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STAMPing at the crossroads of normal physiology and disease states

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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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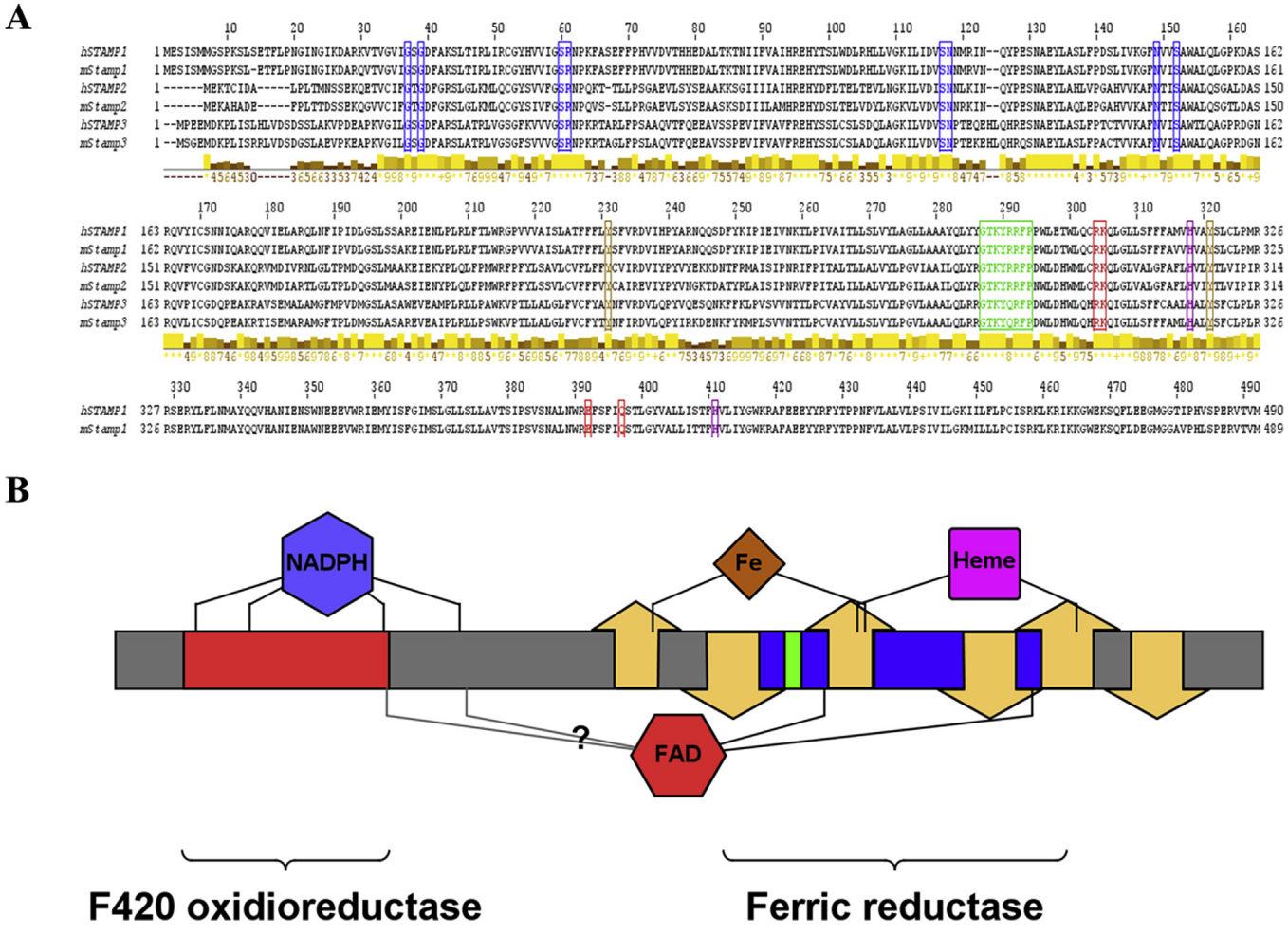

Fig. 1. The STAMP family - overview of the domains and functional motifs. A) A multiple sequence alignment of the members of the human and murine STAMP family (hSTAMP1, NP_001035755.1; mStamp1, NP_083010.2; hSTAMP2, NP_078912.2; mStamp2, NP_473439.2; hSTAMP3, NP_060704.2; mStamp3, NP_573449.2) constructed 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

Table 1B
Regulation of STAMP2. Overview of expression levels of STAMP2 in tissues and the disease states. Also shown are cellular events that STAMP2 are involved in, or stimuli that can regulate its expression in various tissues/cell lines. *Regulation of expression differs in the reports.

