CHEMISTRY RESEARCH AND APPLICATIONS

SUPEROXIDE DISMUTASE

STRUCTURE, SYNTHESIS AND APPLICATIONS

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EDITOR

nova
science publishers
New York

NOTICE TO THE READER

Library of Congress Cataloging-in-Publication Data

ISBN: 978-1-53613-081-2 (eBook)

Published by Nova Science Publishers, Inc. † New York

Chapter

Role of Superoxid Dismutase in Endometrial Functional Integrity

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ABSTRACT

Free radicals and other reactive oxygen species (ROS) are continuously generated as byproducts of normal cellular metabolism. Cells face up against ROS using a primary antioxidant system, characterized by a group of enzymes working together and sequentially, to reduce or eliminate ROS. The three major classes of antioxidant enzymes are the superoxide dismutase, catalase, and glutathione peroxidase. Superoxide dismutase (SOD) refers to a family of enzymes that catalyze the dismutation of superoxide to hydrogen peroxide and molecular oxygen. Superoxide and SOD are necessary to maintain biological homeostasis through various functions involving several cellular signal transduction pathways. Since the discovery of SOD more than four decades ago, there have been extensive studies on their biological activities in health and disease. The unbalanced activity of those enzymes (including SOD) plays a role in the pathogenesis of many diseases such as cancer, neurodegenerative diseases, allergy, ischemia/reperfusion injury or atherosclerosis.

The endometrium is a very peculiar organ that in intact, mature females responds to the effects of cyclic alternance of sex steroids (estrogens and progesterone) to accomplish complex functions, including sperm tolerance, fertilization, embryo implantation and subsequent formation of the placenta. Cyclic changes in both ROS production and SOD activity have been reported to occur in the endometrium of different species. Moreover, it

has been proposed that disturbances in ROS equilibrium might induce damages to tissues and predispose to infertility and many uterine diseases.

Cyclical variations in the expression of superoxide dismutase (SOD) have been reported in the human and bitch endometria. Increased SOD activity has been related to proliferation in the follicular stage of the menstrual cycle and increased levels of estrogen. In contrast, SOD activity decreases in the late secretory phase.

SOD activity has been related to angiogenesis during endometrial growth, regeneration, shedding or in implantation, due to its interplay with the local cytokine network. Also, SOD downregulation may trigger apoptosis, resulting from the accumulation of ROS in tissues. Furthermore, in the uterus, a decrease in SOD activity has been connected to prostaglandin F2-alpha synthesis and the endometrial secretion at progesterone withdrawal and luteolysis in species with short lifespan corpus luteum.

Differences between species are expected in regards to SOD activity during the estrous or menstrual cycles and might be related with some physiological species-specificities concerning the endometrial cycle or the type and chronology of implantation. E.g., estrogen-mediated reduction in SOD activity, as described in the canine endometrium during the early luteal stage, may be associated with an increase in the membrane fluidity of endometrial cells and therefore be favorable to embryo invasion.

In this chapter, we comprehensively investigate SOD effects in the homeostasis of mammal endometrium, using available information on several species and our team experience in the topic. In addition, we will also address its role in endometrial integrity and some uterine clinical conditions and infertility.

Keywords: Superoxide dismutase; reactive oxygen species; oxidative stress; fertility; diseases; mammal endometrium

INTRODUCTION

Free radicals and other reactive oxygen species (ROS) are continuously generated as byproducts of normal cellular metabolism (Gate *et al.* 1999). These ROS are necessary to maintain biological homeostasis through various functions involving several cellular signal transduction pathways (Thannickal & Fanburg 2000; Finkel, 2011; Zhang *et al.,* 2016). However, an excessive production of ROS, an impaired antioxidant system or a combination of these factors, results in oxidative stress (OS) that cause damage to the macromolecules necessary for cell structure and function (Dröge, 2002). Cells face up against ROS using antioxidants, defined as any substance that delays, prevents, or removes oxidative damage to a target molecule (Halliwell & Gutterdige 2015). The primary antioxidants systems are characterized by a group of enzymes working together and sequentially to reduce or eliminate ROS (Halliwell, 2007). The three major classes of antioxidant enzymes are the superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) (Valko *et al.* 2007). Superoxide dismutase refers to a family of enzymes that catalyze superoxide elimination in the first reaction of a free radical removal pathway (Fukai & Fukai, 2011)

The free radical superoxide was first described by L. Pauling in the 1930's (Pauling, 1979). Superoxide synthesis by the enzyme xanthine oxidase was firstly studied by Knowles and coworkers in 1969 (Knowles *et al.,* 1969), and during the following decades several biologically occurring reactions that produce substantial amounts of O_2- were found (Fridovitch, 1978a; Fridovitch, 1978b; Halliwell & Gutteridge 1984). Enzymatic superoxide dismutation by **Cu,ZnSOD** (**SOD1** in mammals) was identified by McCord and Fridovich in 1969 (McCord & Fridovich, 1969), despite that the purification of the enzyme has been achieved 30 years earlier, from bovine blood and liver, as a copper binding protein with an unknown function (Mann & Keil, 1938). In the early 1970s, Fridovich and coworkers further discovered **MnSOD** (**SOD2** in mammals) and **FeSOD** (not present in mammals) (Keele *et al.,* 1970; Yost & Fridovich, 1973). Finally, the third mammal SOD isoenzyme (**ECDOD, SOD3** in mammals) was discovered by Marklund and coworkers in 1982 (Marklund *et al.,* 1982). Recently, a novel prokaryotic SOD isoenzyme has been discovered that relies on nickel (**NiSOD**) (Barondeau *et al.,* 2004; Wuerges *et al.,* 2004).

