28 MARCH AT 11.30 A.M.
ROOM B109 | POVO 2

THE EVOLUTIONARY DEVELOPMENT OF A MOLECULAR SWITCH IN A STEROID RECEPTOR

MARIA PENNUTO DEPARTMENT OF BIOMEDICAL SCIENCES (DBS), UNIVERSITY OF PADOVA

Androgens are sex steroid hormones released into the bloodstream in response to activation of the hypothalamic-pituitary-target endocrine gland axis in a highly regulated fashion. Androgens, i.e., testosterone and its more potent derivative dihydrotestosterone (DHT), are responsible for the development, maintenance, and regulation of male primary and secondary sexual characteristics during gestation and at puberty as well as in adulthood. In addition, androgens have anabolic functions in several tissues, including skeletal muscle and bone, and they exert key functions in the central nervous system, where they are necessary for cognition and male brain development. Androgen signaling is mainly mediated by the androgen receptor (AR). AR is widely expressed in several tissues, from reproductive organs to excitable cells, i.e. myofibers and neurons. **Dysfunction of AR-mediated androgen signaling results in a plethora of disease conditions depending on the type of mutation**. To date, more than 200 mutations have been identified and described, many of which cause androgen insensitivity syndrome due to loss-of-function (LOF) mechanisms, whereas the others cause prostate cancer through combination of LOF and gain-of-function (GOF) mechanisms. AR is a modular protein composed of three domains, an intrinsically disordered, poorly conserved, and highly phosphorylated amino-terminal domain (NTD), a two zinc-finger DNA-binding domain (DBD), a hinge region, and a highly conserved carboxy-terminal domain that assembles as 12 alpha-helices and two beta-sheets upon androgen binding and form the ligand-binding domain (LBD). In its inactive state, AR mainly localizes to cytosol in association with heat shock proteins (HSPs). Binding to ligand results in dissociation from HSPs, intra- and inter-molecular amino (N)/carboxy (C)-terminal (N/C) interactions, concomitant with protein stabilization and nuclear translocation. AR is a ligand-regulated transcription factor. Ligand binding results in a number of post-translational modifications, including phosphorylation. I will show new evidence of the existence of a molecular switch that turn AR “on” and “off” depending on the levels of ligand. I will also provide evidence of the origin of this signal throughout evolution. Finally, I will provide evidence of **how dysfunction of this molecular switch contributes to AR-related diseases**.

DEPARTMENT OF CELLULAR, COMPUTATIONAL
AND INTEGRATIVE BIOLOGY - CIBIO
VIA SOMMARIVE, 9
38123 - POVO (TN)
COMUNICAZIONE.CIBIO@UNITN.IT

UNIVERSITÀ DI TRENTO
Department of
Cellular, Computational and Integrative Biology - CIBIO