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Cardiovascular disease in metabolic syndrome associated with metabolic induction of a hypoxic response

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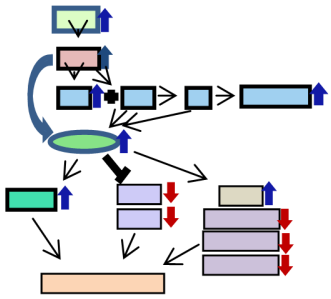
Statement of the Problem: The risk of cardiovascular disease (CVD), asthma, non-alcoholic fatty liver disease (NAFLD) as well as common cancer is increased in subjects with metabolic syndrome (MetS). Interleukin-4 (IL-4), a marker of Th2 immune response, is often upregulated in these contexts and may potentiate aberrant arginine metabolism. Altered arginine/nitric oxide metabolism and mitochondrial dysfunction represent putative common molecular pathways that may connect these diseases, possibly via oxidative-stress driven induction of the cellular hypoxic response. The importance of this pathway is not well studied in MetS associated vascular dysfunction.

Aim: The purpose of this study is to investigate how altered arginine/methyl arginine balance, oxo-nitrative stress, hypoxic response and mitochondrial dysfunction may cause vascular dysfunction in metabolic syndrome.

Methodology & Theoretical Orientation: MetS mice (C57BL/6) were fed chow-diet (CN), high-fat-diet (HFA), or high-fructose-diet (HFR) for six months. HFR and HFA diets induce MetS. Arginine/methyl arginine balance and oxo-nitrative stress were determined in aortic tissue by measuring the levels of ADMA, iNOS and 3-nitrotyrosine. Estimation of hypoxic response done by checking levels of HIF1α and resultant mitochondrial dysfunction by measuring levels of cytochrome c, TFAM, mitochondrial membrane potential and mitochondrial complex I and IV activity.

Conclusion & Significance: IL-4 and ADMA were increased in HFA and HFR mice with MetS, compared to normal controls (CN). Vascular endothelial cells of both these groups also showed an increase in oxo-nitrative stress. IL-4 and ADMA led to potent induction of the cellular hypoxic response (HIF1α), despite normoxic conditions. The hypoxic response was associated with increased levels of the hypoxamir-210 that targets mitochondria, reduced mitochondrial membrane potential, complex I and complex IV activities, decreased TFAM and PGC1α levels, and leak of cytochrome-c to cytosol. In conclusion, IL-4 and ADMA are increased in MetS, leading to mitochondrial dysfunction through oxo-nitrative stress and hypoxic response. This has broad applicability to multiple diseases influenced by the hypoxic response, including cancer.



Recent Publications

1. Eva Kassi et al (2011) Metabolic syndrome: definitions and controversies. BMC Medicine. 9:48
2. Singh VP et al (2015) Metabolic Syndrome Is Associated with Increased Oxo-Nitrative Stress and Asthma-Like Changes in Lungs. PlOS One. 10(6)
3. Sookoian S, Pirola CJ (2008) Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. J Hepatol. 49(4):600-7
4. Sun Q et al (2012) Upregulated Protein Arginine Methyltransferase 1 by IL-4 Increases Eotaxin-1 Expression in Airway Epithelial Cells and Participates in Antigen-Induced Pulmonary Inflammation in Rats. J Immunol. 188(7):3506-3512
5. Pattnaik et al (2016) IL-4 promotes asymmetric dimethylarginine accumulation, oxo-nitrative stress, and hypoxic response–induced mitochondrial loss in airway epithelial cells. JACI. 138(1):130-141.

Biography

Evanka Chopra has her expertise in Molecular/Cell Biology and Computational Biology techniques. She has qualified national level examination viz., CSIR/UGC-JRF and GATE. She is an enthusiastic and hard bench worker with innovative and inquisitive mind and has an outstanding reasoning power reflected by her own alterations and designing in the protocols to get task done with optimum outputs. She has very good writing and communication skills. She can express herself fairly well in group discussion and can communicate scientific ideas and views, as evident from her several poster/oral presentations in conferences, journal club and lab presentations. She has published her doctoral research work in the *Journal of IJC and Oncogene*.

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