Letter to editor

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Journal of Clinical and Molecular Endocrinology
ISSN 2572-5432

2016
Vol.1.No.3: 35

DOI: 10.21767/2572-5432.10035

Is Steroidogenesis Regulated by Er-Mitochondria Contact Sites?

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Rec date: Nov 11, 2016; **Acc date:** Nov 17, 2016; **Pub date:** Nov 20, 2016

Citation: Denis R (2016) Is Steroidogenesis Regulated by Er-Mitochondria Contact Sites?. J Clin Mol Endocrinol 1: 35.

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Steroids are main growth factors, hormones which synthesis in mammals occur in part through mitochondrial-related processes, rendering interesting the relation that could exist between mitochondrial activities (mainly respiration but also lipid synthesis and consumption) and steroids synthesis, particularly their anabolic effects.

From this essential nutriment which is cholesterol, essentially stored in the endoplasmic reticulum compartment of mammalian cells, the mitochondria will produce the essential precursor of steroids, pregnenolone, at a rate-limiting step. Therefore, among the enzymatic processes involved in the production of steroids, a master and controlled step happens in the mitochondria.

Steroids are numerous, and produced by different organs with specific functions. The corticoids are produced by adrenal cortex and corresponds to aldosterone, involved in hydric equilibrium, and cortisol, mainly involved in inflammation. Oestrogens and progesterone are produced by the ovary and the placenta, to control sexual cycle, pregnancy and lactation. Testosterone is the male “equivalent”, produced mainly by testis to promote growth. Out of these organs, only fibroblasts, neurons and glia are today know to produce steroids too.

Since all steroids productions imply a mitochondrial step, it is of big interest to understand how this occurs and how it can be modulated, regulated, as involved in pathologies.

One main question being asked today is to know how the cholesterol transits from ER to mitochondria, as this process is totally unknown. Recent advances in the field [1-3] have shown that the transport can occur through ER-Mitochondria contact sites [4] involving a newly discovered mitochondrial protein, ATAD3 (ATPase family AAA Domain-containing protein 3.

ATAD3 protein was discovered in 2005 as an oncogenic marker of tumours [5,6] and mainly studied at cancer level [7,8]. Inserted in the inner mitochondrial membrane [9,10], ATAD3 is also tethering the outer mitochondrial membrane as well as endoplasmic reticulum structures [11]. By the way, ATAD3 supports mitochondrial biogenesis [12,13]. As can be expected, ATAD3 is vital, as early as at the gastrula/implantation stage.

The recent findings in the field of ATAD3 came from endocrinologists studying progesterone synthesis [1,2]. They found both a molecular complex supporting cholesterol transfer in Leydig cells and that ATAD3 is essential for this function. The involvement of ATAD3 in cholesterol transport was confirmed by others [3].

Then, ATAD3 is the principal candidate protein to function as a link between inner/outer mitochondrial membranes and the endoplasmic reticulum, to support cholesterol transfer.

A focus on this protein might be of particular interest in order to better understand steroid-endocrine based pathologies.

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