The SOD1 isoform is present in the cytosol, liposomes, nucleus and intermembrane mitochondrial space and is a homodimer with a molecular mass of 32 kDa. Both SOD2 and SOD3 are homotetramers with a molecular mass of 86-88 and 135 kDa and are localized in the mitochondrial matrix and extracellular space, respectively. Enzymatic activity of SOD1 and SOD3 depends on the presence of copper (Cu) and zinc (Zn) (Fridovich, 1975). Zn participates in the proper protein folding and stability while Cu directly participates in SOD catalytic activity (Fukai and Fukai, 2011; McCord & Fridovich, 1975). Manganese (Mn) at the active site of SOD2 serves to catalyze the dismutation of superoxide similarly to Cu in SOD1 and SOD3 (Hsu *et al.,* 1996). Table 1 summarizes the general characteristics of the three mammalian SOD isoforms.

Table 1. Characteristics of mammalian superoxide dismutase isoenzymes.

	SOD1	SOD2	SOD3
Isoenzymes	Cu,ZnSOD - Copper, zinc superoxide dismutase	MnSOD – Manganese superoxide dismutase	ECSOD – Extracellular superoxide dismutase
Cellular location	Cytoplasm, lysosomes, peroxisomes, mitochondrial intermembrane space and nuclear compartments	Mitochondrial matrix	Extracellular space
Molecular mass	32 kDa	86-88 kDa	135 kDa
Assembly and molecular mass of subunits	Homodimer (16 kDa monomers with 153 aa)	Homotetramer (22 - kDa subunit)	Homotetramer (30 - kDa subunits)
Metal ions	1 Cu + 1 Zn(1)	Mn(2)	1 Cu + 1 Zn(3)
Chromosomal localization	21q22	6q25	4q21
References	Keller *et al.,* 1991; Crapo *et al.,* 1992; Liou, 1993; Halliwell and Gutteridge, 2015	Halliwell and Gutteridge, 2015	Fattman *et al.,* 2003

(1) Cu interacts with histidine residues at the SOD active site, and Zn stabilizes the enzyme. (2) Mn at the enzyme active center. (3) SOD3 contains a high affinity domain for heparin, which contributes to its localization in the extracellular matrix.

Superoxide and superoxide oxidase studies remain the focus of several studies in biology and health sciences so that 'the discovery and naming of SOD are, in the opinion of many researchers, the most important discovery of modern biology never to win the Nobel Prize' (Lane, 2002).

GENERAL CHARACTERISTICS

Even though the mammal isoenzymes of SOD – SOD1, SOD2, and SOD3 – differ in amino acid sequence, they catalyze essentially the same biochemical reaction (Zelko, 2002). Superoxide dismutase (EC 1.15.1.1) catalyzes the dismutation of superoxide radical according to the reaction:

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

Dismutase refers to a kind of chemical reaction in which the same reactant is both oxidized and reduced (Cammack, 2006). SOD-catalyzed dismutation is characterized by the oxidation of one superoxide anion to molecular oxygen and the reduction of another to hydrogen peroxide (Halliwell & Gutteridge, 2015). Superoxide dismutation process is nearly independent of pH, occurring within the pH range of 5.0 to 9.5. It occurs by a successive oxidation and reduction of a transition metal ion, such as copper (Cu) and manganese (Mn), at the active site of the enzyme (Abreu & Cabelli, 2010; Fridovich, 1975), in a "ping-pong" mechanism (Figure 1), with a high reaction rate of 1.5 x 10^9 $M^{-1}s^{-1}$ (Fridovich, 1975).

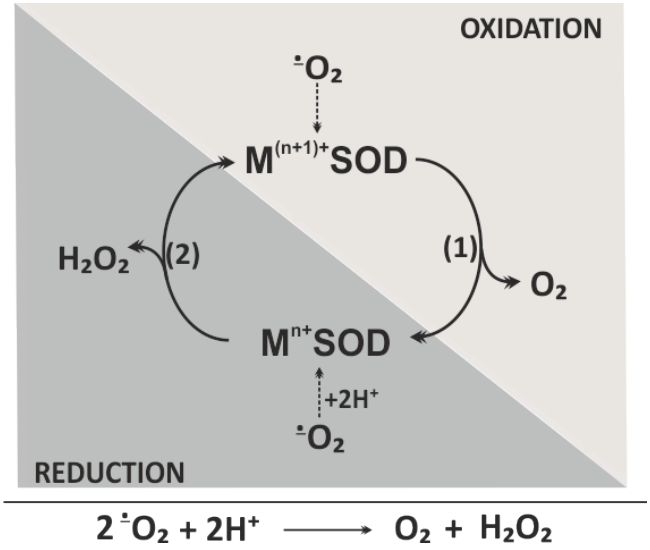

Figure 1. SOD-catalyzed superoxide dismutation. **M** (**M**etal) = copper (**Cu**; n = 1); manganese (**Mn**; n = 2); iron (**Fe**; n = 2); and nickel (**Ni**; n = 2). Oxidation (1) and reduction (2) dismutation half-reactions are presented in two distinct grey triangles. The overall reaction is writing below.

All the SOD isoenzymes bind differentially monovalent anions (e.g., azide, fluoride), with SOD 1 being competitively inhibited in the presence of Fl^-, N_3^-, and CN^- (Leone *et al.,* 1998; Meier *et al*., 1998). The three mammalian SOD isoenzymes have been identified with a distinct pattern of tissue distribution (Zelko, 2002). In humans, the liver has a relatively high

amount and activity of SOD1, while the activity of SOD2 is higher in the renal cortex than in other tissues, and SOD3 has been identified in plasma and lymph (Halliwell & Gutteridge, 2015).

Several transcription factors are involved in SOD cellular control (Miao and St. Clair, 2009). Superoxide can induce the expression of several genes constitutively regulating an inducible expression of SOD genes (Birben *et al.,* 2012). Within these redox-sensitive transcription factors are included Nrf2/Keap1, NF-κB, activator proteins (AP-1, AP-2), specificity protein (SP1) and CCAA/enhancer binding protein (C/EBP) (Miao and St. Clair, 2009; Sies *et al*. 2017). A post-transcriptional regulation of SOD expression includes changes in mRNA stability, mRNA translation and protein post-translational modification (Yamakura & Kawasaki, 2010).

