Elucidating molecular mechanisms of the developmental origins hypothesis: p53 phosphorylation, apoptosis, and nephrogenesis

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Epidemiologic studies show that humans born small for gestational age are disposed to developing type 2 diabetes, obesity, hypertension, and cardiovascular disorders (the “metabolic syndrome”) during adulthood (3, 4). The mechanisms by which intrauterine growth restriction (IUGR) leads to metabolic syndrome are poorly understood, but it is likely that some form of “programming” occurs during fetal life, hence the term “fetal origins of adult disease.” (2) Along with the other components of the metabolic syndrome, kidney disease also is a major public health burden with exponentially increasing trends (8). Many of the cases may have their origins in fetal life. In human fetuses, kidney volumes are reduced to the same extent as the birth weight (6, 7) and the number of nephrons is reduced by ∼35% in infants with a birth weight below the third percentile. Several models of IUGR have been developed in animals that show decreased nephrogenesis similar to that seen in growth restricted humans (5, 9). Growth restriction in these animal models has been induced by maternal dietary protein deprivation, injection of corticosteroid into the pregnant animal, or by uterine artery ligation. Even if aggressive postnatal nutrition results in catch-up growth, the size of the kidneys and number of nephrons remains low in relation to the reduction at birth, suggesting a permanent defect induced by an early insult (12). The offspring of the rats undergoing these various forms of IUGR and decreased nephrogenesis also demonstrate hypertension in the offspring.

One of the many difficulties with clearly defining a pathogenic mechanism relates to the multitude of systems (metabolic-endocrine, renal, cardiovascular, neuroendocrine) that appear to be related to IUGR-related programming. A key to addressing these differences is to finding common pathways that are relied on by the various systems that are involved. Several years ago, Lucas, et al. (10) and Waterland and Garza (15) proposed general mechanisms for the fetal origins of adult metabolic syndrome that included: 1) induced variations in organ structure, 2) alterations in cell number, 3) clonal selection, and 4) metabolic differentiation. However, these do not address the mechanisms on a molecular level. It is unlikely that direct alterations in the DNA genetic code are involved in the programming. More recently, epigenetic mechanisms involving altered gene methylation or histone structures have been invoked as keys to programming through gene activation and/or inactivation (11, 13), but these remain poorly understood.

The report by Baserga et al. (4a) in this issue of American Journal of Physiology-Regulatory, Integrative and Comparative Physiology provides new information linking renal insufficiency with IUGR on a cellular and molecular level. The authors posit that renal cell apoptosis that occurs during early development could lead to a subsequent decrease in nephrogenesis. In previous studies, using a model of IUGR caused by uteroplacental insufficiency rendered by bilateral uterine artery ligation on day 19 of gestation in Sprague-Dawley rats, these investigators observed that nephrogenesis was impaired. Concomitant with this observation, it was found that these IUGR rats have increased kidney p53 protein levels associated with increased apoptosis. To evaluate potential cellular molecular mechanisms of this effect, they focused on phosphorylation of the amino terminal serine 15 (phospho-p53 Ser15) which is known to increase p53 stability and apoptotic activity, and the murine double-minute 2 (MDM2) functional circuit which limits further p53-induced apoptosis by promoting proteosomal degradation of p53. They hypothesized that IUGR induces an increase in p53 phosphorylation at Ser15 through elevated kinases, but p53 proteolytic degradation via MDM2 would not be affected. In their experiments, uteroplacental insufficiency significantly increased phospho-p53 Ser15 as well as three key kinases, which induce phosphorylation of the p53. This was not associated with increases in kidney MDM2 mRNA and protein levels, results that supported their hypothesis. The authors speculated that this response may contribute to the increased apoptosis previously described in the IUGR kidney.

The results of these studies lead to the deeper question of what molecular mechanisms alter kinase-related phosphorylation of p53. Previous studies by this group have evaluated other mechanisms of how p53 might be altered in fetal IUGR rats after uterine artery ligation and demonstrated that the p53 gene is demethylated and thus upregulated (14). Prolonged alteration of methylation constitutes an epigenetic memory, which has a long lasting effect on gene function and may thus partly explain the persistent fetal programming. In the current paper, they describe a mechanism that may be considered as an alternative to their previous findings. One question that arises is whether the altered phosphorylation of the phospho-p53 Ser15 moiety is related to the previous epigenetic findings in a single pathway or whether this is a separate phenomenon. Are there genes for the three kinases described that are also demethylated to allow for their increased activation of p53? Are both of these mechanisms occurring concomitantly or do they depend on severity of the IUGR? How do these findings mesh with several other mechanisms that have been invoked and recently reviewed? (1)

Other questions that arise are whether the animal model used represents the pathogenic stresses leading to IUGR in the human infant. It would be of interest whether nutritional aberrations or hormonal manipulations, such as glucocorticoid administration might lead to similar changes as uterine artery ligation. Further questions arise about postnatal stresses in early infancy and especially premature infants and whether these might also result in molecular alterations that will program for diseases in adulthood.

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The article by Baserga et al. is notable as a part of an emerging literature that takes the “fetal origins” hypothesis out of the realm of epidemiology and begins to explain the basic mechanisms of this fascinating phenomenon.

REFERENCES