This study shows for the first time that Klotho proteins are inherently expressed in human cardiomyocytes and also that cardiac expression of Klotho is down regulated in higher ASCVD risk patients, while the expression of FGFs and other stress-related molecules involved in myocyte damage, such as GRP78, SOD1, NFkB and iNOS, is significantly increased. Further studies are warranted to investigate the association of klotho, FGFs and related molecules expression with cardiovascular risk.

References

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Keywords

Klotho; FGFs; atherosclerotic cardiovascular disease risk; human cardiomyocytes.