SOD ROLE IN HEALTH AND DISEASE

Several animal studies evidenced a crucial role for SOD isoenzymes in protecting against a wide variety of diseases. The substantial number of evidence supporting a causal involvement of superoxide in multiple disease processes came from studies in animal models (Noor *et al.,* 2002). These studies showed that transgenic overexpression of SOD inhibits disease processes, while an opposite effect may be obtained with a genetic deletion of SOD (Li *et al.* 1995; Melov *et al.,* 1998; Shen *et al.,* 2006; Valko *et al.,* 2007). Researchers still look for the role of superoxide and SOD in human disease pathogenesis (Halliwell & Gutteridge, 2015). Changes in superoxide dismutase expression or content in several organs or systems are related to the pathogenesis and pathophysiology of diverse conditions (Hopkins, 2016).

Aging – Changes in SOD activities correlated with the age of animals (McCord, 2002 Melov *et al.,* 2000; Warner, 1994). Lifespan extension has been achieved in *Caenorhabditis elegans* and *Drosophila melanogaster* by an induced over-expression of SOD (Orr & Sohal, 1994; Sohal *et al.,* 1995) or the use of enzymatic synthetic drugs mimicking the enzyme activity (Kregel & Zhang, 2007). However, several studies failed to detect significant lifespan increase with improved antioxidant defenses (including overexpression of SOD1 and SOD2) in vertebrate species (Huang *et al.,* 2000; Van Remmen *et al.,* 2003; Page *et al.,* 2010; Salway *et al*., 2010).

Cancer - Many studies with gene knockout animals showed that reduction of SOD1 or SOD2 results in increased DNA damage, mutations and a higher incidence of cancer development (Van Remmen *et al.,* 2003; Elchuri *et al.,* 2005). Conversely, overexpression of SOD3 inhibits breast carcinoma cell growth and invasion (Kensler *et al.,* 1983; Teoh *et al.,* 2009). SOD levels are lower in cancer cells or higher in tumor cell lines that are resistant to drug treatments (Kim *et al.,* 2005; Sandoval *et al.,* 2006; Hurt *et al.,* 2007; Park *et al.,* 2009).

Immunological disorders - Oxidative stress due to SOD1 deficiency accelerates the destruction of red blood cells, leading to anemia. Antibodies produced against the oxidation products may trigger the autoimmune reaction (Iuchi *et al.* 2009). The expression of SOD2 is decreased in HIV-infected patients, followed by increased oxidative stress with enhanced protein carbonylation and lipid peroxidation (Flores *et al.,* 1993). In contrast, the expression of cytosolic SOD1 in macrophages is increased during HIV infection *in vitro*, most likely to counteract elevated superoxide anion concentrations (Delmas-Beauvieux *et al.,* 1996). SOD-1 plays a significant role in immune processes, because modulation of its activity may

differentially affect the NO-dependent microbicidal activity and release of cytokines by activated macrophages (Marikovsky *et al.,* 2003).

Neurodegeneration – Compelling evidence associates the oxidative stress and SOD activity with neurodegenerative diseases, such as amyotrophic lateral sclerosis (Deng *et al.* 1993; Valentine *et al.* 2005; Kabuta *et al.,* 2009; Bergemalm *et al.,* 2010), Parkinson´s diseases, Huntington´s disease, Alzheimer´s disease (Massaad *et al.,* 2009; Murakami *et al.,* 2011) and other degenerative disorders. Mutations in the SOD1 gene are known to play a role in at least 20% of familial amyotrophic lateral sclerosis cases (Rosen *et al.,* 1993; Perry *et al.,* 2010).

Pulmonary disorders - A beneficial role for all three isozymes of SOD in pulmonary hyperoxic injury has been demonstrated in experimental animals via both gene knockout and transgenic overexpression (Gao *et al.,* 2008; Kinula & Crapo, 2009). SOD attenuate pulmonary inflammatory responses, oxidative stress, and tissue remodeling following hyperoxia (Folz *et al.,* 1999; Yao *et al.,* 2010). Overexpression of SODs also results in amelioration of pulmonary injury induced by drugs, radiation, and environmental chemicals or dust (Kinula & Crapo, 2009). Targeted disruption of SODs aggravates the pathophysiological processes of the pulmonary disorders (St. Clair *et al.,* 1991). Diminished lung SOD activity in patients with pulmonary arterial hypertension (PAH) indicates an impaired capacity to detoxify superoxide radical (Bowers *et al.,* 2004), confirmed by the observation that extracellular SOD overexpression in lungs was able to ameliorate PAH induced by monocrotaline (Kamezaki *et al.,* 2008).

Cardiovascular diseases - Gene knockout and transgenic overexpression animal studies demonstrate a crucial role of SOD isoenzymes in cardiovascular disorders, including myocardial ischemia-reperfusion injury, atherosclerosis, hypertension, heart failure, cardiac hypertrophy, and drug/xenobiotic-induced cardiovascular complications (Yen *et al.,* 1996; Levonen *et al.,* 2001). Deletion of SOD2 in mice is embryonically lethal or causes early neonatal death due primarily to dilated cardiomyopathy (Li *et al.,* 1995; Lebovitz *et al.,* 1996). SOD3 activity is increased in macrophage-rich atherosclerotic lesions of apolipoprotein E-deficient mice (Fukai *et al.,* 1998). In contrast, the enzymatic activity of SOD3 was decreased in atherosclerotic lesions of the human aorta as compared with normal aorta segments of the same individual (Luoma *et al.,* 1998). Vascular SOD3 activity was reduced while activities of SOD1 and SOD2 were similar in the coronary arteries of patients with coronary artery disease and control subjects (Landmesser *et al.,* 2000). After short periods of ischemia, reoxygenation of isolated perfused animal hearts has been shown to produce additional tissue damage that is diminished by adding SOD1 or SOD2 to the reperfusion fluids. In addition, hearts from transgenic animals overexpressing SOD2 or SOD3 show less reperfusion injury, whereas animals lacking such antioxidant enzymes show more severe heart injuries (Levonen *et al*., 2008; Richters *et al*., 2011; Obal *et al*., 2012).