STAMP2 (STEAP4)		Tissue/cell line	Reference
High expression		Human: Bone Marrow, Placenta, Lung, Adipose Murine: White Adipose Porcine: Lung, Kidney, Adipose	(Arner et al., 2008; Korkmaz et al., 2005; Ohgami et al., 2006; Zhang et al., 2008) (Wellen et al., 2007) (Wang et al., 2013b)
Medium expression		Human: Fetal Liver, Liver, Heart, Prostate, Pancreas, Testis Murine: Heart, Brown Adipose, Liver, Prostate Porcine: Cerebellum, Heart, Liver, Small Intestine	(Korkmaz et al., 2005; Ohgami et al., 2006; Zhang et al., 2008) (Wellen et al., 2007) (Wang et al., 2013b)
Low expression		Human: Skeletal Muscle, Small Intestine, Kidney Murine: Spleen, Skeletal Muscle Porcine: Cerebrum, Spleen, Stomach, Large Intestine, Skeletal Muscle	(Korkmaz et al., 2005; Ohgami et al., 2006; Zhang et al., 2008) (Wellen et al., 2007) (Wang et al., 2013b)
Regulated expression			
Stimuli/event/ disease	**Effect**		
Cancer progression	Increase	Prostate cancer, Squamous cell carcinoma	(Jin et al., 2015; Korkmaz et al., 2005; Wu et al., 2015)
Adipogenesis	Increase	3T3-L1 murine preadipocytes, hASC, human preadipocytes	(Fasshauer et al., 2003; Moldes et al., 2001; Moreno-Navarrete et al., 2011; Narvaez et al., 2013; Sikkeland and Saatcioglu, 2013; Wellen et al., 2007)
Osteoclastogenesis	Increase	Murine preosteoclasts	(Zhou et al., 2013)
Macrophage maturation	Increase	Human THP-1 monocytes	(ten Freyhaus et al., 2012)
Arthritis	Increase	Spleen, Joints and Lymph nodes of mice with glucose-6-phosphate isomerase (GPI) or collagen induced arthritis; peripheral blood mononuclear cells and synovial fluid of rheumatoid arthritis patients	(Inoue et al., 2009; Inoue et al., 2012; Noh et al., 2014; Takai et al., 2015)
Obesity/Metabolic syndrome	Increase	Human: Visceral* and subcutaneous adipose tissue Murine: Liver* of HFD or genetically induced mice Rabbit: Prostate in animals on high fat diet	(Arner et al., 2008; Catalan et al., 2013) (Ramadoss et al., 2010; Sohet et al., 2009) (Vignozzi et al., 2012)
	Decrease	Human: Visceral* adipose tissue, livers obtained from NAFLD patients Murine: Liver*, visceral and brown adipose tissue of HFD or genetically induced mice	(Kim et al., 2015; Moreno-Navarrete et al., 2011; Zhang et al., 2008) (Han et al., 2013; Kim et al., 2015; Ramadoss et al., 2010)
Feeding	Increase	Murine: Liver, and visceral, subcutaneous and brown adipose tissue	(Ramadoss et al., 2010; Wellen et al., 2007)
Fasting	Decrease	Murine: Liver, Skeletal Muscle, and visceral, subcutaneous and brown adipose tissue	(Ramadoss et al., 2010; Wellen et al., 2007)
Glucose	Increase	MES13 murine mesangial cells	(Chuang et al., 2015)
Oleic acid	Increase	3T3-L1 murine adipocytes	(Wellen et al., 2007)
High serum media	Increase	3T3-L1 murine adipocytes	(Wellen et al., 2007)
Insulin	Decrease	3T3-L1 murine adipocytes	(Fasshauer et al., 2003)
Isoproterenol	Decrease	3T3-L1 murine adipocytes	(Fasshauer et al., 2003)
Dexamethasone	Decrease	3T3-L1 murine adipocytes	(Fasshauer et al., 2003)
Androgen	Increase	Human prostate cancer cells: LNCaP, VCaP, 22Rv1 Visceral adipose tissue of rabbits on HFD	(Jin et al., 2015; Korkmaz et al., 2005) (Maneschi et al., 2012)
	Decrease	Prostate tissue of rabbits fed on high fat diet	(Vignozzi et al., 2012)
TNFα	Increase	3T3-L1 murine adipocytes, mouse adipose tissue, human adipocytes, MH7A human synovial cell	(Chen et al., 2010; Fasshauer et al., 2003; Moldes et al., 2001; Tanaka et al., 2012; Wellen et al., 2007; Zhang et al., 2008)
IL-6	Increase	3T3-L1 murine adipocytes, murine adipose and liver tissue, human adipocytes	(Chen et al., 2010; Fasshauer et al., 2004; Ramadoss et al., 2010),
IL-1β	Increase	3T3-L1 murine adipocytes, differentiated human mesenchymal stem cells	(Kralisch et al., 2009)
Growth hormone	Increase	3T3-L1 murine adipocytes	(Fasshauer et al., 2003)
LPS	Increase	Primary peritoneal macrophages, HepG2	(ten Freyhaus et al., 2012; Wang et al., 2013b)
Zymosan	Increase	Primary peritoneal macrophages	(ten Freyhaus et al., 2012)
Poly I:C	Increase	Primary peritoneal macrophages	(ten Freyhaus et al., 2012)
IL-17	Increase	Murine keratinocyte	(Wu et al., 2015)
Thiazolidinediones	Decrease	Adipose tissue of *ob*/*ob* mice	(Wellen et al., 2007)
Leptin	Decrease	Human adipocytes	(Chen et al., 2010)
Q10	Decrease	Liver of mice on high fat and fructose diet	(Sohet et al., 2009)

regulated by androgens, but it requires an intact androgen receptor (Korkmaz et al., 2002). However, a recent study reported STAMP1 expression in the PC3 and DU145 cell lines which was higher than expression in the normal prostate cell line PNT2 (Whiteland et al., 2014); the basis for these different observations is not clear at present.

2.2. STAMP2

In humans, *STAMP2* is expressed in the prostate, placenta, lung, heart, bone marrow, adipose tissue, and liver (Arner et al., 2008; Korkmaz et al., 2005; Zhang et al., 2008). Murine *Stamp2* was first identified using mRNA differential display comparing post-confluent untreated 3T3-L1 cells upon exposure to tumor necrosis factor alpha (TNFα) (thus the name Tiarp) (Moldes et al., 2001). TNFα strongly induced *Stamp2* expression in differentiating adipocytes, but not in preadipocytes. TNFα potently induced *Stamp2* expression also in cultured primary hepatocytes (Moldes et al., 2001).

Recent independent studies showed that STAMP2 expression, in either adipocytes or hepatocytes, could be induced and regulated by various cytokines or hormones, such as IL-6 (Chen et al., 2010; Fasshauer et al., 2004; Ramadoss et al., 2010), IL-1β (Kralisch et al., 2009), growth hormone (GH) (Fasshauer et al., 2003), or

Table 1C
Regulation of STAMP3. Overview of expression levels of STAMP3 in tissues and the disease states. Also shown are cellular events that STAMP3 are involved in, or stimuli that can regulate its expression in various tissues/cell lines.

STAMP3 (STEAP3)		Tissue/cell line	Reference
High expression		Human: Liver, Fetal Liver, Pancreas, Mammary Gland, Stomach, Spinal Cord,	(Lu et al., 2009; Ohgami et al., 2005b; Passer et al., 2003; Porkka et al., 2003)
Medium expression		Human: Heart, Placenta, Bone Marrow, Skeletal Muscle, Thyroid, Trachea	(Lu et al., 2009; Ohgami et al., 2005b; Passer et al., 2003; Porkka et al., 2003)
		Murine: Heart, Spleen, Liver, Lung, Skeletal Muscle	(Passer et al., 2003)
Low expression		Human: Prostate, Kidney, Ovary, Colon, Small Intestine, Brain, Lung, Adrenal Gland	(Lu et al., 2009; Ohgami et al., 2005b; Porkka et al., 2003)
Regulated expression			
Stimuli/event/disease	**Effect**		
Cancer progression	Decrease	Hepatocellular carcinoma	(Caillot et al., 2009; Coulouarn et al., 2005)
Adipogenesis	Increase	3T3-L1 murine preadipocytes	(Sikkeland and Saatcioglu, 2013; Ye et al., 2011)
Stress/p53 activation	Increase	M1 and LTR6 murine myeloid leukemia cells	(Amson et al., 1996; Passer et al., 2003)
Non-steroidal anti-inflammatory drugs	Increase	Tumors of colon cancer patients	(Slattery et al., 2015).
Iron deficiency	Increase	Raji human Burkitt's lymphoma cells	(Isobe et al., 2011)
Francisella/Salmonella spiA and *spiC* infection	Increase	RAW264.7murine macrophage cells	(Pan et al., 2010)
Capsaicin	Decrease	Epididymal white adipose tissue of rats fed on high fat diet	(Joo et al., 2010)
LPS	Decrease	Murine Bone marrow-derived macrophages	(Zhang et al., 2012)

