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Autophagy Defects That Modify Human Immune Cell Metabolism and Promote Aging-Associated Inflammation

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Abstract : Age is a non-modifiable risk factor for the inflammation that underlies pathologies such as type 2 diabetes mellitus (T2DM). Inflammation, as indicated by circulating cytokines, rises in aging, but mechanisms that promote this 'inflammaging' remain poorly defined. Furthermore, downstream consequences of inflammaging, including the development of an inflammatory profile that predicts comorbidities like T2DM, remain speculative. We tested the possibility that natural aging-associated changes in autophagy, a process that is compromised in both aging and T2DM, regulates inflammatory profiles in older subjects. Our data showed that circulating $CD4^+$ T cells from older compared to younger subjects have (i) defects in autophagy; (ii) higher mitochondria accumulation; (iii) a failure to metabolically shift from oxidative phosphorylation to anaerobic glycolysis upon αCD3/CD28 activation; (iv) more reactive oxygen species (ROS) accumulation; and (v) a cytokine profile that recapitulates the Th17 profile that predicts T2DM. ROS scavenging in cells from older subjects restored mitochondrial mass and membrane potential (indicators of improved autophagy) and reduced Th17 cytokines to amounts made by T cells from younger subjects. Knock-down of the autophagy protein Atg3 in T cells from younger subjects increased mitochondrial accumulation and Th17 cytokines. To begin translating these findings to clinical practice, we showed that physiological concentrations of the diabetes drug metformin (100 μM) added in vitro enhanced autophagy, prevented mitochondria and ROS accumulation, increased anaerobic glycolysis, and decreased Th17 cytokines in activated $CD4^+$ T cells from older subjects. Metformin therefore improves autophagy and multiple downstream pro-inflammatory mechanisms $CD4^+$ T cells from older subjects. We conclude that autophagy improvement ameliorates the development of a T2DM-predictive Th17 profile in aging, and thus holds promise for delay or prevention of aging-associated metabolic decline.

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