Hepatic and Gastrointestinal Diseases - Several animal studies demonstrate a protective role for all three SOD isoenzymes in hepatic disorders (Laukkanen *et al.,* 2001; Wheeler *et al.,* 2001), including graft dysfunction after liver transplantation, nonalcoholic fatty liver disease, liver ischemia-reperfusion injury, and liver injury induced by alcohol and other drugs/xenobiotics. Homozygous SOD2-deficient mice died within a month of life with a cardiac disorder and increased concentration of lipids in the liver (Li *et al.,* 1995). Viral vector-mediated delivery of either SOD1 or SOD2, but not SOD3 increases animal survival and attenuates graft dysfunction after transplantation of fatty livers in rats. It has also been reported that SOD1 deficiency increases hepatic lipid accumulation in mice (Uchiyama *et al.,* 2006).

Overexpression of either SOD1 or SOD2 in mice inhibits alcohol-induced liver injury, whereas knockout of SOD1 aggravates the liver damage (Wheeler *et al.,* 2001; Kessova *et al.,* 2003). Overexpression of SOD1 also protects against carbon tetrachloride-elicited hepatotoxicity in mice. However, mice deficient in SOD1 are resistance to acetaminophen-induced hepatotoxicity, suggesting a possible pro-oxidant role for the physiological level of SOD1 activity in acetaminophen-mediated liver injury (Lei *et al.,* 2006). A transgenic overexpression of SOD1 in mice protects tissue from neutrophil infiltration and lipid peroxidation during intestinal ischemia-reperfusion. Oral co-administration of SOD1 and catalase is reported to attenuate stress-induced gastric mucosal lesions in rats. In an animal model of chemically-induced acute colitis, transgenic overexpression of SOD1 results in amelioration of colonic inflammation and improves animal survival (Kruidenier *et al.,* 2003).

Diabetes - Several experimental findings suggest a critical role for SOD1 and SOD2 in protecting against diabetes development and various diabetes complications (Kubisch *et al.,* 1994; Halliwell & Gutteridge, 2015). Overexpression of SOD1 or SOD2 attenuates diabetic retinopathy, neuropathy, renal injury and cardiomyopathy (Kowluru *et al.,* 2006; Shen *et al.,* 2006; Vincent *et al.,* 2007). The overexpression of SOD1 protects against end-organ damage in models of type II diabetic nephropathy (DeRubertis *et al.,* 2007). Studies in mice with genetic deletions of various antioxidant enzymes have also provided insight into the specific relative contributions of SOD2 to the development of diabetes complications (Hinerfeld *et al.,* 2004). Further strengthening a potential role for the antioxidant SOD2, specific polymorphisms in the SOD2 gene were associated with the development of diabetic complications (Mollsten *et al.,* 2004).

Renal diseases – In transplanted human kidneys that had been subjected to cold storage, SOD infusion into the renal artery at implantation produced significant improvement in renal function (Pollak *et al.,* 1993). Either viral vector-mediated or transgenic overexpression of SODs is reported to attenuate renal ischemia-reperfusion injury in animal models. Targeting a synthetic cationic SOD to renal proximal tubular cells inhibits oxidative stress and nephrotoxicity of cisplatin (an anticancer drug that may cause severe renal injury) and increases the survival of cancer-bearing mice (Nishikawa *et al.,* 2001). SOD1 deficiency causes salt sensitivity and aggravates hypertension in hydronephrosis in mice (Carlstrom *et al.,* 2009). Similarly, mice with heterozygous knockout of SOD2 (SOD2+/-) developed salt-sensitive hypertension and accelerated renal senescence (Rodriguez-Iturbe *et al.,* 2007). Viral delivery of SOD1 gene reduces cyclosporine A (an immunosuppressive agent used in organ transplantation but is nephrotoxic) induced free radical formation and nephrotoxicity.

Reproductive disorders – In the testes, endogenous SOD protects spermatozoa from excessive ROS (Tsunoda *et al.,* 2012). SOD was shown to preserve sperm motility and reduce lipid peroxidation. Sperm incubation with high concentrations of SOD preserved motility in mouse spermatozoa and enhanced mice embryo development (Nonogaki *et al.,* 1992). Another study, evaluating the effects of SOD on sperm viability, motility, and morphology, found that SOD was associated with improved semen quality (Perumal, 2014). A higher proportion of sperm exposed to superoxide anion exhibited capacitation and hyperactivation, as opposed to those not exposed to SOD (de Lamirande *et al.,* 1997). Moreover, the gene transfer of SOD3 to the penis reduces superoxide levels and improves erectile function in aged or diabetic rats (Bivalacqua *et al.,* 2003; Deng *et al.* 2010). An increased level of oxidative stress associated with a decreased SOD activity was associated with the polycystic ovarian syndrome. It may play a pathogenetic role in the development of insulin resistance (Suresh *et al.,* 2015;

Kucukaydinet *et al.,* 2016; Victor *et al.,* 2016), hyperandrogenism (Gonzalez *et al*., 2012; Suresh *et al.* 2015), and chronic inflammation observed in this disease (Papalou *et al.,* 2012; Seleem *et al.,* 2014; Pertynska-Marczewska *et al.,* 2015; Zuo *et al.,* 2016).

