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| **Metformin Mitigates Cigarette Smoking-induced Muscle Loss: An In vitro Study** |
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| **Introduction/Aim:**  Skeletal muscle wasting is a common comorbidity of COPD and smokers. Our previous work suggested this may be related to anabolic resistance. Metformin, an anti-diabetic medication, has shown promise in preserving muscle mass in various contexts, by improving anabolic sensitivity of skeletal muscle. This makes metformin a promising candidate for preserving muscle mass in COPD and smokers. Using a cell culture model, this study aimed to demonstrate (i) the role of anabolic resistance in COPD-related skeletal muscle wasting; and (ii) the benefit of reversing anabolic resistance on skeletal muscle wasting by cigarette smoking.  **Methods:**  Bronchial epithelial cells (BEAS-2B) were stimulated with either cigarette smoke extract (CSE) or H2O2 to generate conditioned media, recapitulating the secretome of smokers and COPD. The conditioned media was then transferred onto fully differentiated C2C12 myotubes with or without metformin (1 mM) for the assessment of myotube size, protein content and myogenic signalling.  **Results:**  Exposure to CSE or H2O2 conditioned media led to reduction in myofibre size and loss of myofiber integrity (n=6, *p*<0.001), which were associated with an increase in protein carbonylation (n=5, *p*<0.01) suggesting oxidative stress. In the untreated myotubes, insulin stimulated the phosphorylation of Akt (120-fold vs unstimulated control, n=6, *p*<0.001) and FoxO1 (Ser259; 35-fold vs unstimulated control, n=6, *p*<0.001), which were blunted following exposure to CSE or H2O2 conditioned media. Metformin preserved myofiber size and integrity against the insults of CSE or H2O2 conditioned media (n=6). This was associated with preserved insulin-stimulated phosphorylation of Akt and FoxO1. However, metformin only attenuated protein carbonylation from the H2O2, but not the CSE conditioned media.  **Conclusion:**  Anabolic resistance is likely to drive skeletal muscle wasting in COPD and smokers which may be mitigated by metformin. The discrepancy in protein carbonylation suggests the existence of an oxidative stress-independent mechanism for cigarette smoke induced muscle wasting. Our study underscores the importance of unravelling the intricacies of the secretome for new insights into the lung-muscle axis in COPD.  **Grant Support:**  NHMRC project grant APP1138915 |