leptin (Chen et al., 2010). Combinatorial experiments showed synergistic effect of cytokine treatment on STAMP2 induction in adipocytes (Kralisch et al., 2009). Interestingly, the regulation of STAMP2 expression by cytokines was dependent on cell type or cellular context. For example, IL-6 did not induce *Stamp2* expression in C2C12 myocytes (Fasshauer et al., 2004). *In vivo*, TNFα and IL-6 induced Stamp2 expression in mouse adipose tissue (Wellen et al., 2007) and liver (Ramadoss et al., 2010), respectively. In addition, nutritional status, such as fasting or (re)feeding, changed STAMP2 expression in multiple tissues, including liver, adipose tissue and muscle (Kim et al., 2015; Ramadoss et al., 2010; Wellen et al., 2007). These data suggest that STAMP2 has a role in responding to environmental cues in metabolic tissues.

Adipocyte differentiation is dominantly controlled by peroxisome proliferator-activated receptor gamma (PPARγ) and CAAT/Enhancer binding protein (C/EBP) family transcription factors. Stamp2 expression in adipocytes is mainly dependent on C/EBPα, and on LXRα to a lesser extent, based on promoter reporter assays (Wellen et al., 2007). While PPARγ did not bind to or directly regulate the *Stamp2* promoter, its agonist, thiazolidinedione, reduced *Stamp2* expression in white adipose tissue (WAT) of ob/ob mice (Wellen et al., 2007). Transcriptional regulation of *Stamp2* by C/EBPα was further confirmed in liver cells (Ramadoss et al., 2010). In addition to C/EBPα, binding sites for STAT3 at the proximal promoter region were also characterized in both mouse and human *STAMP2* genes. Furthermore, chromatin immunoprecipitation (ChIP) and reporter assays confirmed STAT3 binding to these sites in murine liver cells (Ramadoss et al., 2010). In summary, the studies to date suggest that C/EBPα regulates *STAMP2* transcription during feeding/fasting, whereas C/EBPα and STAT3 act in concert to control *STAMP2* expression in response to liver inflammation (Ramadoss et al., 2010).

In immortalized bone marrow-derived mouse macrophages Stamp2 expression was significantly upregulated by treatment with lipopolysaccharide (LPS) and two other toll-like receptor (TLR) agonists: Zymosan and Polyinosinic:polycytidylic acid (ten Freyhaus et al., 2012). LPS also induced expression of STAMP2 in HepG2 cells (Wang et al., 2013b). Furthermore, C/EBPβ regulated the porcine *Stamp2* promoter activity, which, at least in part, could be the pathway for inflammatory stimulation of STAMP2 expression (Wang et al., 2013b). Interestingly, in the same study, a shorter variant of Stamp2 was identified with a more potent anti-inflammatory effect than the longer form when overexpressed in RAW264.7 macrophage cells. However, the function of this variant *in vivo*, if any, is not clear at present.

Consistent with enrichment of STAMP2 expression in prostate tissue, analysis of expression profiles of multiple cell lines showed that STAMP2 is highly expressed in several lines of androgen responsive/AR positive PCa cells, such as LNCaP, VCaP and 22Rv1 (Jin et al., 2015). Unlike in adipocytes and hepatocytes, regulation of STAMP2 expression does not respond to TNFα in LNCaP cells (Gonen-Korkmaz et al., 2014), as opposed to its tight androgen regulation therein (Korkmaz et al., 2005).

2.3. STAMP3

Stamp3 is highly expressed in fetal liver and labyrinthine placenta of the mouse embryo, as well as human tissues that have a role in erythropoiesis, such as liver, bone marrow, placenta, skeletal muscle and pancreas (Ohgami et al., 2005b). The first direct regulator of *Stamp3* expression identified was p53, which increased *STAMP3* expression and induction of apoptosis in human M1 and LTR6 myeloid leukemia cells (Amson et al., 1996; Passer et al., 2003). In contrast to STAMP2, *Stamp3* is downregulated by LPS stimulation in murine bone marrow derived macrophages (Zhang et al., 2012).

In a microarray analysis of samples taken from the colon of patients with Crohn's disease, *STAMP3* was found increased in the smoker group compared to non-smoking patients (Nielsen et al., 2009). Recently, *STAMP3* mRNA levels were found to be elevated in response to aspirin and/or non-steroidal anti-inflammatory drugs in colonic non-tumor tissue in colon cancer patients (Slattery et al., 2015). These data suggest that STAMP3 may have a role in normal colon physiology and development of colon cancer.

3. Physiological functions of STAMPs and implication in disease

3.1. Metalloreductase activity

The members of the STAMP family are metalloreductases (Ohgami et al., 2006). Stamp3 was first found to reduce ferric to ferrous iron during transferrin (Tf) dependent iron uptake in erythroid cells (Ohgami et al., 2005b). Furthermore, *Stamp3* deficient mice develop hypochromic microcytic anemia (Ohgami et al., 2005a). All murine Stamps reduced both iron and copper when

ectopically expressed in HEK-293T cells, where Stamp2 had significantly higher activity for both metals compared with Stamp1 and Stamp3 (Ohgami et al., 2006). Interestingly, only human STAMP2, but not STAMP1 or STAMP3, displayed iron reductase activity when ectopically expressed in the same cell background (Jin et al., 2015; Ohgami et al., 2006). The basis for these differences is currently not known.

