Molecular and Cellular Endocrinology 425 (2016) 26–36

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

STAMPing at the crossroads of normal physiology and disease states

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ARTICLE INFO

Article history:
Received 22 December 2015
Received in revised form
11 February 2016
Accepted 14 February 2016
Available online 18 February 2016

Keywords:
STAMP
STEAP
Ironreductase
Prostate cancer
Metabolism
Inflammation

ABSTRACT

The six transmembrane protein of prostate (STAMP) proteins, also known as six transmembrane epithelial antigen of prostate (STEAPs), comprises three members: STAMP1-3. Their expression is regulated by a variety of stimuli, including hormones and cytokines, in varied settings and tissues with important roles in secretion and cell differentiation. In addition, they are implicated in metabolic and inflammatory diseases and cancer. Here, we review the current knowledge on the role of STAMPs in both physiological and pathological states.

1. Discovery of the STAMP family

The six transmembrane protein of prostate (STAMP) proteins, also known as six transmembrane epithelial antigen of the prostate (STEAPs), consists of three members (STAMP1-3) (Fig. 1). STAMPs were characterized independently in different organisms within a short time period: *STAMP1* (*STEAP2*) was identified as a human gene that is highly expressed in the prostate (Korkmaz et al., 2002; Porkka et al., 2002). *STAMP2* (*STEAP4*) was then identified due to its sequence similarity to *STAMP1* (Korkmaz et al., 2005). The murine *Stamp2*, first called tumor necrosis factor-α-induced adipose-related protein (Tiarp) was cloned in 3T3-L1 adipocytes (Moldes et al., 2001). *Stamp3* (*Steap3*), also known as tumor suppressor activated pathway 6 (*Tsap6*), was first identified in murine myeloid M1 cells (Amson et al., 1996), and later cloned by the same group (Passer et al., 2003). The rat ortholog, pHyde, was independently discovered and cloned (Rinaldy et al., 2000).

STAMP proteins share high sequence similarity (Korkmaz et al., 2005, 2002; Moldes et al., 2001; Ohgami et al., 2005b; Porkka et al., 2002). As the name indicates, STAMPs contain a six α-helical transmembrane domain in the C-terminal half and an N-terminal domain that shares similarity to the prokaryotic F_{420}:$NADP^+$ Oxidoreductase (FNO) (Warkentin et al., 2001). The C-terminal transmembrane domain has distant homologies to yeast ferric reductases (FRE) and to mammalian NADPH oxidase (NOX). Since STAMPs also have metalloreductase activity, they are now placed along with NOX and FRE families within the ferric reductase domain (FRD) superfamily (Zhang et al., 2013). *STEAP1* encodes a significantly truncated protein compared to STAMP1-3 that was first cloned as a gene predominantly expressed in human prostate and overexpressed in prostate cancer (PCa) (Hubert et al., 1999). Unlike STAMPs, STEAP1 lacks the N-terminal cytosolic domain that contains the essential motifs for oxidoreductase activity, and thus cannot reduce iron (Ohgami et al., 2006). Since this review mainly focuses on STAMP functions in which the iron reductase activity is involved, discussion of STEAP1 biology is not included herein. Detailed information about STEAP1 has been provided in previous reviews (Gomes et al., 2012; Grunewald et al., 2012).

2. Regulation of STAMP expression

STAMP expression has been found in multiple tissues and is regulated by a number of different stimuli (Table 1A, B, andC). This indicates the potential roles of the STAMP family in various physiological processes, tissues, and disease states. These data are summarized below.

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http://dx.doi.org/10.1016/j.mce.2016.02.013
0303-7207/

