Abstract: **P82**

**ATM regulates cardiac mitochondrial oxidative phosphorylation potential**

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Ataxia Telangiectasia (A-T) is a rare, recessive genetic disease that arises due to a decrease or absence of Ataxia Telangiectasia mutated protein kinase (ATM). A-T results in insulin resistance, type 2 diabetes and cardiovascular disease, while the absence of ATM has been associated with increased oxidative stress. ATM also maintains myocardial glucose and redox homeostasis. Using animal models, we demonstrated that myocardial ATM expression is (i) low in obesity and (ii) located on the inner mitochondrial membrane. In light of the potential importance of mitochondrial dysfunction associated with cardiovascular disease, this study aimed to investigate the role of mitochondrial ATM in cardiac oxidative phosphorylation (oxphos) using male Wistar rats.

Methods: TEM and SR-SIM microscopy and western blotting were employed to localize ATM. Ex vivo perfusion (n=6-9/group) of hearts ± the specific ATM inhibitor, KU60019 (3 uM) or insulin (0.3 IU/L), was performed prior to mitochondrial isolation and oxidative phosphorylation measurements (Clarke-type electrode) using either a carbohydrate (glutamate) or fatty acid (palmitoyl-carnitine) substrate.

Results: Sequential shearing off of mitochondrial membranes coupled to western blot analysis of marker proteins demonstrated the localization of ATM to the inner mitochondrial membrane. SR-SIM using fluorescently labelled antibodies confirmed this by showing co-localization with ANT (inner membrane) but not VDAC (outer membrane). Inhibition of ATM significantly decreased active (State 3) and resting (State 4) mitochondrial respiration (O2 consumption) which was associated with a decreased oxphos rate (ADP/O x QO2 State 3) and respiratory control index (RCI) (p<0.05) with both substrates. In contrast, stimulation of hearts with insulin, increased mitochondrial respiration parameters that, in turn, were reversed by inhibition of ATM. Moreover, inhibition of ATM resulted in decreased total mitochondrial Drp1 levels indicating less fission. Conclusions: Taken together, this suggests that ATM plays an important role in mitochondrial oxidative phosphorylation and may be involved in mitochondrial dysfunction in insulin resistance.