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The Effect of Low-Density Lipoprotein Cholesterol on T-Cell Mitochondrial Respiration

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Aging is associated with an increase in chronic, sterile, low-grade inflammation, known as "inflammaging". Inflammaging is implicated in the development of multiple diseases, including cardiovascular disease. Immune cells are one of the primary sources of inflammaging, of which T-cells play a major contributing role. Mitochondria are essential for maintaining proper T-cell function and reduced mitochondrial respiration ($Mito_{RESP}$) induces T-cell dysfunction and shifts T-cells towards a pro-inflammatory phenotype. Aging has been shown to impair T-cell $Mito_{RESP}$; however, the mechanisms have not been fully elucidated. Age-related increases in circulating low-density lipoprotein cholesterol (LDL-C) are cross-sectionally associated with lower $Mito_{RESP}$ in circulating immune cells, but whether LDL-C is causally related to impaired $Mito_{RESP}$ in T-cells is not known. We hypothesized that treating T-cells *in vitro* with a high concentration of exogenous LDL-C would impair T-cell $Mito_{RESP}$. **METHODS**: Seven young adults were recruited for this study (6 female / 1 male, age: 23 ± 2 years, BMI: 23.29 ± 6.4 kg/m^2, total cholesterol: 154 ± 16 mg/dl, high-density lipoprotein cholesterol: 59 ± 17 mg/dL, & LDL-C: 78 ± 14 mg/dL). $CD4^+$ and $CD8^+$ T-cells were separated from peripheral blood mononuclear cells isolated using magnetic bead separation (Miltenyi). $CD4^+$ and $CD8^+$ T-cells were treated exogenously with a physiologically normal (1.8 mMol/L) and high (4.9 mMol/L) concentration of LDL-C for 24 hours. $Mito_{RESP}$ was assessed using extracellular flux analysis (Agilent). **RESULTS:** High LDL-C lowered basal (1.8 mMol/L: 0.47 ± 0.06 pMol/min/10^5 cells vs. 4.9 mMol/L: 0.35 ± 0.10 pMol/min/10^5 cells, p=0.031) and ATP-linked oxygen consumption rate (OCR) (1.8 mMol/L: 0.51 ± 0.13 pMol/min/10,000 cells vs. 4.9 mMol/L: 0.35 ± 0.12 pMol/min/10^5 cells, p=0.016) in $CD8^+$ T-cells. High LDL-C also lowered ATP-linked OCR in $CD4^+$ T-cells (1.8 mMol/L: 0.69 ± 0.23 pMol/min/10^5 cells vs. 4.9 mMol/L: 0.54 ± 0.22 pMol/min/10^5 cells, p=0.031), but did not statistically alter basal OCR (p=0.063). **CONCLUSION:** Treatment with a high LDL-C impaired $Mito_{RESP}$ in T-cells. Future studies should explore the relation between T-cell $Mito_{RESP}$ and cardiovascular function in humans.

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