In HEK-293T cells, epitope-tagged Stamp3 colocalized with Tf and Tf receptor 1 (TfR1), as well as epitope-tagged divalent metal transporter 1 (DMT1), three key components of Tf-dependent iron uptake (Ohgami et al., 2005b). Using chemically induced mutagenesis in C57BL/6 mice and screening for anemia, a missense mutation in Stamp3 (Y288H) was found in a conserved motif between transmembrane domain two and three (Lambe et al., 2009). This mutation led to overall lower ferric reductase activity of whole blood preparations from these animals, and resulted in significantly higher iron (in females only) and copper concentrations in the liver. This effect was linked to the inability of FLAG-tagged Stamp3^{Y288H} to localize to endosomal structures when expressed in HEK-293T cells. Consistently, regenerative anemia and iron overload was discovered in three human siblings with a heterozygous nonsense mutation in STAMP3 (Grandchamp et al., 2011). These data suggest that STAMP3 is important for normal erythroid cell function.

Characterization of STAMP1 expression and localization in human brain microvascular endothelial cells (hBMVEC) indicated a potential role for STAMP1 in iron transport across the blood brain barrier (McCarthy and Kosman, 2012). Further supporting this role, STAMP1 in primary hippocampal neurons, similar to in HEK-293T cells (Ohgami et al., 2006), colocalizes with Tf and also partially colocalizes with a ferrous iron transporter ZRT/IRT-like Protein 8 (Zip-8) (Ji and Kosman, 2015). Whether STAMP1 may have iron reductase activity in this setting in addition to its potential role in regulating iron transport requires further investigation.

There is currently limited information on possible effects of human STAMP2 on iron metabolism. STAMP2 expression was negatively correlated with serum levels of free iron in visceral adipose tissue (Catalan et al., 2013). Furthermore, in PCa cells the iron reductase activity of STAMP2 was linked to the generation of reactive oxygen species (ROS) that plays a role in cancer cell growth (Jin et al., 2015). Additional studies are required to more directly assess the possible role of STAMP2 in iron metabolism in humans.

3.2. Crystal structures and functional motifs

N-terminal domain crystal structures of human STAMP3 and rat Stamp2 have been solved showing great similarity (Gauss et al., 2013; Sendamarai et al., 2008). According to these models, the N-terminal oxidoreductase domain is mainly formed by a classic dinucleotide binding fold consisting of six-stranded parallel β-sheet. In both studies, NADPH, but interestingly not any type of flavin, was co-crystallized with either protein. However, the NADPH oxidase activity of STAMP2 was flavin dependent (Gauss et al., 2013) suggesting an inter-domain flavin binding site. A recent study supports this hypothesis, where the αII/III and αIV/V intertransmembrane loops form a flavin adenine dinucleotide (FAD) binding site in human STAMP3 (Kleven et al., 2015). Interestingly, this positioning of the FAD replaces a cytoplasmic heme group, leaving only the luminal/extracellular heme in the protein, which is unique in the FRD superfamily. Further structural studies, including the transmembrane domains, will be required to facilitate full understanding of STAMP structure and function.

3.3. STAMPs on exocytic and endocytic pathways

Several studies examined intracellular localization and mobility of STAMPs (Fig. 2). Live cell imaging of Green Flourescent Protein (GFP) tagged STAMP1 and STAMP2 showed that they are present in vesiculotubular structures that shuttle between the plasma membrane and the trans-Golgi network (TGN)/Golgi/ER (Korkmaz et al., 2005, 2002; Porkka et al., 2002). In addition, STAMP2 colocalized with caveolin-1 in 3T3-L1 adipocytes (Chambaut-Guerin and Pairault, 2005). Furthermore, STAMP1 and STAMP2 both colocalized with the early endosomal marker EEA1 (Chambaut-Guerin and Pairault, 2005; Korkmaz et al., 2005, 2002; Tanaka et al., 2012). This suggested that STAMPs may be involved in endocytic and/or exocytic pathways.

STAMP3 interacted directly with translationally controlled tumor protein (TCTP) (Amzallag et al., 2004). Interestingly, STAMP3 co-localized with TCTP to vesicular-like structures at the plasma membrane and around the nucleus; in addition, STAMP3 increased TCTP levels in exosome preparations, indicating a role in vesicle trafficking and exosome secretion (Amzallag et al., 2004). The role of STAMP3 in p53-mediated exosome secretion was subsequently confirmed and characterized in different models: For example, comparison of the γ irradiation response of two small cell lung cancer cell lines, one with a wild-type p53 gene and the other harboring a mutated p53 allele, revealed that STAMP3 is involved in p53-induced exosome secretion (Yu et al., 2006). Further evidence of Stamp3 as a mediator of p53-dependent exosomal secretory pathway was obtained in Stamp3 knockout mice that develop microcytic anemia and exhibit delayed reticulocyte maturation (Lespagnol et al., 2008). Mouse embryonic fibroblasts (MEFs) from the Stamp3 knockout mice showed a severely dampened exosome production again supporting the notion that Stamp3 has an important role in exocytosis.

4. Cell differentiation

4.1. STAMP1

High levels of *Stamp1* was detected in mesenchymal stem cell (MSC) clones isolated from bone marrows of both BALB/b and BALB/c mice compared with differentiated clones (adipocyte lineage), primary bone marrow adherent cells, isolated bone marrow mononuclear cells, and mouse embryonic fibroblasts. In addition, there was considerable *STAMP1* expression in human multipotent bone marrow adherent cultures (Vaghjiani et al., 2009). Significant upregulation of *STAMP1* was also observed in the crypt bottom of human colon, a known stem cell-enriched region, compared to the top of the crypts, at the mRNA level (Bhatlekar et al., 2014). Furthermore, in murine 3T3-L1 cells, a frequently used adipogenesis model, suppression of *Stamp1* expression led to inhibition of the mitotic clonal expansion phase with subsequent reduction in adipogenic conversion (Sikkeland and Saatcioglu, 2013). These data suggest that STAMP1 has a role in cellular differentiation programs.

