Crosstalk between Nrf2 Signalling and Zinc in Human Coronary Artery Cells under Hyperoxia, Physiological Normoxia and Hypoxia

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Zinc is an important component of the cellular antioxidant defence and dysregulation of zinc homeostasis is a risk factor for coronary heart disease and is associated with oxidative damage in ischemia-reperfusion injury. This study aimed to (i) characterise the metallomics and redox phenotype of human coronary artery smooth muscle cells (HCASMC) and human coronary artery endothelial cells (HCAEC) adapted long-term (5 days) to hyperoxia (18 kPa O_2), physiological normoxia (5 kPa O_2) or hypoxia (1 kPa O_2) and (ii) investigate crosstalk between Zn and Nrf2 signalling under 18 or 5 kPa O_2. When HCASMC and HCAEC were adapted to 18, 5 or 1 kPa O_2, HIF-1α stabilisation was only observed in cells under 1 kPa O_2. The redox phenotype of HCASMC adapted long-term to 5 kPa O_2, was affected negligibly as evidenced by negligible changes in intracellular GSH levels and Nrf2-targeted HO-1, whilst both were significantly lower in HCAEC adapted to 5 and 1 kPa compared to 18 kPa O_2. Total Zn66 levels determined by ICP-MS analysis were similar in HCASMC under 18, 5 kPa or 1 kPa O_2 (18 kPa = 0.345 ± 0.090 ng/µg protein, 5 kPa = 0.298 ± 0.020 ng/µg protein, 1 kPa = 0.441 ± 0.058 ng/µg protein) but decreased as pericellular O_2 decreased in HCAEC (18 kPa = 0.345 ± 0.056 ng/µg protein, 5 kPa = 0.267 ± 0.032 ng/µg protein, 1 kPa = 0.177 ± 0.020 ng/µg protein). The effects of pericellular O_2 levels on redox phenotype and total Zn66 content are thus cell-type specific. Notably, Zn supplementation induced Nrf2 nuclear accumulation in HCASMC not in HCAEC under 18 or 5 kPa O_2, and whilst Nrf2 siRNA silencing did not significantly alter Zn66 content in HCASMC it led to a significant decrease in HCAEC under 18 kPa O_2. Our study highlights the critical importance of adapting cells in vitro to physiological O_2 levels and provides the first insights into the crosstalk between Nrf2 and Zn in human coronary artery cells.