Abstract citation ID: suac121.413

514 ATAXIA TELANGIECTASIA MUTATED PROTEIN MODULATES GLUCOSE AND LIPID METABOLISM IN THE HEART

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Background: Ataxia Telangiectasia Mutated (ATM) protein kinase is the major sensor of DNA damage response (DDR) and oxidative stress, variously implicated in cellular metabolism. Previous studies on ATM functions in the heart have produced conflicting results. Here we hypothesized that ATM might regulate cardiomyocyte metabolic homeostasis and function.
Methods: *Atm*-mutated mice ($Atm^{-/-}$) and their wild-type littermates ($Atm^{+/+}$) were used to assess the effects of ATM inactivation on cardiomyocyte hypertrophy, cardiac structure, function, DDR and metabolism under sham conditions or after pressure overload by transverse aortic constriction (TAC).
Results: ATM inactivation induced cardiomyocyte hypertrophy (FIG.1 A), fetal gene expression re-activation and a specific metabolomic signature in the heart, characterized by significant accumulation of pyruvate, branched chain amino-acids, short-medium acyl-carnitines and metabolites of tricarboxylic acid cycle (FIG.1 C, D),. Importantly, pyruvate was trapped in the cytosol because mitochondrial carriers were suppressed and the enzymes that process pyruvate were dysregulated. As a consequence of pyruvate metabolic block, fatty acids oxidation was inefficient and resulted in the accumulation of acyl-carnitines and insulin resistance. Although these metabolic changes were present constitutively in $Atm^{-/-}$ mice, they were amplified by TAC, which rapidly induced heart failure (FIG.1 B) in $Atm^{-/-}$ mice. ATM inactivation also increased basal and TAC-induced genomic stress in cardiomyocytes, as shown by the levels of p-γ-H2AX, 8-oxodG glycosylase (OGG1/2) and apurinic site nuclease (APE1). Cardiac metabolic changes induced by ATM loss (rise of pyruvate, lactate and succinate levels) were also present in $Atm^{-/-}$ brains, although the basal conditions were different.
Conclusions: ATM rewires the metabolism of cardiac cells by inducing glycolysis and fatty acids oxidation. Combining metabolomic, DNA damage and cardiac phenotypes, we deduce that ATM stimulates glycolysis to repair DNA lesions and protect the heart against stress-induced dysfunction.

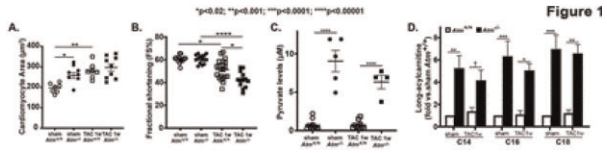

Figure 1