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Review

Mitochondrial protein import and the genesis of steroidogenic mitochondria

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ABSTRACT

The principal site of regulation of steroid hormone biosynthesis is the transfer of cholesterol from the outer to inner mitochondrial membrane. Hormonal stimulation of steroidogenic cells promotes this mitochondrial lipid import through a multi-protein complex, termed the transduceosome, spanning the two membranes. The transduceosome complex is assembled from multiple proteins, such as the steroidogenic acute regulatory (STAR) protein and translocator protein (TSPO), and requires their targeting to the mitochondria for transduceosome function. The vast majority of mitochondrial proteins, including those participating in cholesterol import, are encoded in the nucleus. Their subsequent mitochondrial incorporation is performed through a series of protein import machineries located in the outer and inner mitochondrial membranes. Here we review our current knowledge of the mitochondrial cholesterol import machinery of the transduceosome. This is complemented with descriptions of mitochondrial protein import machineries and mechanisms by which these machineries assemble the transduceosome in steroidogenic mitochondria.

Contents

Abbreviations: Fdx, ferredoxin; FdxR, ferredoxin reductase; IMM, inner mitochondrial membrane; IMS, intermembrane space; MPP, mitochondrial processing peptidase; OMM, outer mitochondrial membrane; PAM, preprotein assembly and machinery; PKA, protein kinase A; SAM, sorting and assembly machinery; STAR, steroidogenic acute regulatory protein; TIM, translocase of inner mitochondria; TOM, translocase of outer mitochondria; TSPO, translocator protein; VDAC, voltage-dependent anion channel.

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1. Introduction

Steroid hormones produced by the adrenal glands and gonads of vertebrates are crucial determinants of a wide range of physiological functions, driving processes such as development, reproduction, and behavior. To generate steroid hormones, these tissues are equipped with a number of metabolic enzymes that metabolize precursor steroids into their products, with each tissue expressing an individual battery of steroidogenic enzymes (Payne and Hales, 2004). Despite the diversity of the steroid hormone family, all steroids derive from a single precursor, cholesterol, which is transformed to the steroid pregnenolone in the mitochondrial matrix by the cytochrome P450 cholesterol side chain cleavage enzyme, CYP11A1 (Jefcoate, 2002). By limiting access of the hydrophobic cholesterol molecule to CYP11A1, steroidogenic cells are able to control the amount of steroids they produce (Rone et al., 2009a). Much has been learned concerning the cellular expression and function of proteins involved in mitochondrial cholesterol movement and metabolism. However, in light of the vast body of knowledge accumulated over the past decade pertaining to mitochondrial protein import, comparatively little is known concerning their incorporation into the mitochondria. This review describes the mitochondrial steroidogenic and protein import machineries and subsequently focuses on how the interplay of the two generates steroidogenic mitochondria.

2. Steroid biosynthesis

Cholesterol serves as the metabolic precursor of all steroid hormones and is principally stored in the plasma membrane and lipid droplets of steroidogenic cells (Jefcoate, 2002; Mesmin and Maxfield, 2009). Steroid hormones are acutely synthesized in response to circulating peptide hormones, such as adrenocorticotropic hormone, luteinizing hormone, or chorionic gonadotropin. These hormones bind their cognate receptors on the surface of steroidogenic cells (adrenocorticotropic hormone for the adrenal and luteinizing hormone/chorionic gonadotropin for the gonad) and stimulate intracellular signaling cascades, of which the cAMP pathway, through protein kinase A (PKA), is the most prominent. Acutely, these events stimulate the flow of cholesterol to the inner mitochondrial membrane (IMM), where it is converted to pregnenolone by CYP11A1 (Jefcoate, 2002). In addition, hormonal and cAMP stimulation of steroidogenic cells is important for the chronic regulation of steroidogenesis, as continued exposure is necessary to ensure proper expression levels of steroidogenic proteins and steroidogenic metabolic flux (Simpson and Waterman, 1988).