4.2. STAMP2

Stamp2 expression has been associated with three differentiation processes to date: adipogenesis (Moldes et al., 2001; Sikkeland and Saatcioglu, 2013; Wellen et al., 2007), osteoclastogenesis (Zhou et al., 2013), and macrophage maturation (covered in section 5) (ten Freyhaus et al., 2012). During differentiation of 3T3-L1 cells into adipocytes, *Stamp2* mRNA and protein levels are low in preadipocytes and remained low at confluence, and then dramatically increased along with the differentiation process (Moldes et al., 2001; Sikkeland and Saatcioglu, 2013). Stamp2 knockdown in 3T3-L1 cells reduced the level of adipogenic conversion in regular differentiation medium, accompanied by reduction in the expression of adipogenic markers aP2, C/ebpα and Pparγ (Sikkeland and

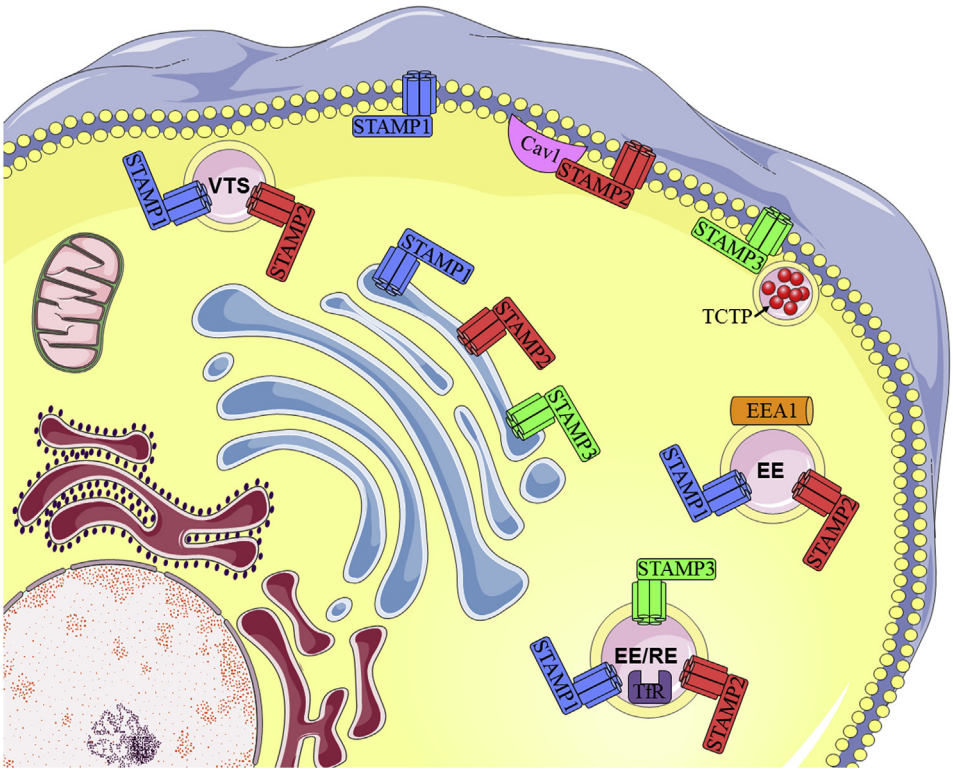

Fig. 2. Intracellular localization of the STAMPs. The localization of STAMPs has been linked to markers of the ER/Golgi/TGN axis, as well as the plasma membrane. STAMP1 and STAMP2 display a dynamic trafficking pattern in vesiculotubular structures. STAMP2 and STAMP3 colocalize with caveolin-1 and TCTP (in exosomes), respectively, at the plasma membrane and in intracellular structures. Furthermore, STAMP1 and STAMP2 colocalize with EEA1, and all the STAMPs colocalize with TfR. VTS, vesiculotubular structure; RE, recycling endosome; EE, early endosome.

Saatcioglu, 2013) suggesting that Stamp2 is a pivotal factor for adipogenesis. However, this is in contrast to the intact adipose tissue development, albeit its deregulated distribution, observed in *Stamp2* knockout mice *in vivo* (Wellen et al., 2007). Interestingly, the defect in adipogenesis of 3T3-L1 cells by Stamp2 knockdown was completely rescued in the presence of pioglitazone or rosiglitazone (Sikkeland and Saatcioglu, 2013), which are Pparγ agonists used to induce adipogenesis (Hausman et al., 2008). These observations implicate Stamp2 in regulation of the Pparγ pathway.

In human preadipocytes, pretreatment with STAMP2 antibody or ectopic expression of STAMP2 prior to rosiglitazone-induced differentiation did not interfere with the adipogenic conversion process (Chen et al., 2010; Cheng et al., 2011; Qin et al., 2010). This, however, is not surprising given that Stamp2 knockdown mediated-decrease in adipogenesis in 3T3-L1 cells is robustly rescued by Pparγ agonists (Sikkeland and Saatcioglu, 2013).

Stamp2 mRNA expression was undetectable in mouse bone marrow macrophages (BMMs), but dramatically increased during osteoblast differentiation (Zhou et al., 2013). Stamp2 knockdown in BMMs markedly inhibited osteoclast formation, along with significantly reduced expression of osteoclast markers, such as Cathepsin K, calcitonin receptor and Nucler Factor of Activated T cells 1 (NFATc1). However, ectopic expression of Stamp2 in osteoclast precursors slightly inhibited osteoclast differentiation, rather than an increase that would be expected based on the knockdown experiments (Zhou et al., 2013). The reason for this inhibition could be a reduction in TNFα expression, a critical enhancer of RANKL induced osteoclastogenesis (Lam et al., 2000). For both adipogenesis and osteoclastogenesis Stamp2 knockdown affected the cellular ROS production (Sikkeland and Saatcioglu, 2013; Zhou et al., 2013) which plays a central role in several differentiation processes including those for adipocytes and osteoclasts (Sart et al., 2015). Although further work is needed, these data indicate a mechanistic pathway through which STAMP2 may affect cellular differentiation processes.

4.3. STAMP3

During adipogenesis, in contrast to the distinct upregulation of *Stamp1* and *Stamp2* expression, *Stamp3* had a biphasic expression pattern: an increase of approximately 2-fold when cells were confluent, a significant decrease at day 2, and then an increase again by day 8 (Sikkeland and Saatcioglu, 2013). A liquid chromatography/mass spectrometry based study reported that Stamp3 expression was slightly elevated (about 1.75 fold) in adipocytes compared to fibroblasts (Ye et al., 2011). However, the possible function of STAMP3 in adipocyte differentiation and lipid metabolism is largely unknown at present.

As noted above, *Stamp3* knockout mice develop anemia (Ohgami et al., 2005a). It was recently found that this is due, at least in part, to abnormal erythroid maturation, where there is fewer proerythroblastocysts in the bone marrow of Stamp3 deficient mice compared to wild type mice (Blanc et al., 2015). This defect appears to be caused by impaired progression of proerythroblastocysts to the orthochromatic stage. These data show that Stamp3 has a key role in erythroid lineage maturation, but further work is required to uncover the molecular details in this regard.

