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Monocyte priming by metabolic stress: A novel NADPH oxidase 4-dependent mechanism for the development and progression of atherosclerosis

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We reported that metabolic stress primes blood monocytes for chemokine-induced adhesion and migration. This gain-of function phenotype is observed in both dyslipidemic and diabetic mice and is associated with increased Nox4 expression and protein-S-glutathionylation, and results in increased macrophage recruitment and accelerated atherogenesis, but the underlying mechanism was not known. The goal of this study was to determine the role of Nox4 in monocyte priming and to identify the molecular targets of Nox4-derived H_2O_2 induced by metabolic stress. Prolonged exposure of monocytes to human low density lipoprotein (LDL), high glucose concentrations (HG) or LDL plus HG (LDL+HG) induced Nox4 expression, increased intracellular H_2O_2 formation, promoted protein S-glutathionylation, and increased chemotaxis in response to MCP-1, PDGF-B and RANTES. Overexpression of Nox4 sensitized monocytes to MCP-1-induced chemotaxis, whereas Nox4 knockdown or overexpression of glutaredoxin 1 (Grx1) protected against both metabolic stress-induced protein-S-glutathionylation and increased chemotaxis. We identified MKP-1 and actin as targets of Nox4-mediated S-glutathionylation and showed that S-glutathionylation of these two proteins accelerates monocyte chemotaxis by hyper-activating ERK and p38MAPK signaling and increasing actin remodeling. We also show that MKP-1 deficiency in monocytes of dyslipidemic LDL-R-null mice mimics monocyte priming and accelerates both MCP-1-induced macrophage recruitment and atherosclerotic lesion formation. In conclusion, monocyte priming for chemokine activation induced by metabolic stress requires the induction of Nox4 and is mediated by the S-glutathionylation of actin and MKP-1. We identified a novel, proatherogenic mechanism through which metabolic disorders promote macrophage recruitment to sites of vascular injury.

Biography

Reto Asmis received Ph.D.in Biochemistry from the University of Fribourg in Switzerland. He completed Postdoctoral fellowships at the University of California in San Diego and the University of Berne in Switzerland. He is a tenured Professor in the Departments of Clinical Laboratory Sciences and Biochemistry and the Associate Dean of the Graduate School of Biomedical Sciences at the University of Texas Health Science Center at San Antonio. He is well-funded both by NIH and private foundations, and has published more than 60 papers. He is currently serving as Associate Editor of Atherosclerosis.

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