Other diseases and conditions - In septic patients, production of superoxide anion is increased, and its levels in plasma are elevated compared to healthy normal (Warner *et al.,* 1995). Increased levels of SOD were also reported in a pediatric septic population, although no prognostic correlation with outcome was observed (Batra *et al.,* 2000). Oxidative stress is involved in the pathogenesis of several skin disorders, including ultraviolet light-induced injury, skin carcinogenesis, and skin aging (Murakami *et al.* 2009). Treatment with SOD1 ameliorates ischemic skin injury in experimental animals (Galenko-Yaroshevskii *et al.,* 2006). Levels of SOD are increased in proliferating keratinocytes of injured mouse skin, and mice lacking SOD1 show impaired wound healing (Taylor *et al.,* 1993; Bennaars-Eiden *et al*., 2002). Activated leukocytes release Inflammation mediators including cytokines, eicosanoids, and nitric oxide (NO). Excess NO can react with superoxide to form peroxynitrite anion, a potent ROS. It has been reported that overproduction of tumor necrosis factor (TNF)-α, which is mainly released by macrophages, is associated with a decrease in SOD1 expression, whereas TNF-α, IL-1, IL-4, and IL-6 activate SOD2 (Kiningham *et al.,* 2001; Afonso *et al.,* 2006). Interferon-γ plus TNF-α exposure has been shown to increase SOD3 secretion in dermal fibroblasts and SOD3 expression along with inducible NO synthase in rat type II pneumocytes (Marklund, 1992; Brady *et al.,* 1997). SODs may be essential protectors in anemia. Deficiency of either SOD1 or SOD2 in mice causes oxidative stress in red blood cells and hemolytic anemia (Friedman *et al.,* 2004; Iuchi *et al.,* 2009). Studies also demonstrate a protective role for SODs in aging-related cognitive decline and muscle atrophy (Muller *et al.,* 2006).

SOD ROLE IN THE ENDOMETRIAL FUNCTION

The mammalian endometrium is an utterly complex structure that undergoes finely tuned morphological changes in response to ovarian sex steroids, with the ultimate goal of guaranteeing embryo survival, implantation, and the success of pregnancy (Ponnampalam *et al.,* 2004; Sherwin *et al.,* 2006). These cyclic changes encompass a species-specific pattern of proliferation, differentiation, and remodeling, which is supposedly related to the species physiology, namely the characteristics of ovarian cycle, litter size and the placental type (Payan-Carreira *et al.,* 2016).

Like any other highly dynamic tissue, the metabolism of endometrial cells continuously generates reactive oxygen species. Various studies identified ROS and several antioxidant enzymes in the mammal endometrium. It was also demonstrated that OS modulates the cyclic changes in the endometrium (Gupta *et al.,* 2008). ROS are now acknowledged as crucial for female fertility (Rizk *et al.,* 2013). ROS homeostatic concentrations are kept in equilibrium by a pro-oxidant/antioxidant balance, whose disruption would predispose to disease (Burton & Jauniaux, 2011).

SOD has been identified in the endometrium in human (Narimoto *et al.,* 1990; Sugino *et al.,* 2004; Sugino, 2007), sheep (Al-Gubory *et al.,* 2008, 2017), cows (Giergiel & Kankofer, 2014), guinea pigs (Makker *et al.,* 2006) and dogs (Payan-Carreira *et al.,* 2016), as well as in uterine cell preparations in mice (Jain *et al.,* 1999). Cyclic hormonal changes across the

endometrial cycle modulate the local antioxidant activity, since ROS and antioxidant enzymes respond to sex steroid stimulation, as it was demonstrated by Serviddio *et al.* (2002).

Sugino´ studies showed that SOD is highly expressed in the glandular epithelia and stroma of the human endometrium (Sugino *et al.,* 1996; Sugino *et al.,* 2000) (Sugino, 2007). Both SOD and ROS were evidenced in the endometrium. The changes in SOD and ROS described throughout the endometrial cycle were proposed to support a critical role in the regulation of endometrial function.

SOD role in the cyclic endometrium

The immunolocalization of SOD in the human endometrium showed that SOD content increase from the proliferative to the secretory phase, peaking in mid- to late-secretory phases (Narimoto *et al.,* 1990; Sugiro *et al.,* 1996). A similar pattern of expression was found by Payan-Carreira *et al.* (2016) in the canine endometrium. There, SOD immunolabeling was higher in all the epithelia compared to the stroma. Also, the intensity of the reaction decreased from anestrus (low estrogen and progesterone levels) to proestrus (rise in estrogens), and then increased from estrus (transition from estrogen to progesterone dominance) to early and mid diestrus (luteal phase) (Payan-Carreira *et al.,* 2016). Furthermore, differences in the pattern of SOD immunoexpression were described in the different epithelial elements of the canine endometrium (surface epithelium and superficial and deep glandular epithelia), which could be due to the distinct involvement and function of these structures in the canine implantation and placentation.

SOD was also detected in the endometrial fluid of humans (Rahiminejad *et al.,* 2016), cows (Ramos *et al.,* 2015) and dogs (Kobayashi *et al.,* 2014). Rahiminejad *et al.,* (2016) found higher SOD levels in endometrial secretions in women with ongoing pregnancies than in those that failed IVF cycles, but no differences were detected among women with successful pregnancies and miscarriage. Ramos *et al.,* (2015) reported that, in cows, SOD activities in uterine washings were not affected by the periovulatory sex steroid milieu and suggested that this could be related to a dilution effect in the secretions that minimized any putative changes. In contrast, these authors reported an increased expression of SOD before ovulation, which might contribute to cell survival. In dog uterine fluid, SOD activity was higher in diestrus compared with anestrus or estrus (Kobayashi *et al.*, 2014), which according to the authors would improve sperm quality and fertility at breeding. It is important to notice that in dogs, ovulation occurs under progesterone levels around 5ng/mL, due to pre-ovulatory luteinization of granulosa cells (Concannon, 2011), while in the cow it occurs in an estrogenic environment (Ramos et al., 2015).

