

Review

Naturally Occurring and Experimentally Induced Rhesus Macaque Models for Polycystic Ovary Syndrome: Translational Gateways to Clinical Application

David H. Abbott ^{1,*}, Jeffrey Rogers ², Daniel A. Dumesic ³ and Jon E. Levine ⁴

- ¹ Department of Obstetrics and Gynecology, Wisconsin National Primate Research Center, University of Wisconsin, Madison, WI 53715, USA
- ² Human Genome Sequencing Center and Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA; jr12@bcm.edu
- ³ Department of Obstetrics and Gynecology, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095, USA; DDumesic@mednet.ucla.edu
- ⁴ Department of Neuroscience, Wisconsin National Primate Research Center, University of Wisconsin, Madison, WI 53715, USA; levine@primate.wisc.edu
- * Correspondence: abbottd@primate.wisc.edu; Tel.: +1-608-698-1953

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Abstract: Indian rhesus macaque nonhuman primate models for polycystic ovary syndrome (PCOS) implicate both female hyperandrogenism and developmental molecular origins as core components of PCOS etiopathogenesis. Establishing and exploiting macaque models for translational impact into the clinic, however, has required multi-year, integrated basic-clinical science collaborations. Paradigm shifting insight has accrued from such concerted investment, leading to novel mechanistic understanding of PCOS, including hyperandrogenic fetal and peripubertal origins, epigenetic programming, altered neural function, defective oocytes and embryos, adipogenic constraint enhancing progression to insulin resistance, pancreatic decompensation and type 2 diabetes, together with placental compromise, all contributing to transgenerational transmission of traits likely to manifest in adult PCOS phenotypes. Our recent demonstration of PCOS-related traits in naturally hyperandrogenic (High T) female macaques additionally creates opportunities to employ whole genome sequencing to enable exploration of gene variants within human PCOS candidate genes contributing to PCOS-related traits in macaque models. This review will therefore consider Indian macaque model contributions to various aspects of PCOS-related pathophysiology, as well as the benefits of using macaque models with compellingly close homologies to the human genome, phenotype, development and aging.

Keywords: developmental programming; androgen excess; infertility; adipogenic constraint; insulin resistance; transgenerational transmission; testosterone-associated traits

1. Introduction

Polycystic ovary syndrome (PCOS) bestows detrimental life-long consequences on a woman's health and wellbeing [1,2]. Elevated testosterone (T) levels are the most common endocrinopathy [3]. Newly published International Guidelines for the Assessment and Management of PCOS [1] support a clinical diagnosis requiring at least two out of the following three (Rotterdam) criteria: high circulating T levels or excessive body hair, intermittent or absent menstrual cycles, and polycystic

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