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Manipulation of the Embryonic Environment - Generation of a Human-Like Hypertensive Nephropathy Model by Excess Salt Ingestion into MEM Mice Model of Diabetic Nephropathy

Shiori Ishiyama

University of Yamanashi, Faculty of Life and Environmental Sciences

Summary

Objective: Effective treatment and prevention of chronic kidney disease (CKD) remain undeveloped, in part due to the lack of animal models that can reproduce the human condition. Recently, we have successfully created a mouse model of diabetic kidney disease (DKD) by combining in vitro culture of preimplantation embryos in a specific culture medium and subsequent environmental manipulation of their diet after birth, as in humans. The aim of this study was to create a model of CKD that spontaneously develops due to excessive salt intake using embryonic environment manipulation MEM mice and to establish a model in which the pathogenesis can be observed.

Methods: MEM mice cultured in vitro in αMEM medium (control: KSOM) during embryogenesis and allowed to give birth were treated with 10% sugar water for 1.5 months immediately after weaning. After that, the following test solutions were administered *ad libitum* for 1 month: 1) control KSOM mice without additional salt and 2) MEM mice, 3) MEM mice receiving 1.0% NaCl solution (mild-salt group), and 4) MEM mice receiving 3.0% NaCl water (severe-salt group).

Results: In pathological evaluation of liver, progression of liver fibrosis was observed in the perivascular area in the mild-salt and severe-salt groups. Inflammation-related gene expression in the liver was significantly increased in the severe-salt group compared to the mild-salt group for *Tnfa* and the control MEM group for *Ly6c*. HE staining of ileum sections showed disruption of villi structure in the mild-saline and severe-saline groups. *Muc4* gene expression related to intestinal barrier function in the ileum was significantly decreased in the mild-salt and severe-salt groups compared to the control MEM group.

Discussion: This study suggests that the poor nutritional environment before and after birth, additional stimuli that increase inflammatory response, such as excess salt intake, may induce and exacerbate steatohepatitis, in addition to disruption of ileum villi structure, which may lead to severe disease. This model resembles the human phenomenon, suggesting that it may be a model animal that causes organ damage due to exacerbation of chronic inflammation.