

ASAS Western Section Symposium: Perinatal Programming of Offspring

Quality 1: Basic Concepts and Experimental Evidence

775 Key principles of developmental programming of later life events: Observations in primate development. P. W. Nathanielsz^{*1}, L. Cox¹, T. McDonald¹, S. Ford², K. Mitsuya¹, and M. Nijland¹, ¹*Center for Pregnancy and Newborn Research, The University of Texas Health Science Center, San Antonio,* ²*University of Wyoming, Laramie.*

Mammals pass more biological milestones before birth than the rest of life. Critical developmental phases are windows of potential susceptibility to adverse gene-environment epigenetic influences that may predispose to chronic later life diseases e.g., hypertension, obesity, and diabetes. Compelling human epidemiological and animal research studies clearly demonstrate that a suboptimal intrauterine environment alters the trajectory of development and epigenetically modifies cell function. The controlled animal studies to evaluate normal and abnormal fetal development have mostly been conducted in rodents or sheep. There are, however, considerable differences in pregnancy between primates and other species. Rodents are polytocous species delivering up to 16 altricial pups which with their placentas are a biomass equivalent to a woman delivering a sixty pound baby. Many fetal stages of development in precocial species occur postnatally in rodents when oxygenation, metabolic and hormonal status differ significantly. The developmental challenges most extensively investigated are poor maternal nutrition and maternal stress. Developmental programming represents a convergence of environmental influences on genotype. This presentation will focus on our studies in baboon fetal and postnatal life with offspring of control (CTR) ad lib fed baboons and baboons undergoing maternal nutrient reduction (MNR) that eat 70% of the global diet consumed by CTR females in pregnancy and lactation. At term, MNR reduces islet cell number and protein content of insulin and key growth factors such as IGF-I and IGF-II. Gene array studies show dysregulation of several pathways in the placenta, liver, kidney and brain – many of these pathways involve nutrient signaling and energy generation and utilization. These changes and epigenetic marks resulting from altered methylation will be discussed.

776 Epigenetic transgenerational actions of environmental factors on reproduction and disease: The ghosts in your genome. M. K. Skinner^{*}, *Washington State University, Pullman.*

Transgenerational effects of environmental factors (e.g., nutrition and endocrine disruptors) significantly amplify the impact and health hazards of these factors. One of the most sensitive periods to exposure is during embryonic gonadal sex determination when the germ line is undergoing epigenetic programming and DNA re-methylation. A model endocrine disruptor tested was vinclozolin, which acts as an anti-androgenic compound. Previous studies have shown that this endocrine disruptor can affect embryonic testis development to subsequently cause an increase in spermatogenic cell apoptosis in the adult. Interestingly, this spermatogenic defect is transgenerational (F1, F2, F3 and F4 generations) and shown to be due in part to a permanent altered DNA methylation of the germ-line. This appears to involve the induction of new imprinted-like DNA methylation sites that regulate transcription distally. Differential DNA methylation regions were identified with ChIP-Chip analysis in

F3 generation sperm. The impact of these epigenetic changes have on the genome used transcriptome analysis. The expression of hundreds of genes were found to be altered in the embryonic testis and surprisingly this altered transcriptome was similar for all generations (F1-F3). All tissues examined had a transgenerational transcriptome effect that was tissue specific. In addition to detection of the male testis disorder, as the animals age transgenerational effects on other disease states were observed including tumor development, prostate disease, kidney disease and immune abnormalities. Therefore, the transgenerational epigenetic mechanism appears to involve the actions of an environmental compound at the time of sex determination to alter the epigenetic (i.e., DNA methylation) programming of the germ line permanently that then alters the transcriptomes of developing organs to induce disease development transgenerationally. Similar Transgenerational effects have now been observed with nutrition, BPA and phthalates. The suggestion that environmental factors can reprogram the germ line to induce epigenetic transgenerational disease is a new paradigm in disease etiology.

777 Even her uterus can't protect you. Stress in life: A multi-species review. D. C. Lay Jr.^{*}, *USDA-Agricultural Research Service, Livestock Behavior Research Unit, West Lafayette, IN.*

All environments can pose challenges to animals which cause stress; they meet these challenges by making behavioral and physiologic adjustments. These adjustments include behavioral responses of fighting or hiding; and physiologic adjustments which include such processes as regulation of blood glucose, altered cardiac function and others that help the animal to react to the stress and to bring the body back to its normal state. However, when this occurs to animals which have developing ova, are pregnant, or caring for young; there is a potential for the stress to also influence the development of these individuals. Although the literature is not always consistent in how the individuals are affected, alterations due to early exposure to stress have been shown in mice, guinea pigs, poultry, swine, sheep, cattle, horses and humans, to name a few. It is clear that stress during these early developmental stages can alter how the animals respond to stressors later in life, with changes seen in both their behavior and physiologic responses to stressors. In mammals, the uterus is an affective barrier to many of the external threats to which the fetus may be exposed; however it is clear it is not full-proof. In avian species, stress responses can alter the hormonal content of the yolk which then later alter the development of the embryo. One theory suggest that alterations due to stress are adaptive, preparing the offspring for a stressful environment. The timing of such events during fetal and neonatal development is critical to the integrity and normal function of all animals. The observation that stress can alter the later responses of so many species of animals is profound. In addition, the fact that exposure to stress can have deleterious effects to all the livestock and poultry species which we raise, necessitates our complete understanding. It also may provide a mechanism with which we could facilitate animals' adaptation to environments in which they will be housed in the future.

Key Words: stress, development, programming