Enzymatic assays testing SOD activity in explants or extracts of endometrial tissue in humans showed that SOD activity rises from early to the mid-late proliferative stage, transiently decreasing during the early secretory and resuming high activity levels in the middle secretory stage and early pregnancy (Sugino *et al.,* 1996). In dogs, total SOD activity (Figure 2) was found higher in anestrus (basal estrogen and progesterone levels) and proestrus (rising estrogen levels) but it was inhibited by increasing levels of progesterone (progesterone levels start rising in dogs in estrus –when estrogen levels fall - and remain above basal levels through the early and mid diestrus) (R. Payan-Carreira & D. Santos, unpublished data). Conversely, this pattern in SOD activity seems to contradict the previous Immunohistochemistry (IHC) study (Payan-Carreira *et al.,* 2016). Still, the differences could be explained by the fact that in the IHC study,

only the protein expression of SOD 1 was identified in the canine uterus, and it was not limited to the activated enzyme. In mice, estrogen reduces the total SOD activity in the uterus, which could favor the endometrial plasticity of endometrial cells and favor embryo interaction (Jain *et al.,* 1999).

It has been shown that SOD, and thereby ROS in physiological concentrations, mediates hormone signaling, apoptosis, cell migration, angiogenesis, and prostaglandin secretion (Sugino *et al.,* 2001; Agarwal *et al.*, 2005; Sugiro, 2007), and is of primordial importance in embryo implantation and decidualization (Sugino *et al.,* 2001; Rizk *et al.,* 2013).

In humans, SOD content decreases in the late secretory phase preceding menstruation (Sugiro *et al.,* 1996), which has been associated with a decrease in both estrogen and progesterone stimulation. The decrease in SOD activity is followed by an increase in local ROS. These, in turn, would stimulate prostaglandin F2alpha secretion via activation of nuclear factor kappa B and consequently command endometrial shedding (Sugino *et al.,* 2001; Wu *et al.,* 2014), as well as luteolysis (Du Plessis *et al.,* 2017). A decrease in SOD activity was not detected in the canine endometrium (Figure 2), but this may be related to the species particularities, such as the low levels of PGF2alpha recorded at the end of the secretory phase (Luz *et al.,* 2006), and the existence of a prolonged lifespan corpora lutea (in dogs, cyclic and gestational corpora lutea are of similar lifespan – Concannon, 2011). Besides, the activation of the COX2 enzyme will also stimulate pro-inflammatory cytokines like TNF (Sugino, 2007; Agarwal *et al.,* 2016).

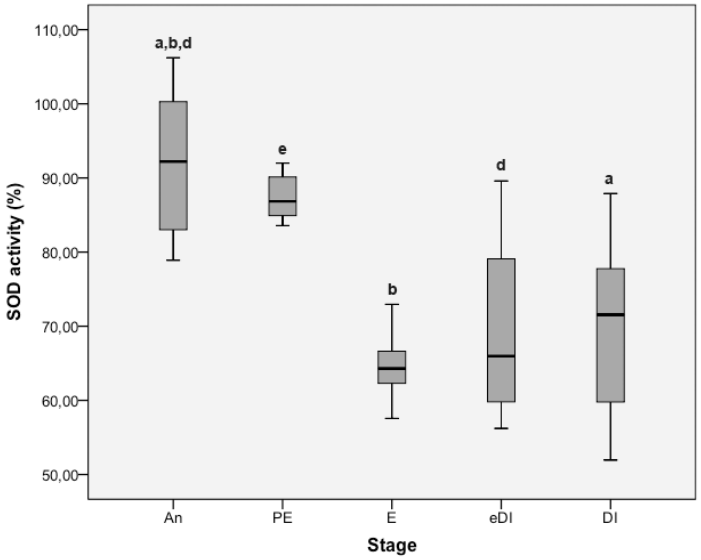

Figure 2. Box-plot graph for superoxide dismutase (SOD) activity in the different stages of the canine estrous cycle: anestrus (A), proestrus (PE), estrus (E), early diestrus (eDI) and diestrus (DI). Five animals were used per group. Values sharing the same letter are significantly different: $P<0.05$ (a/d/e); $P<0.01$ (b).

SOD1 interacts with several cytokine pathways mediated by TNF-α (Afonso *et al.,* 2006) or the transforming growth factor (TGF)-beta (Valko *et al.,* 2007), through which it may

interfere with both cell apoptosis and proliferation pathways, respectively. Under an increased production of ROS, TNF activates Caspase 3, thereby stimulating apoptosis via the extrinsic pathway (Figure 3) (Sugino, 2007; Agarwal *et al.,* 2016). It is accepted that an increase in SOD activity will protect cells from TNF pro-apoptotic effects (Sugiro, 2007; Burton & Jauniaux, 2011). However, it is important to remember that SOD activity - and thereby, ROS - may also mediate cell apoptosis in the uterus through different mechanisms (Figure 3) (Leitão *et al.,* 2010; Burton & Jauniaux, 2011), using both the intrinsic and the extrinsic pathways. The activation of one or the other pathway is context-dependent and therefore may vary with the stage of the cycle or the reproductive status of the female, possibly depending on the activation of different concurrent regulatory pathways.

