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Review

Expression and roles of steroidogenic acute regulatory (StAR) protein in 'non-classical', extra-adrenal and extra-gonadal cells and tissues

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ABSTRACT

The activity of the steroidogenic acute regulatory (StAR) protein is indispensable and rate limiting for high output synthesis of steroid hormones in the adrenal cortex and the gonads, known as the 'classical' steroidogenic organs (StAR is not expressed in the human placenta). In addition, studies of recent years have shown that StAR is also expressed in many tissues that produce steroid hormones for local use, potentially conferring some functional advantage by acting *via* intracrine, autocrine or paracrine fashion. Others hypothesized that StAR might also function in non-steroidogenic roles in specific tissues. This review highlights the evidence for the presence of StAR in 17 extra-adrenal and extra-gonadal organs, cell types and malignancies. Provided is the physiological context and the rationale for searching for the presence of StAR in such cells. Since in many of the tissues the overall level of StAR is relatively low, we also reviewed the methods used for StAR detection. The gathered information suggests that a comprehensive understanding of StAR activity in 'non-classical' tissues will require the use of experimental approaches that are able to analyze StAR presence at single-cell resolution.

Contents

Abbreviations: OMM, outer mitochondrial membrane; IMM, inner mitochondrial membranes; TSPO, translocator protein; VDAC, voltage dependent anion channel; CNS, central nervous system; SR-BI, class-B type-I scavenger receptor; PTII, type II pneumonocytes; CCHCR1, Coiled-Coil α-Helical Rod protein 1; NR5A1, nuclear receptor subfamily 5, group A, member 1, SF-1; NR5A2, liver receptor homolog-1; HMG-CoA, hydroxymethylglutaryl-coenzyme (reductase); LXR, liver X receptors; PPAR, peroxisome proliferator-activated receptor; SERM, selective estrogen receptor modulator; COUP-TFII or NR2F2, nuclear receptor subfamily 2, group F, member 2; WT1, Wilm's tumor tumor suppressor gene1.

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1. Introduction

1.1. StAR discovery in 'Classical' steroidogenic tissues

1.1.1. StAR – the rate limiting step in steroidogenesis

The "classical" steroidogenic tissues expressing StAR include the adrenal cortex and the reproductive organs consisting of the ovary, testis, and the placenta in non-human mammals. The first step in steroidogenesis is the conversion of cholesterol to the first steroid, pregnenolone, formed in the mitochondria of these cells. This conversion occurs via the action of the cholesterol side chain cleavage cytochrome P450 (CYP11A1) that resides in the inner mitochondrial membrane in all steroidogenic cells (Farkash et al., 1986; Hall, 1985; Simpson and Waterman, 1983). Pregnenolone then exits the mitochondria and in steroidogenic tissues of most species, is converted to progesterone by 3β-hydroxysteroid dehydrogenase (HSD3B), which resides in the microsomal compartment; subsequently, pregnenolone is transformed to a variety of active steroid hormones, depending on the specialized cells in each tissue, e.g., glucocorticoids (cortisol in humans or corticosterone in rodents) and mineralcorticoids (aldosterone) in the adrenal cortex, and sex hormones (progesterone, androgens, estrogens) in the gonads (Payne and Hales, 2004).

Like most biosynthetic pathways, the steroidogenic pathway has a rate-limiting step, which was believed to be the activation of the CYP11A1 enzyme (Karaboyas and Koritz, 1965). However, it soon became clear that the regulated, and more accurately defined rate-limiting step was the acute delivery of the substrate cholesterol from the outer mitochondrial membrane (OMM) to the inner mitochondrial membrane (IMM) where CYP11A1 is located (Black et al., 1994). This step turned out to have an absolute requirement for the synthesis of new proteins since puromycin inhibited ACTH induction of corticoid synthesis in cells of the adrenal gland (Ferguson, 1963). Hence, a three decades long search sought putative candidate regulator proteins that are hormone stimulated, acutely synthesised and puromycin/cycloheximide sensitive, as previously reviewed (Stocco and Clark, 1996). A leading candidate among those was described as an ACTH-induced 30 kDa phosphoprotein in rat and mouse adrenocortical cells, and as an LH-induced protein in rat ovary corpus luteum cells and mouse testicular Leydig cells (Alberta et al., 1989). Later studies determined that the 30 kDa mitochondrial protein was processed from a 37 kDa precursor form (Epstein and Orme-Johnson, 1991; Stocco and Sodeman, 1991; Stocco and Ascoli, 1993). The protein purification and cloning of the cDNA for the 37 kDa protein precursor was successfully accomplished in 1994 (Clark et al., 1994). Expression of the novel cDNA-derived protein resulted in a significant increase in steroid production in the absence of hormone stimulation, indicating a direct role for the 37–30 kDa proteins in hormone-regulated steroid production. The protein was named the Steroidogenic Acute Regulatory Protein or StAR (Clark et al., 1994) and in the earliest of the studies on StAR, this protein was indeed thought to be confined to the "classical" steroidogenic tissues of the adrenals and gonads.

1.1.2. StAR mutations and StAR independent placental steroidogenesis

Shortly following the cloning of the StAR cDNA it was demonstrated that mutations in the StAR gene resulted in congenital lipoid adrenal hyperplasia (lipoid CAH), the etiology of which provided compelling evidence for the essential role of this vital protein in the regulation of steroidogenesis (Lin et al., 1995). Targeted disruption of the StAR gene in mice successfully produced StAR knockout mice that displayed characteristics very similar to human lipoid CAH and further substantiated the necessity for StAR action in stimulated steroid biosynthesis in the adrenal cortex and the gonads (Caron et al., 1997; Miller and Strauss, 1999; Stocco, 2002). In this regards, an exceptional steroidogenic tissue that does not express StAR is the human placenta (Sugawara et al., 1995b). Yet, this organ produces as much as 300 mg progesterone daily in order to maintain uterine muscle tranquility and avoid preterm labor (Tang et al., 2001; Hardy et al., 2006; da Fonseca et al., 2009). Strauss et al. (1996) calculated that per trophoblast cell mass (100 g syncytiotrophoblasts/placeta), such a rate of steroidogenesis is roughly 8–10 times less efficient when compared to the rate of luteal steroidogenesis (1 g tissue producing 25 mg/day progesterone). That suggests that, as expected, the absence of StAR in the human placenta probably accounts for the lower rate of placental steroidogenesis, which is probably required to compensate for the much larger mass of the steroidogenic component of this organ.

As for the mechanism of StAR-free steroidogenesis in the human placenta, it has been suggested that a truncated form of MLN64, known as a StAR like late-endosome protein expressed in several human tissues, might substitute, at least in part, for StAR activity in this tissue (Watari et al., 1997; Bose et al., 2000). In this regard, it should be mentioned that StAR independent 'basal' rate of steroidogenesis is also possible in steroidogenic cell types, where the OMM translocator protein (18-kDa TSPO, further