Report of the XIV Adrenal Cortex Conference 2010- San Diego, CA June 16-18 2010

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The organizers of the XIV Adrenal Cortex Meeting were delighted to receive generous support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Office of Rare Diseases. The funds enabled the organizers to mount a program that included outstanding presentations of cutting edge research directly relevant to the topic of Rare Diseases and to provide a forum for active discussions of current findings and projections for future research and drug therapy approaches.

A number of talks focused specifically on genetic and regulatory events related to adrenocortical tumorogenesis and on rare genetic disorders that affect steroidogenesis and/or other endocrine processes causing significant phenotypes. Enzo Lalli (Valbone, France) presented data demonstrating that the proliferation of adrenocortical tumor cells is dependent on the gene dosage of the transcription factor steroidogenic factor 1 (SF-1), and that inverse agonists for SF-1 inhibit the proliferation of these tumors in vitro. Lalli’s team also identified a set of micro RNAs (miRNAs) that are differentially regulated in childhood adrenocortical tumorogenesis. In addition, his work demonstrated a new mechanism of regulation of IGF/mTOR signaling with potential for drug therapy of adrenocortical cancer. In connection with this general subject, Thomas Giordano et al  (Ann Arbor, MI) examined the miRNA expression profiles of adrenocortical tumors (benign and malignant) and found that adrenocortical carcinomas are characterized by the loss of a specific subset of miRNAs. Further studies by Constantine Stratakis (NICHD, NIH) revealed that miRNAs have a regulatory role in macronodular adrenocortical disease (MMAD), and that miR-130a and miR-382 expression are associated with the degree of disease severity as indicated by the midnight cortisol levels. The studies also demonstrated an inverse correlation of miR-200b and matrin (MTR3) expression in MMAD. MTR3, a nuclear matrix protein that interacts with nuclear proteins to regulate transcription, was identified as an miR200b gene target. Overall, these studies provided markers for MMAD severity and insights into the molecular etiology of MMAD. Jerome Bertherat (Reference Center for Rare Adrenal Diseases, Paris, France) presented results from studies on gene expression profiling from adrenocortical tumors that identified molecular predictors of malignancy and survival. The gene expression profiles of adrenocortical adenomas (ACA) and malignant cancers (ACC) showed significant differences; among the ACCs two distinct groups with different survival outcomes were identified. From these studies it was concluded that the analysis of a few molecular markers by RT-qPCR could distinguish among benign, malignant, and aggressive malignant tumors and provide a useful guide for therapy.

Walter Miller (San Francisco, California) presented an update on P450 oxidoreductase (POR) mutations and polymorphisms in human populations. POR is a protein that transfers electrons from NADPH to microsomal (Type II) cytochrome P-450 enzymes that participate in the biosynthesis of steroids (P450c17, P450c21 and P450aro) and in drug metabolism (e.g., CYP1A2, CYP2C19 and CYP3A4). It also functions as reductase for non-P450 enzymes (squalene monoxygenase, fatty acid elongase, and cytochrome b5). He summarized the large number of known POR mutations and polymorphisms, their degrees of impact on P450 enzymatic activity and their contributions to clinical phenotypes, which range from mild forms to more severe forms including Antley-Bixler skeletal malformation syndrome and genital abnormalities. Miller’s studies of POR variants
utilizing assays of P450c17 activity showed good correlations with the clinical phenotype. His studies also established that most POR mutants lacking activity in the P45017c assay were unable to support the activities of hepatic CYP1A2, CYP2C19; importantly, the most common POR mutations causing Antley-Bixler skeletal malformation syndrome significantly affected the activities of CYP2D6 and CYP3A4, both principal metabolizing enzymes of clinically used drugs. His studies on the transcriptional regulation of the POR gene determined that the polymorphism observed at -152 reduced the promoter activity of the gene in cultured cells. Helen Storr (London, England) provided insights into the pathogenesis of Triple A syndrome, a rare autosomal recessive disorder with mutations of the AAAS gene, characterized by alacrima, achalasia of the cardia, ACTH-resistant adrenal failure and progressive neurological manifestations. ALADIN, the gene product of AAAS, was found to interact with and enhance the nuclear localization of ferritin heavy chain (FTH1). As a consequence, fibroblasts from AAAS patients lacked nuclear FTH1. Of note, transfection of both genes (AAAS and FTH1) significantly reduced hydrogen peroxide-induced apoptosis in neuronal cells, providing a mechanistic basis for the progressive neurological manifestations of AAAS. John Achermann (London, UK) described SF-1 mutations and their impact in human disease. SF-1, a product of NR5A1 gene, is a member of the nuclear receptor family that regulate the transcription of genes essential for steroidogenesis, gonadal development and reproduction. Targeted deletion of NR5A1 in mice causes adrenal and gonadal dysgenesis, XY sex-reversal, partial hypogonadotropic hypogonadism, ventromedial hypothalamic abnormalities and persistent Müllerian structures in males. Ackermann’s group has demonstrated that SF-1 mutations in humans are more frequent than anticipated in 46 XY individuals with impaired fetal and postnatal testicular function, and in men with spermatogenic failure of unknown cause. Several heterozygous missense mutations of NR5A1 were identified and these were shown to have impaired transcriptional activity. Mutations of NR5A1 also have been found in 46XX women with familial and sporadic primary ovarian insufficiency. From their studies, Ackermann concluded that human adrenal development seems to be more resistant to the effects of SF-1 haploinsufficiency than gonadal development. In related studies, K. Miyamoto and T. Yazawa (Fukui, Japan) showed that SF-1 induced cell differentiation of bone marrow-derived mesenchymal stem cells (MSCs) into steroidogenic cells such as Leydig cells and adrenocortical cells, and in further studies demonstrated that LRH-1 is another key regulator of steroidogenic lineage in MSCs and in steroid production in the gonads. Furthermore, studies presented by W. Rainey (August, Georgia) described the role of nuclear receptors in the regulation of adrenal zonation. The results presented indicated that zone-specific expression of aldosterone synthase (CYP11B2) and 11β hydroxylase (CYP11B20) results from opposing activities of nuclear receptor NURR1 (NR4A2), which was shown to stimulate the CYP11B2 gene promoter activity in the zona glomerulosa and SF-1 which is a repressor of CYP11B2 and aldosterone production and an activator of CYP11B1. Studies on aldosterone-producing adenomas revealed elevated expression of NURR1 and CYP11B2, indicating that disregulation of their expression may contribute to the disease process. Finally, the meeting included a number of presentations on the regulation of genes responsible for congenital lipoid adrenal hyperplasia (StAR), familial glucocorticoid resistance (MC2R; MRAP), which enhanced our understanding of the molecular bases for these diseases.

The meeting brought together a diverse group of basic and clinical scientists with interests in the Adrenal Cortex. It covered a broad group of subjects that were presented by authorities in fields and generated in-depth formal and informal discussions. There was ample opportunity for interactions between seasoned scientists and young investigators, many of them presenters of excellent work in poster sessions. Over 120 investigators from this country and abroad attended the meeting, which was a major success as judged by the enthusiasm that it engendered and the overall evaluation. The excellence of the presentations and the exceptional role that many of the speakers had in defining mechanism of adrenal tumorogenesis and rare genetic diseases has placed this area of study at the forefront of this highly successful meeting.