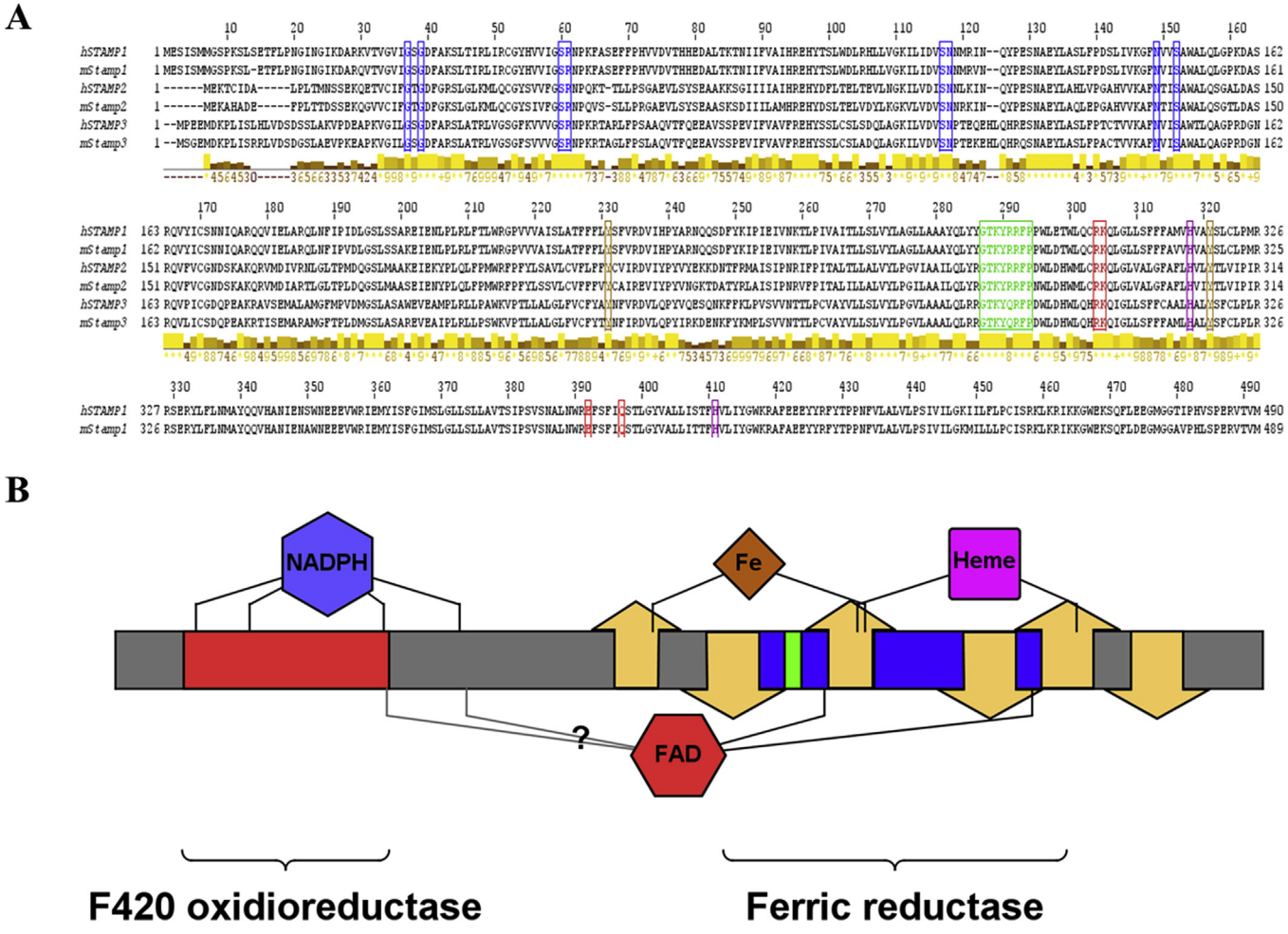

Fig. 1. The STAMP family - overview of the domains and functional motifs. A) A multiple sequence alignment of the members of the human and murine STAMP family (hSTAMP1, NP_001035755.1; mStamp1, NP_083010.2; hSTAMP2, NP_078912.2; mStamp2, NP_473439.2; hSTAMP3, NP_060704.2; mStamp3, NP_573449.2) constructed using Clustal Omega (Sievers et al., 2011). Brown to yellow numbers and bars below is similarity scores using AMAS method of multiple sequence alignment analysis built in Jalview (Livingstone and Barton, 1993; Waterhouse et al., 2009). Colored regions are highly conserved residues that are important for STAMP catalytic activity (Gauss et al., 2013; Kleven et al., 2015). These residues have been verified through resolving of crystal structures and/or mutagenesis studies (Gauss et al., 2013; Kleven et al., 2015; Lambe et al., 2009; Sendamarai et al., 2008). The color-coding corresponds to the structural overview built with Illustrator for Biological Sequences (IBS). B) Different domains/sites in STAMP proteins (using tools as described in (Liu et al., 2015)). NADPH interaction (blue), FAD interaction (red), iron interaction (brown), heme-group interaction (purple), endosomal targeting motif (green). Question mark indicates conserved, but putative sites of interaction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1A
Regulation of STAMP1. Overview of expression levels of STAMP1 in tissues and the disease states. Also shown are cellular events that STAMP1 are involved in, or stimuli that can regulate its expression in various tissues/cell lines.

STAMP1 (STEAP2)		Tissue/cell line	Reference
High expression		Human: Prostate	(Korkmaz et al., 2002; Ohgami et al., 2006; Porkka et al., 2002)
Medium expression		Human: Brain, Pancreas, Fetal Liver, Ovary	(Korkmaz et al., 2002; Ohgami et al., 2006; Porkka et al., 2002)
Low expression		Human: Heart, Lung, Kidney, Liver, Bone Marrow, Colon, Small Intestine; Stomach, Thymus	(Korkmaz et al., 2002; Ohgami et al., 2006; Porkka et al., 2002)
Regulated expression			
Stimuli/event/ disease	**Effect**		
Cancer progression	Increase	Prostate Cancer	(Korkmaz et al., 2002; Porkka et al., 2002; Wang et al., 2010a; Whiteland et al., 2014)
Adipogenesis	Decrease	3T3-L1 murine preadipocytes, murine mesenchymal stem cell	(Sikkeland and Saatcioglu, 2013; Vaghjiani et al., 2009)
TNFα	Decrease	LNCaP human PCa cell line	(Gonen-Korkmaz et al., 2014)
AR dependency	Maintenance	Human PCa cell lines	(Korkmaz et al., 2005; Korkmaz et al., 2002; Porkka et al., 2002)

2.1. *STAMP1*

The expression of *STAMP1* mRNA is highly prostate-enriched, but is also detectable at low levels in several other tissues such as heart, brain, kidney, pancreas, and ovary. *STAMP1* is highly expressed in the androgen-responsive PCa cell line LNCaP, but not the AR-negative cell lines PC3 and DU145 (Korkmaz et al., 2002; Porkka et al., 2002). Interestingly, STAMP1 expression is not