5. STAMPs in metabolic and inflammatory diseases

The vast majority of the research on STAMPs in terms of metabolism and inflammation has so far focused on STAMP2. Upon its

cloning, it was quickly established that STAMP2 expression is enriched in various metabolic tissues, such as adipose, heart, and liver (Korkmaz et al., 2005; Moldes et al., 2001; Wellen et al., 2007). Dysregulation of STAMP2 was then implicated in metabolic and inflammatory diseases, such as obesity (Arner et al., 2008; Miot et al., 2010; Moreno-Navarrete et al., 2011; Wellen et al., 2007), rheumatoid arthritis (Noh et al., 2014), and atherosclerosis (ten Freyhaus et al., 2012; Wang et al., 2014,). In addition, recent population screening studies found significant evidence of an association between single nucleotide polymorphisms in the STAMP2 gene and metabolic syndrome (Qi et al., 2015; Sharma et al., 2015).

An interesting aspect of Stamp2 expression is that it is regulated in lean mice by nutritional status which is impaired in obese mice (Ramadoss et al., 2010; Wellen et al., 2007). *Stamp2* knockout mice has elevated levels of inflammatory cytokines and reduced levels of metabolic markers selectively in the visceral adipose tissue at an early age on a regular chow diet (Wellen et al., 2007). *Stamp2* knockout mice also display various metabolic and inflammatory deficiencies, such as impaired glucose uptake and insulin action in tissues that are critical for glucose homeostasis, as well as macrophage infiltration into adipose tissue and lipid accumulation in the liver (Wellen et al., 2007). Conversely, adenovirus mediated expression of Stamp2 in the diabetes model $ApoE^{-/-}/LDLR^{-/-}$ mice significantly reduced macrophage infiltration, inhibited expression of pro-inflammatory cytokines in epididymal and brown adipose tissue, and improved glucose tolerance, insulin resistance, and a range of other metabolic parameters (Han et al., 2013; Wang et al., 2014). The Jnk pathway, which has been implicated in diabetes, was identified as a potential route through which Stamp2 inhibits inflammation since ectopic expression of Stamp2 in diabetic mice inhibited Jnk1 phosphorylation (Han et al., 2013). These results indicate that STAMP2 plays an important role in countering inflammation and insulin resistance in metabolic tissues.

As noted above, liver is one of the tissues in which *STAMP2* expression is enriched and that *Stamp2* knockout mice develop fatty livers (Kim et al., 2015; Wellen et al., 2007). In line with these results, STAMP2 expression was reduced in the livers from non-alcoholic fatty liver disease (NAFLD) patients and in the hepatocytes from high fat diet-fed mice (Kim et al., 2015). In these mice, liver-specific depletion of Stamp2 by *in vivo* siRNA delivery induced hepatic steatosis, indicated by markedly increased vacuolization, increased liver weight, and elevation of plasma total cholesterol, triglyceride and nonesterified fatty acid levels, as well as increased insulin resistance (Kim et al., 2015). Conversely, these symptoms were improved when Stamp2 was re-introduced in the liver. Stamp2 rescue effect was through downregulation of lipogenic and adipogeneic transcription factors, sterol response element binding protein 1 (SREBP1) and PPARγ, resulting in reduced lipid accumulation (Kim et al., 2015). Overall, it was proposed that STAMP2 prevents NAFLD development by repressing lipogenic and adipogenic factors and modulating insulin signaling (Kim et al., 2015).

The details of STAMP2 effects on the whole body and tissue metabolic homeostasis is currently unclear; however, some insight has been gained regarding STAMP2 effects on insulin resistance. For example, siRNA-mediated Stamp2 knockdown led to decreased glucose transporter type 4 (Glut4) translocation to the plasma membrane resulting in lower insulin-induced glucose uptake in 3T3-L1 adipocytes (Wellen et al., 2007). Similar observations were made in human cell lines: *STAMP2* knockdown or disturbing STAMP2 function at the plasma membrane of human adipocytes using a monoclonal STAMP2 antibody decreased insulin-induced GLUT4 exocytosis and glucose import compared to control (Cheng et al., 2011; Qin et al., 2010, 2011). The failure in GLUT4 translocation was connected to inhibition of the insulin signalling pathway as shown by a decrease in the phosporylation of AKT, PI3K, and IRS-1 (Cheng et al., 2011; Qin et al., 2011). In addition, overexpression of STAMP2 in human adipocytes led to enhanced glucose uptake in response to insulin (Chen et al., 2010). STAMP2 antibody treatment of human preadipocytes increased apoptosis, and in the mature adipocytes resulted in mitochondrial damage and increased ROS generation; however, the specificity of this latter effect is open for discussion (Qin et al., 2011).

STAMP2 may also have important roles in regulating inflammation indicated by its expression in both human and mouse atherosclerotic plaques (ten Freyhaus et al., 2012). En face analysis demonstrated a marked increase of atherosclerotic lesion area in the aortas of $Stamp2^{-/-}ApoE^{-/-}$ mice, a model system to study atherosclerosis, compared to $Stamp2^{+/+}ApoE^{-/-}$ controls. The lesional inflammation was also higher in sections from $Stamp2^{-/-}ApoE^{-/-}$ mice (ten Freyhaus et al., 2012). In atherosclerotic plaques, STAMP2 expression was colocalized with the expression of macrophage markers, indicating that the role of STAMP2 deficiency in atherosclerosis is related to macrophage function. *STAMP2* expression was previously detected in circulating monocytes and its expression correlated with macrophage marker CD68 (Arner et al., 2008; Wang et al., 2010b). Furthermore adenoviral ectopic expression of Stamp2 in $ApoE^{-/-}/LDLR^{-/-}$ diabetic mice suppressed atherosclerosis by preventing macrophage apoptosis (Wang et al., 2014). This effect was correlated with Stamp2 regulation of the Pi3k/Akt signaling pathway.

STAMP2 is also strongly upregulated during marcrophage differentiation and its expression is induced by inflammatory stimuli, such as Toll-1ike receptor agonists (ten Freyhaus et al., 2012). Similar to adipocytes, $Stamp2^{-/-}$ macrophages exhibit a deregulated response to inflammatory stimuli. However, unlike in adipocytes, Stamp2 deficiency did not affect insulin sensitivity in macrophages (ten Freyhaus et al., 2012; Wellen et al., 2007). The exaggerated inflammatory response in Stamp2 deficient macrophages is due to disruption of cellular NADPH levels which increase significantly in $Stamp2^{-/-}$ macrophages. Re-expression of wild type Stamp2, but not an oxidoreductase-deficient mutant, caused a significant reduction in NADPH levels in $Stamp2^{-/-}$ macrophages, and decreased LPS-induced inflammatory response. The anti-inflammatory functions of Stamp2 is executed by an NADPH sensor protein, NMRAL1 (NmrA-like family domain-containing protein 1), which inhibits NF-κB activity through targeting nuclear p65 for degradation (Dai et al., 2009; Lian and Zheng, 2009).