Due to its hydrophobicity, cholesterol movement within the aqueous microenvironment of the cell requires the assistance of intracellular proteins (Mesmin and Maxfield, 2009). The translocation of cholesterol to the IMM is such a case, as the mitochondrion is a double-membrane organelle and cholesterol must traverse the aqueous intermembrane space (IMS) between the outer mitochondrial membrane (OMM) and the IMM where CYP11A1 resides. To accomplish this, steroidogenic cells possess a multicomponent protein machine recently named the transduceosome. This mitochondrial transduceosome is an ensemble of cytoplasmic and resident mitochondrial proteins, which receives hormonal signals and assists in the translocation of cholesterol across the IMS at contact sites between the IMM and OMM (Rone et al., 2009a) (Fig. 1). The core steroidogenic protein of the IMM, CYP11A1, associates with, and receives electrons from, the flavoprotein ferrodoxin reductase (also known as adrenodoxin reductase; FdxR) and the iron/sulphur protein ferrodoxin (also known as adrenodoxin; Fdx) (Miller and Auchus, 2010). Such steroidogenic cytochrome P450 enzymes and their associated electron transport chains have also been demonstrated to organize into higher order complexes (Praporski et al., 2009).

Also present in the IMM is the 35-kDa mitochondrial adenine nucleotide translocator (ANT). Though this protein has yet to have a definable role in mitochondrial cholesterol transport, immunoprecipitation experiments have demonstrated that ANT coprecipitates with two integral OMM proteins, presumably anchoring contact sites between the OMM and IMM. These OMM proteins were identified as the 31-kDa voltage-dependent anion channel (VDAC) and the 18-kDa translocator protein TSPO, previously named the peripheral-type benzodiazepine receptor (McEnery et al., 1992; Papadopoulos et al., 2006). These particular OMM proteins have attracted considerable interest in steroidogenic research, as the benzodiazepine class of drugs is able to stimulate steroid biosynthesis (Krueger and Papadopoulos, 1990; Papadopoulos et al., 1991a) and the VDAC–TSPO pair is the site of benzodiazepine binding to the OMM (Garnier et al., 1994). TSPO itself is able to bind different classes of drugs with the capacity to stimulate steroidogenesis (Papadopoulos et al., 1991b; Rupprecht et al., 2009) in addition to cholesterol (Lacapere et al., 2001), and knockdown

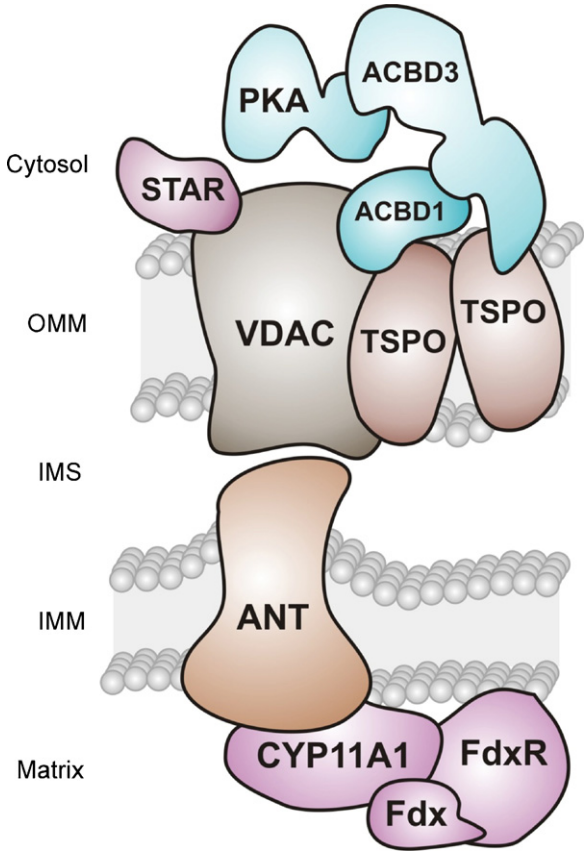

Fig. 1. Transduceosome formation at the mitochondria upon hormonal stimulation. Cytosolic transduceosome proteins PKA, ACBD3, and ACBD1 are shown in blue while mitochondrial matrix proteins STAR, CYP11A1, Adx, and AdxR are shown in purple. OMM transduceosome proteins VDAC and TSPO, and the IMM protein ANT, are represented in brown.