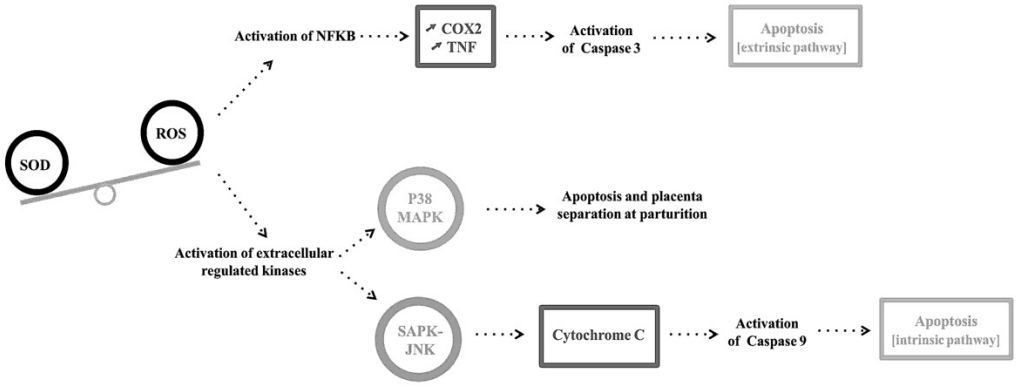

Figure 3. Superoxide dismutase (SOD) involvement in the pathways regulating cell apoptosis.

In addition, SOD has been associated with cell proliferation and tissue remodeling, by controlling the activity of metalloproteinases 2 or 9 through the modulation of the local concentration of ROS (Fukai *et al.,* 2011).

Remodeling of the vascular network occurs in all stages of the endometrial cycle, under a tightly regulated process; these changes provide the necessary support to cell growth and differentiation in the endometrium. Local temporary hypoxia, associated with decreased SOD activity, is a major regulator of the endometrial angiogenesis in the endometrium. It also plays a crucial role in embryo implantation and formation of the placenta in mammals (Okada *et al.,* 2016). In general, during the proliferative phase, the growth of new vessels should accompany endometrial proliferation and promote the regulation of vascular permeability, while in the secretory phase the endometrium possessess a well-developed vascular network (Smith, 2001) that supports the glandular secretory activity and foster receptivity towards any embryo. In this aspect, induction of angiogenesis occurs similarly to the observed in wound healing and neoplasia, and in close relation with a disruption in circulation induced by hypoxia, altogether with a rapid proliferation and growth characteristic of these states (Marikovsky *et al.,* 2002).

Available information raises the hypothesis that different pathways are involved in the regulation of endometrial angiogenesis besides the activation of SOD enzyme. Some studies showed that hypoxia and ROS are involved in the regulation of endometrial microvasculature. It can be achieved by the vascular endothelial growth factor (VEGF, proangiogenic factor) and Angiopoietin-2 (Ang-2, angiogenic antagonist) (Agarwal *et al.,* 2016); VEGF activity is modulated via TNF and TGFbeta1 pathways (Okada *et al.,* 2016). An increase in SOD activities, along with the derived hypoxia, around the time of implantation serves to trigger endometrial angiogenesis, via VEGF activation (Du Plessis, 2017), under a very precise mechanism.

SOD role in implantation and decidualization

Placenta formation follows the embryo implantation. If the embryo implantation follows a more or less similar mechanism across species, despite its different chronologies, the placentation varies greatly between species, particularly respecting the invasion of the maternal endometrium and the gross placenta morphology, which in turn originates differences in the degree of modification of the endometrial layers and of the vascular network supporting the placenta (Carter & Enders, 2016).

In animals developing a decidua, after the apposition phase at implantation, the embryonic trophoblast invades the endometrium, triggering a more or less important, species-specific, tissue remodeling that is accompanied by the proliferation of stromal and glandular epithelial cells, as well as by changes in the local vascular network. The occurrence of oxidative stress at the embryo-maternal interface starts on early pregnancy and, particularly in this stage, ROS play a dual role in early pregnancy events. Its homeostatic regulation is decisive to the outcome of pregnancy (Burton & Jauniaux, 2011).

Early embryonic development and placentation occur in a state of low oxygen. Modest hypoxia favors trophoblast differentiation and its invasive ability toward the maternal endometrium (Sugino, *et al.,* 1996; Sugino, 2007; Rizk *et al.,* 2013). In mice, a decrease in SOD activity, and a subsequent sharp increase in superoxide anion radical was observed at the time of implantation (Nivsarkar *et al.,* 2005).

The initial differentiation of the decidual cells, located below the surface epithelia in humans (Kajihara *et al.,* 2016) and dogs (Payan-Carreira *et al.,* 2014) occurs even in the absence of an embryo, at the mid-late luteal phase of the cycle (Kajihara *et al.,* 2016). In the pregnant endometrium, this preliminary decidualization is sustained by the progesterone secretion. The withdraw of progesterone receptors observed in non-pregnant cycles at the end of the luteal stage is reversed by the decrease in SOD activity that is recorded at mid to late secretory phases in pregnant cycles (Sugino, 2007; Kajihara *et al.,* 2016; Du Plessis *et al.,* 2017), impairing the release of prostaglandin F2alpha that would trigger luteolysis.

It has also been demonstrated that decidual cells are more resistant to oxidative cell death than non-decidualized stromal cells (Kajihara *et al.,* 2016). This resistance is associated with the inhibition of the c-Jun NH-terminal kinase (JNK) stress signaling (intrinsic) pathway by SOD2 (Kajihara *et al.,* 2016). Inhibition of SOD2 led to increased ROS production, triggering apoptosis in rabbit endothelial cells (Liu *et al.* 2011). The inactivation of this pathway will also contribute to the maintenance of the progesterone receptor activity in decidual cells (Leitão *et al.,* 2010).

In sheep, around the moment of embryo attachment, an increase in the total SOD activity has been reported, particularly in the caruncular areas of the endometrium, which was mainly due to an increased in SOD 2 activity (Al-Gubory *et al.,* 2016; Al-Gubory *et al.,* 2017). The authors hypothesized that a switch in the activities of SOD 1 and 2 compared with those reported at the end of the luteal phase occurs in response to conceptus derived factors (Al-Gubory *et al.,* 2016).