An additional aspect of STAMP2 in the context of inflammation is its emerging role in arthritis. STAMP2 expression is induced by TNFα and its expression in the synovia correlates with the progression of joint swelling in both murine models and arthritis patients (Inoue et al., 2009; Noh et al., 2014; Takai et al., 2015; Tanaka et al., 2012). *Stamp2* knockout mice also develop rheumatoid arthritis (RA)-like pathology (Inoue et al., 2012). The development of RA in these mice was linked to increased inflammation through deregulation of IL-6 production. In primary cells from patients with RA *STAMP2* knockdown increased while its ectopic expression led to suppression of IL-6 expression (Tanaka et al., 2012).

STAMP3 has also been implicated in macrophage biology. *Stamp3* was highly expressed in macrophages and hepatocytes in mice and its deletion impaired iron homeostasis and led to impaired TLR4-mediated inflammatory responses in macrophages (Zhang et al., 2012). Stamp3 protein was also linked to obesity. In rats that were fed on a high fat diet and treated with capsaicin, a known inducer for thermogenesis, Stamp3 was found to be significantly repressed in the epididymal white adipose tissue compared to saline control treatment (Joo et al., 2010). Functional studies are required to assess the potential role of Stamp3 on metabolic disease.

6. STAMPS and cancer

All three members of the STAMP family have been implicated in cancer. Whereas STAMP1 and STAMP2 have been shown to promote carcinogenesis, STAMP3, at least in some contexts, appears to have a protective role against cancer. The molecular details of these effects are starting to be characterized as depicted in Fig. 3. These studies are summarized below.

6.1. STAMP1

STAMP1 expression is highly enriched in the prostate, and its expression is higher in PCa compared with benign tissue (Korkmaz et al., 2002; Porkka et al., 2002; Wang et al., 2010a). STAMP1 knockdown impedes growth as well as promotes apoptosis in LNCaP cells, whereas DU145 cells proliferate faster when STAMP1 is ectopically introduced (Wang et al., 2010a). This effect may be mediated, at least in part, by mitogen activated protein kinase (MAPK) signaling, as ERK activation in response to epidermal growth factor positively correlates with STAMP1 levels in these two cell models (Wang et al., 2010a). STAMP1 is also implicated in migratory and invasive abilities when transfected into PNT2 benign PCa cells (Whiteland et al., 2014). Furthermore, stable knockdown of STAMP1 impairs LNCaP tumor growth *in vivo* (Wang et al., 2010a). STAMP1 is now generally regarded to play an important role in PCa progression and may serve as a potential diagnostic marker. Interestingly, it was recently shown that STAMP1 is among a few genes for which there is a greater proportion of unspliced RNA in a cohort of CRPC specimens compared to untreated primary PCa, normal prostate epithelium, and cultured PCa cell lines (Sowalsky et al., 2014). Further work is required to characterize the molecular mechanism(s) underlying STAMP1 effects on PCa cells as well as its potential role in progression to CRPC.

6.2. STAMP2

STAMP2 was originally identified as a gene that had sequence similarity to *STAMP1* and which had high expression in the prostate. It was then found to be regulated by androgens, with increased mRNA levels in PCa cells compared with normal prostate (Korkmaz et al., 2005). STAMP2 protein expression was also significantly increased in human PCa compared with normal prostate, and it also correlated with tumor grade (Jin et al., 2015). STAMP2 knockdown induced apoptosis and cell cycle arrest, and markedly inhibited growth of PCa cell lines, including LNCaP, VCaP and 22Rv1, both *in vitro* and *in vivo*. Remarkably, *STAMP2* targeting by systemic administration of nanoliposome-encapsulated siRNA resulted in profound tumor regression in two independent preclinical models of human PCa. Furthermore, mechanistic studies indicated that STAMP2 effects on PCa growth and survival are through modulating activating transcription factor 4 (ATF4) expression and activity (Jin et al., 2015).

ATF4 signaling pathway is required for survival and proliferation of cancer cells in response to nutrient deprivation (Ye and Koumenis, 2009; Ye et al., 2010). ATF4 target genes, such as L-type amino acid transporters, were recently shown to promote PCa cell survival and are upregulated in advanced PCa (Wang et al., 2013a). STAMP2 knockdown cells exhibited significantly reduced expression of ATF4 and its target genes, and ectopic expression of STAMP2 enhanced ATF4 expression in PCa cells (Jin et al., 2015). The modulation of ATF4 activity by STAMP2 is mediated by increased intracellular ROS which was dependent on the oxidoreductase activity of STAMP2. Consistently, ectopic expression of oxidoreductase-dead mutant of STAMP2 in LNCaP cells failed to increase ROS or ATF4 expression (Jin et al., 2015). These findings suggest that STAMP2 could have utility in the clinic as a biomarker, as well as a therapeutic target. Interestingly, STAMP2 expression was significantly upregulated in CRPC and correlated with neo-adjuvant hormone therapy response. However, the possible role of STAMP2 in CRPC development is currently not known.

STAMP2 was recently implicated in other cancers as well. Wu et al. found that in keratinocytes STAMP2 expression is regulated by IL-17, which is emerging as an important cytokine that can promote cancer (Wu et al., 2015). STAMP2 was critical for IL-17 induced

