

## **57. TEMPORO-SPATIAL ALTERATIONS IN PROSTATE BRANCHING MORPHOGENESIS IN ESTROGEN-DEFICIENT AROMATASE KNOCKOUT (ArKO) MICE**

*Ghanim Almahbobi<sup>1</sup>, Shelley Hedwards<sup>1</sup>, Vikrant Reddy<sup>1</sup>, Stephen McPherson<sup>1</sup>, Gabriel Fricout<sup>2</sup> and Gail P. Risbridger<sup>1</sup>*

<sup>1</sup>Monash Institute of Reproduction and Development, Monash University, Melbourne; <sup>2</sup>Centre de Morphologie Mathématique, Ecole des Mines de Paris, France.

The development and growth of the prostate gland requires branching morphogenesis, a process that continues during the neonatal period. Estrogen is involved in prostate development but its temporo-spatial effects during early development are not understood. Using new methods of confocal microscopy and volume-rendering image analysis, the aim was to detect and quantify the temporo-spatial changes in prostate branching morphogenesis in neonatal estrogen-deficient ArKO mice. In wild type animals, the lateral and medial ducts of anterior prostatic lobes reveal developmental asymmetry with significant increases in branching morphogenesis of the lateral duct, which is retained during day 0-3. In ventral lobes, similar asymmetrical growth is observed but increases in branching occur randomly in lateral or medial ducts. At day 14, ArKO mice exhibit prostatic hypertrophy and significant increases in the stromal, epithelial and luminal volume. To determine whether estrogen deficiency has specific immediate effects on neonatal prostate branching morphogenesis, prostatic lobes were analysed at days 1 and 3. At day 1, anterior lobe from knockout mice exhibits significant increase in the duct volume only. At day 3, all events of branching morphogenesis are significantly accelerated in both knockout and heterozygous mice. In the ventral lobe, the effect of estrogen deficiency results in significant increases in some branching parameters in knockout animals at day 3 only. To determine the spatial distribution of these alterations within prostatic lobes, branching events were assessed in individual ducts. In the anterior lobe, all parameters are significantly increased in both lateral and medial ducts in knockout animals with significantly pronounced increases in the medial ducts, resulting in less asymmetry. In the ventral lobe, however, no significant alteration is found in either duct. In summary, estrogen deficiency in ArKO mice leads to significant neonatal age-related lobe- and duct-specific alterations; being more detrimental in anterior than in ventral lobes and more pronounced in medial than in lateral ducts. We conclude that estrogen is a critical regulator of prostate gland development, exerting significant early effects on gland growth. Therefore, the detection and quantification of aberrant branching morphogenesis within the first 4 days of neonatal life predicts prostate pathology that is known to occur in adulthood.