It has been shown that, in humans, the formation of placental villi and the subsequent formation of the placental disc is mediated by the local oxidative stress, which also regulates the remodeling of the endometrial spiral arteries (Burton & Jauniaux, 2011). Simultaneously with villi formation, the endometrium goes through an intensive remodeling of its vascular network to support embryo development and growth (Burton & Jauniaux, 2011). This remodeling occurs on both the maternal and fetal sides of the placenta. It results from either the elongation of pre-existing endothelial tubes (non-branching angiogenesis) and the extension of those tubes (spouting angiogenesis) (Shaman *et al.,* 2013). It may also be originated by vasculogenesis (development of new vessels from mesenchymal stem cells) (Pereira *et al.,* 2015), which starts on the trophoblast side (Torry *et al.,* 2007). These changes in the endometrial vascular network are mediated by the trophoblast, which usually reverses the physiological pathways associated with luteolysis and progesterone withdraw, namely by inhibiting the NF-kB pathway, which up-regulates VEGF and modulates TNF and other cytokines (e.g., Interleukin 6 and 8 and TGF-beta 1) (Pereira *et al.,* 2015). The homeostasis of the system is finely tuned by diverse molecules, including the Hypoxia Inducible Factor (HIF).

SOD INVOLVEMENT IN THE ENDOMETRIAL PATHOLOGY

Across species, disruption of the oxidative stress balance has been associated with endometrial diseases that can originate in cyclic or pregnant endometria (Rizk *et al.,* 2013). However, little is known about the involvement of ROS or SOD in mammals' uterine diseases other than human or rodents.

Endometriosis is an important disease in human medicine, often leading to chronic pain and abdominal surgery, as well as infertility. It derives from the implantation of endometrial tissue within the pelvis, possibly favored by retrograde menstruation (Gupta & Agarwal, 2014). Although the results from different studies give contradictory information, it is now generally agreed that patients with endometriosis show an increase in the generation of ROS by activated peritoneal macrophages (Agarwal *et al.,* 2006), derived from the decreased activity of enzymatic antioxidants in the peritoneal fluid, that together with increased lipid peroxidation, promote the growth and adhesion of endometrial cells in the peritoneal cavity (Sharma *et al.,* 2017). This generates an unfavorable balance between antioxidants, particularly SOD, and ROS, originating cell damage, disturbed angiogenesis and bleeding, and persistence of inflammation.

A specific mutation in SOD2 enzyme has been associated with unexplained infertility in women (Gupta *et al.,* 2014; Agarwal *et al.,* 2016), impairing the role of some protein pathways that could lead to the pathophysiology of female infertility. Interference with the matrix metalloproteinases or with SOD2 regulated angiogenesis at placentation has been mentioned (Gupta *et al.,* 2014), among other putative adverse effects at the level of ovaries and tuba.

Increased SOD activity has been reported in endometrial curettage samples of patients diagnosed with endometrial adenomyosis and with endometrial polyps when compared with endometrial hyperplasia and endometrial adenocarcinoma, the latter showing the lowest activities; however, in this study, the authors did not compare the enzyme activity with normal controls. The authors suggest that women with common benign gynecological diseases are more susceptible to develop precancerous lesions and cancer since the increased oxidative stress would stimulate cell cycle progression and promote cell proliferation.

Long-term progestin contraceptive treatment may induce disturbed endometrial angiogenesis with concurrent abnormal endometrial bleeding, which has been associated with ROS imbalance (Hickey *et al.,* 2006).

Disturbed angiogenesis at embryo attachment has also been pointed out as one reason for idiopathic recurrent pregnancy loss (Aziz, 2013), which would originate endothelial damage, impaired placental vascularization and immune malfunction (Gupta *et al.,* 2007). Aziz (2013) refers to a significant reduction in SOD activities when pregnancy loss occurs during the first trimester, while the staining intensity in trophoblast samples was higher in women that miscarriage before the day 77 compared with controls (Gupta *et al.,* 2007).

Pre-eclampsia, a human pregnancy-specific condition, is a complex heterogeneous syndrome characterized by hypertension and proteinuria. Even though its exact etiology remains obscure, it is thought that may be originated on disrupted maternal endothelial function, which is probably related to a progressive ROS and SOD disequilibrium that will interfere with the normal vascular support to the placenta (Jauniaux & Burton, 2016). Sharma *et al.* (2006) showed that SOD circulating levels are elevated in women with pre-eclampsia, compared to matched control pregnancies. However, other syndromes associated with placental insufficiency and embryo growth retardation may develop in women without leading to pre-eclampsia. In the case of placental insufficiency, the endothelial dysfunction may be established during early pregnancy, when the development of placental vessels might be compromised by multiple causes (e.g., chromosomic abnormalities, chronic infections, immune-mediated pathologies, or trophoblast abnormalities) (Jauniaux & Burton, 2016).

CONCLUDING REMARKS

SOD, as one of the primary antioxidant enzymes acting in oxidative stress, is involved in multiple and complex of regulation of physiologic processes, some of which occurring in the endometrium. ROS are kept in tightly controlled levels in tissues that guarantee the homeostasis of the organ. Excessive or deficient production of reactive oxygen species and/or a deficiency or excessive activities in the antioxidative defenses in the body triggers the disease.

Modest fluctuations in oxidative stress are allowed as part of the homeostatic process that is itself tightly regulated through the interaction with other regulatory pathways. This may contribute to the still limited amount of knowledge that is available on SOD and ROS participation in health and disease, despite the numerous studies that already contributed to explore the involvement of oxidative stress in female uterine diseases and infertility and putatively relevant treatment options.

We hope that this chapter provides the researchers with a concise reference on SOD and ROS involvement in endometrial physiology and medicine.

ACKNOWLEDGMENTS

We are gratefull to Dr. Gustavo Paixão for the English language review.

The authors would like to acknowledge funding from the Portuguese Science and Technology Foundation (FCT) under the Projects PEst-OE/AGR/UI0772/2011 and PEst-OE/AGR/UI0772/2014.

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