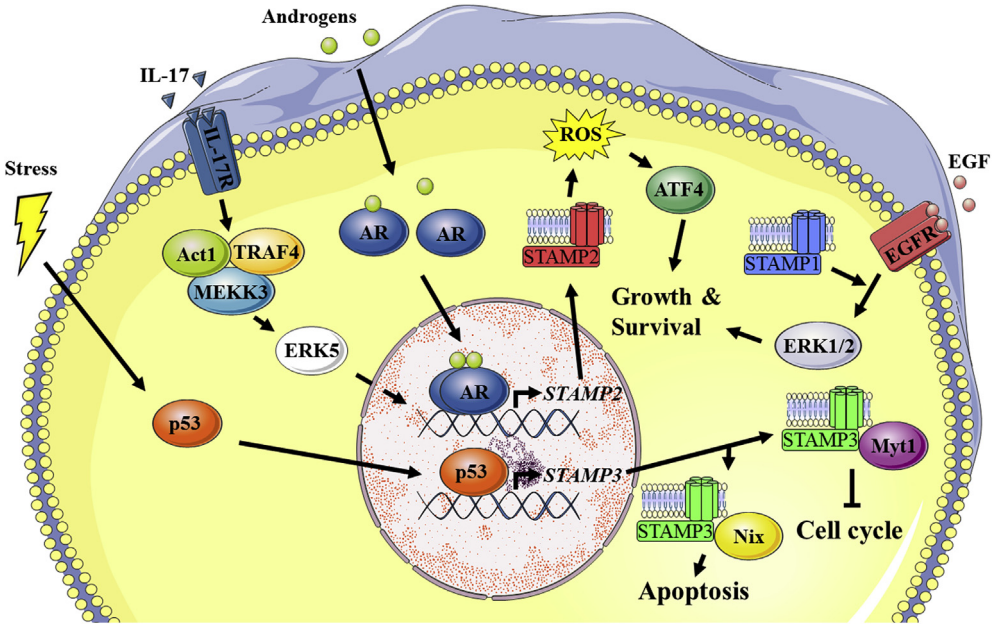

Fig. 3. Involvement of STAMPs in cancer. STAMP1 promotes PCa cell growth by mediating activation of ERK1/2. STAMP2 expression can be directly induced by androgens in AR-positive PCa cells, and it plays a pro-survival role in these cells by increasing ROS, which subsequently induces ATF4. In keratinocytes, IL-17, via its receptor IL-17R, initiates a pro-proliferative signaling cascade Act1-TRAF4-MEKK3-ERK5 that results in elevated STAMP2 expression. In contrast, STAMP3 can be directly activated by p53 and plays a tumor suppressor role by interacting with Nix or Myt1.

proliferation in cultured keratinocytes. STAMP2 was required for IL-17-dependent sustained activation of the TRAF4-ERK5 axis for keratinocyte proliferation and tumor formation. Further work is needed to uncover the details as to how STAMP2 affects keratinocyte biology and tumorigenesis (Wu et al., 2015).

6.3. STAMP3

The rat Stamp3 homologue pHyde was first cloned from Dunning rat PCa cells and inhibited PCa cell proliferation both *in vitro* and *in vivo* (Rinaldy and Steiner, 1999; Steiner et al., 2000). This is in contrast to the pro-proliferative activities of STAMP1 and STAMP2 in PCa cells. It was then discovered that Stamp3 stimulates p53 expression and induces apoptosis via a caspase 3 dependent pathway (Steiner et al., 2000; Zhang et al., 2001). Stamp3 expression, in turn, can be directly activated by p53 and functions as a tumor suppressor which may be due to its physical interactions with Nix, a proapoptotic Bcl-2-related protein, and Myt1 kinase, a negative regulator of the G2/M transition, to promote apoptosis and interfere with cell cycle progression, respectively (Passer et al., 2003). However, while STAMP3 overexpression renders Raji cells (derived from a Burkitt's lymphoma patient) sensitive to apoptosis, STAMP3 protects tumor cells from iron deprivation-induced cell death and promotes tumor growth in mice on a low iron diet (Isobe et al., 2011). These data suggest that STAMP3 may either inhibit or promote PCa depending on environmental factors.

An early study evaluated the mRNA expression of STAMP3 in PCa cell lines, xenograft tumors and clinical human tumor specimens by qPCR and found that *STAMP3* expression in PC3 and DU145 cells were much higher than in LNCaP and 22Rv1 cells (Porkka et al., 2003). *STAMP3* was expressed in all 8 LuCaP xenograft tumors with no clear differences among them. There was no difference between the benign, untreated and hormone-refractory clinical samples, but the sample size studied was rather small. However, when untreated tumors were divided by their degree of differentiation, *Stamp3* levels were low in the poorly differentiated samples (Porkka et al., 2003). In line with its tumor suppressor role in PCa cells, ectopic expression of *STAMP3* and treatment with cisplatin showed a synergistic effect on DU145 cell growth *in vitro*, and an additive effect was observed *in vivo* (Lu et al., 2009).

STAMP3 mRNA was strikingly repressed in hepatocellular carcinoma (HCC) compared with control adult livers (Coulouarn et al., 2005), while STAMP3 protein also inversely correlated with the differentiation level of HCC tumors (Caillot et al., 2009). This suggests that STAMP3 could potentially serve as a marker for the transition from carcinoma-free cirrhosis to cancerous liver, as well as the differentiation status of HCC (Caillot et al., 2009; Coulouarn et al., 2005).

A global gene expression analysis comparison between squamous cell lung carcinoma and normal lung epithelium cells from smokers found that *STAMP3*, along with several other known tumor suppressor genes, were significantly down-regulated in the cancerous cells (Boelens et al., 2009). The pathological association of *STAMP3* in colorectal and colon cancer is controversial at present. *STAMP3* was deregulated in the descending colonic mucosa between smoking and never-smoking Crohn's disease patients (Nielsen et al., 2009). However, *STAMP3* expression was increased in colorectal cancer tissue compared with normal colon (Isobe et al., 2011). In another study on colorectal cancer, the level of circulating exosomes was shown to correlate with poor prognosis and shorter survival, but not with STAMP3 expression (Silva et al., 2012).

These studies suggest that STAMP3 may be involved in different cancers as both a pro- and anti-cancer protein, depending on the context and the tissue type. Additional in depth studies are required to delineate STAMP3 function in different cancer types.

7. Conclusions

STAMP family members have common structural features, can act as metalloreductases, and are implicated in endocytic and exocytic processes, cell differentiation, and in various physiological functions. In addition, STAMPs are involved in a number of disease states. STAMP expression is dynamically regulated as a cellular response to environmental ques. This is exemplified by androgen and cytokine regulation of STAMP2 and p53 regulation of STAMP3. Whereas all three STAMPs have been implicated in cancer, it is primarily STAMP2 that has been found to be critical for metabolic homeostasis. To date, some of the molecular details of STAMP function have been uncovered, e.g. as they relate to in cancer and metabolic disease, but significant new knowledge through further biochemical, molecular, and cell biological studies are needed for full delineation. An interesting avenue of future exploration would be to assess whether STAMPs are involved in cancer metabolism. In addition, translational studies will conclusively evaluate the potential utility of STAMPs as diagnostic or prognostic biomarkers, or therapeutic targets.

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