Roles of Arginase-II in vascular endothelial inflammation under hypoxia

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Background and Aim: Hypoxia remains the major pathogenicity of cardiovascular diseases. It is a deprived O_2 condition in the vascular system of all mammalian living organisms. Hypoxia acts as a culprit in development of cardiovascular disease. Hypoxia-inducible factors (HIF) namely HIF-1 and HIF-2 are the central regulating mechanistic mediators of cellular functions under the hypoxic condition. Under normoxic condition, the enzyme prolyl-4-hydroxylase (PHD) senses O_2, leading to degradation of HIFs by proteasomes, while under hypoxic condition, PHD remains inactive and therefore leads to HIF accumulation in the cells. Studies report that the mitochondrial enzyme arginase type 2 (Arg-2) causes endothelial nitric oxide synthase (eNOS)-uncoupling, leading to endothelial dysfunction and enhanced expression of endothelial inflammatory adhesion molecules, i.e., vascular cell adhesion molecule (VCAM-1) and intercellular cell adhesion molecule (ICAM-1). The aim of this study is to investigate whether hypoxia causes endothelial dysfunction and adhesion molecule expression through Arg-2.
Methods: Primary human endothelial cells were isolated and cultured from umbilical veins and exposed to hypoxia condition i.e., 0.2% O_2 for up to 72 hours in the hypoxia chamber. In some experiments, the cells were treated with the drug dimethyl oxalyl glycine (DMOG) that inhibits PHD and causes HIF accumulation in the cells and mimic the hypoxia condition. Expression levels of Arg-II, VCAM-1 or ICAM-1 were analysed by immunoblotting using specific antibodies. Arg-2 gene silencing was achieved using adenovirus-mediated shRNA. Human monocyte THP1 cell line was labelled with a fluorescent dye CFDA-SE and used for studying monocyte-endothelial cell adhesion in vitro.
Results: Exposure of the cells to hypoxia causes a time-dependent increase in Arg-II, HIF1α, HIF2α, and ICAM-1 (but not VCAM-1), which reaches maximal effects between 48 to 72 hours. Similar effects were obtained in cells treated with DMOG which elevates HIFs and mimics the hypoxic condition. Silencing Arg-2 prevents the ICAM expression induced by DMOG. In line with this result, endothelial cells treated with DMOG have enhanced monocyte adhesion, which is inhibited in cells with Arg-2 silencing.
Conclusion: Hypoxia enhances Arg-2 expression which mediates endothelial ICAM-1 expression and causes enhanced monocyte-endothelial interaction. This effect of hypoxia on endothelial cells may play an important role in cardiovascular diseases. It remains to be investigated whether HIF1α or HIF2α or both are responsible for upregulation of Arg-2 under the hypoxic condition. Our results suggest that Arg-2 could be a promising therapeutic target to prevent hypoxia-induced vascular damage/dysfunction.

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