Intrauterine growth restriction and reduced glomerular number: role of apoptosis

Barbara T. Alexander
Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi 39216

As proposed by Barker (2, 3), limitations in fetal nutrition contribute to intrauterine growth restriction and the increased risk for development of cardiovascular disease and hypertension in later life. Although this observation was derived from numerous epidemiological studies, experimental studies in animals further support fetal programming of hypertension and the role of the kidney. Specifically, animal models of fetal malnutrition induced by either maternal protein restriction during gestation or uteroplacental insufficiency lead to intrauterine growth restriction (IUGR) and offspring predisposed to the development of hypertension (1, 14, 16). The kidneys are known to play an important role in the long-term regulation of arterial pressure (6). An important role for kidneys in the programming of hypertension is suggested as animal models that induce IUGR via an adverse fetal environment are often associated with marked reductions in glomerular number (4, 8, 10, 14, 16). Hypertension induced by fetal programming may be due to a decrease in glomerular filtration rate mediated by a decrease in nephron number and/or an increase in tubular reabsorption. Thus, in low birth weight individuals, nephron number compromised during renal development may contribute to adult hypertension (5, 7). However, the exact molecular mechanisms linking IUGR with reduced glomerular number and hypertension remain unclear.

As nephron number is reduced in different animal models of fetal programming, involvement of a common pathway is suggested. Vehaskari et al. (14) first noted a possible link between maternal protein restriction and nephron deficiency as renal apoptosis was increased at 8 wk of age in hypertensive offspring from protein-restricted dams (14). Welham and associates (15) further investigated this link in the low-protein model of fetal programming as aberrant nephrogenesis was associated with increased renal apoptosis in the metanephric mesenchyme, the embryonic precursor of adult kidney. In their paper, Welham and associates speculate that protein restriction during gestation may enhance apoptosis by altering expression of apoptosis-related genes, specifically Bcl-2, an anti-apoptosis gene, and Bax, a pro-apoptosis gene. Apoptosis plays an important role in normal nephrogenesis (12, 13, 17), and alterations in the apoptosis cascade characterize experimental models of fetal obstructive nephropathy (9).

In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Pham and colleagues (11) examined this molecular mechanism, the role of apoptosis, in linking an adverse fetal environment with reduced nephron number. Using a model of uteroplacental insufficiency, the authors characterized the relationship between reduced nephron number and renal apoptosis (11). The authors first examined glomerular number to confirm a reduction was associated with IUGR induced by bilateral uterine artery ligation. The authors then examined apoptosis as a molecular mechanism whereby uteroplacental insufficiency leads to a reduced glomerular number. They found a significant reduction in Bcl-2 mRNA, an important survival molecule, and a significant increase in Bax, a death-enhancing gene, in the IUGR kidney (11). Alterations in these key components of the apoptosis cascade were associated with a significant increase in apoptotic nuclei in the IUGR kidney as measured by transferase uridine nick end-label technique (TUNEL) assay (11). In addition, a significant increase in caspase-3 activity, which is required for the morphological changes associated with apoptosis, and expression of p53, a regulator of Bcl-2 transcription, were also noted (11).

Thus the paper by Pham et al. shows that uteroplacental insufficiency is associated with a decrease in nephron number, an increase in renal apoptosis, and alterations in the apoptosis cascade. Although these results suggest a potential role for apoptosis in mediating abnormal nephrogenesis and decreased glomerular number in uteroplacental insufficiency, the relationship between apoptosis and decreased nephron number is only correlative. Future studies will be necessary to determine a direct cause and effect relationship between apoptosis and a nephron deficiency induced by an adverse fetal environment.

REFERENCES


Address for reprint requests and other correspondence: B. T. Alexander, Dept. of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, MS 39216-4504 (E-mail: balexander@physiology.umsmed.edu).