KSN 2016 Abstract Submission

Clinical & Experimental CKD & Genetics

KSN2016ABS-1326

Inactivation of Placental Growth Factor is Associated with Perirenal Inflammation and Renal Impairment

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Background: There is a growing body of evidence that obesity related disorders are associated with pathological angiogenesis in the adipose tissues and the kidney. In the metabolically active brown adipose tissue, active angiogenesis can increase the metabolic rate in response to energy surplus, leading to a lean phenotype. Placental growth factor (PlGF), originally discovered in human placenta, exerts functional homology with VEGF, which has favorable angiogenetic activity of adipose tissue, through its interaction with VEGFR1 and it is widely expressed in adipocytes and the kidney. We investigated the role of PlGF in adipose tissue-related angiogenesis and in control of fat mass, perinephric fat in particular and whether the inactivation of PlGF would further aggravate renal phenotypes and contribute to its functional deterioration.

Methods: Male wild-type or PlGF-deficient ($PlGF^{-/-}$, PlGF KO) mice were obtained and fed a regular diet chow. Systolic blood pressures were measured and mice were sacrificed at 9^{th} and 32^{nd} weeks to compare biochemical parameters and analyze relevant molecular expressions and ultrastructure of kidney and perinephric adipose tissues at each distinct time point.

Results: At nine weeks of age, there were no significant changes in body weight and blood pressure between PlGF KO and control mice. However, perinephric adipose tissues of nine week old PlGF KO mice showed sparsely adjoined adipocytes as opposed to dense and tightly packed crowd of fat cells in the control group. Quantitative analysis revealed significantly decreased number and larger size of perinephric fat cells in PlGF KO mice. At thirty-two weeks of age, significant high systolic blood pressures and weight gain were recorded within PlGF KO mice when compared to the control group. Thirty-two week old PlGF KO phenotype revealed variously increased size of perinephric adipocytes as compared to large size of adipocytes uniformly distributed within the perinephric tissues in the control group and infiltration of F4/80-positive cells was markedly increased as well. This finding suggests that PlGF may be essential in retaining intact adipocyte in both structural and functional aspects as evidenced by disrupted size and structure of adipocytes and increased inflammatory reactions in PlGF deficient mice. The expressions of phospho-AMPK and PGC-1α were significantly decreased in both perinephric fat and kidney of PlGF KO mice. Consistent down regulations in the expressions of both PlGF

and PECAM-1 were shown. In regard to renal ultrastructure, PlGF KO mice exhibited unfavorable renal phenotypic changes including glomerular sclerosis and inflammation.
Conclusion: Our study suggests that PlGF KO mice represent impaired vasculature and adipogenesis both in the perirenal fat and the kidney. This derangement would promote hypoxia, inflammation, and oxidative stress-induced perirenal adipose tissue inflammation which may further impair lipid metabolism and deteriorate renal phenotypic and functional parameters.

Keywords: Perirenal Inflammation , Placental growth factor , Renal Impairment