Review Article

Indian J Med Res 148 (Supplement), December 2018, pp 100-106
DOI: 10.4103/ijmr.IJMR_494_18

Quick Response Code:

S100 proteins: An emerging cynosure in pregnancy & adverse reproductive outcome

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Received March 9, 2018

S100 proteins are calcium (Ca^{2+})-binding proteins and these have an important function in progression, manifestation and therapeutic aspects of various inflammatory, metabolic and neurodegenerative disorders. Based on their involvement in intracellular or extracellular regulatory effects, S100 proteins are classified into three subgroups: one subgroup is specialized in exerting only intracellular effects, other performs both intracellular and extracellular functions and the third subgroup members only display extracellular regulatory effects. S100 proteins are expressed particularly in vertebrates and have cell-specific expression. Functionally, S100 proteins act through their surface receptors and regulate cell functions in autocrine or paracrine mode. Receptor for advanced glycation end products (RAGEs) and toll-like receptor 4 are the main surface receptors. S100 proteins participate in the regulation of cellular differentiation, proliferation, apoptosis and inflammation along with Ca^{2+} homeostasis, energy metabolism and cellular migration, and perform the respective functions through their interaction with transcription factors, nucleic acids, enzymes, receptors, cytoskeleton system, *etc*. Currently, their role in adverse pregnancy outcomes and compromised reproductive health is being explored. These proteins are present in amniotic fluid, endometrium tissue and foetal brain; therefore, it is quite likely that alterations in the expression levels of S100 family members will be affecting the particular function they are involved in and ultimately affecting the pregnancy in adverse manner. The current review discusses about an association of S100 proteins in pregnancy disorders such as endometriosis, intrauterine growth retardation and miscarriage.

Key words Calcium signalling - early pregnancy loss - high-risk pregnancy - implantation - inflammation - intrauterine growth retardation

Introduction

Early miscarriage and pregnancy-associated problems are of major concern. The reason behind this is not only genetical or physiological but also environmental and modern lifestyle. Moderate levels of inflammatory reactions are also pre-requisite during the first trimester of pregnancy for implantation and embryo development. These early stages of pregnancy resemble 'an open wound'[1]. For invasion and proper blood supply of embryo neovascularization and tissue remodelling occur during early gestational weeks of pregnancy[1,2]. An appropriate tuning of anti-inflammatory and inflammatory mediators is required for adequate repair of the uterine epithelium

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and the removal of cellular debris. Thus, this critical period of pregnancy is marked by expression of specific cytokines and adhesion molecules by both foetal and maternal side ensuring successful pregnancy. Any alteration and dysfunction of this balanced inflammatory milieu and any perturbation or disturbance in this during the critical period result in miscarriage or pregnancy-associated complications[3].

Earlier studies in mice and human revealed the role of important calcium (Ca^{2+})-binding S100 proteins in pregnancy-related complications[4,5]. This group of proteins helps in the recruitment of leucocytes at inflammatory site and functions like cytokines[4]. These proteins regulate a variety of cellular functions such as cellular differentiation, cell cycle progression and energy intracellular signal transduction by interacting with several other mediatory proteins[6]. S100 proteins were found to be tumorigenic in function and get elevated in several cancer and melanoma cases[6]. An earlier study in human also showed elevated level of S100 group proteins in high-risk pregnancy cases, in amniotic fluid and cord blood of foetus with brain damage[7]. The role of S100 protein in immunomodulation of high-risk pregnancy cases is an active area of research and clinical investigation. This review focuses on new advances regarding the role of S100 protein in diagnosis and treatment of high-risk pregnancies.

S100 protein structure and function

Ca^{2+} regulates several cellular processes and acts as a messenger[8]. Many Ca^{2+}-binding proteins, having the EF-hand structural motif, make Ca^{2+} signalling network in combination with many molecular components[9]. S100 proteins are the largest subgroup within this family of Ca^{2+}-binding proteins and found to be involved in several diseases such as rheumatoid arthritis, acute inflammatory lesions, cardiomyopathy, Alzheimer's disease and cancer[10,11].

S100 proteins are acidic, Ca^{2+}-binding proteins initially identified in the brain of several mammalian species and called S100 because of their solubility in 100 per cent ammonium sulphate[12,13]. Genes responsible for the synthesis of most S100 proteins are located on human chromosomes 1q21[14]. Initially, S100 proteins were found to be located in glial cells and used as a marker of glial cell differentiation and mammalian brain development[15-17]. S100 protein family has 21 members having the same basic structural moiety but entirely different function, and are found in cerebrospinal fluid, urine, serum, seminal plasma and saliva mainly in active disease states. These proteins are found to be present in Ca^{2+} free (apo); Ca^{2+}-bound and target bound states as a symmetric dimer, with each monomer containing two EF-hand motifs[18]. The EF-hand motif on N-terminal site contains helix I with pseudo Ca^{2+}-binding site, and the EF-hand of C-terminal is associated with helix III, helix IV and second Ca^{2+}-binding site (Fig. 1).

S100 proteins undergo structural and conformational changes on binding with Ca^{2+}, and this conformational change allows interaction of these proteins with target molecules. Activated S100 proteins perform all cellular functions by both extracellular and intracellular methods (Table I). All S100 proteins function in the form of dimmers, and only S100G protein acts as monomer[39]. A few hetero-dimmers are also reported: S100A1/B, S100A8/A9, S100A1/A4 and S100A1/P[40,41]. S100 proteins can also form active tetramers, hexamers or larger oligomers (S100B[42], S100A4[43], S100A8/A9[44] and S100 A12[45]).

S100 receptors

Function of S100 proteins is determined by their oligomeric forms and their respective binding partners[46]. Extracellular S100 proteins act via activation of surface receptors such as G protein-coupled receptors, receptor for advanced glycation end products (RAGEs) and toll-like receptors and aid in regulatory processes such as cell proliferation, differentiation and migration in normal as well as different pathological conditions. Intracellular S100 proteins also act via interaction with different target enzymes, cytoskeleton subunits, receptors and transcription factors or nucleic acids regulate Ca^{2+} homeostasis, energy metabolism and cellular differentiation.

Role of S100 proteins in high-risk pregnancy cases

In maternal endometrium, S100 proteins are expressed by both immune cells and non-immune cells. A few groups of S100 proteins such as S100A8, S100A9 and S100A12 are mainly secreted from myeloid origin of immune cells such as granulocytes, monocytes and early stages of macrophages[4]. As myeloid origin cells are well known as crucial regulators for other immune cells (T, Treg, uNK and non-inflammatory macrophages and neutrophils cells) in successful pregnancy, any alteration in inflammatory or immunomodulatory stage may change S100 protein levels[4] (Fig. 2). Some non-immune

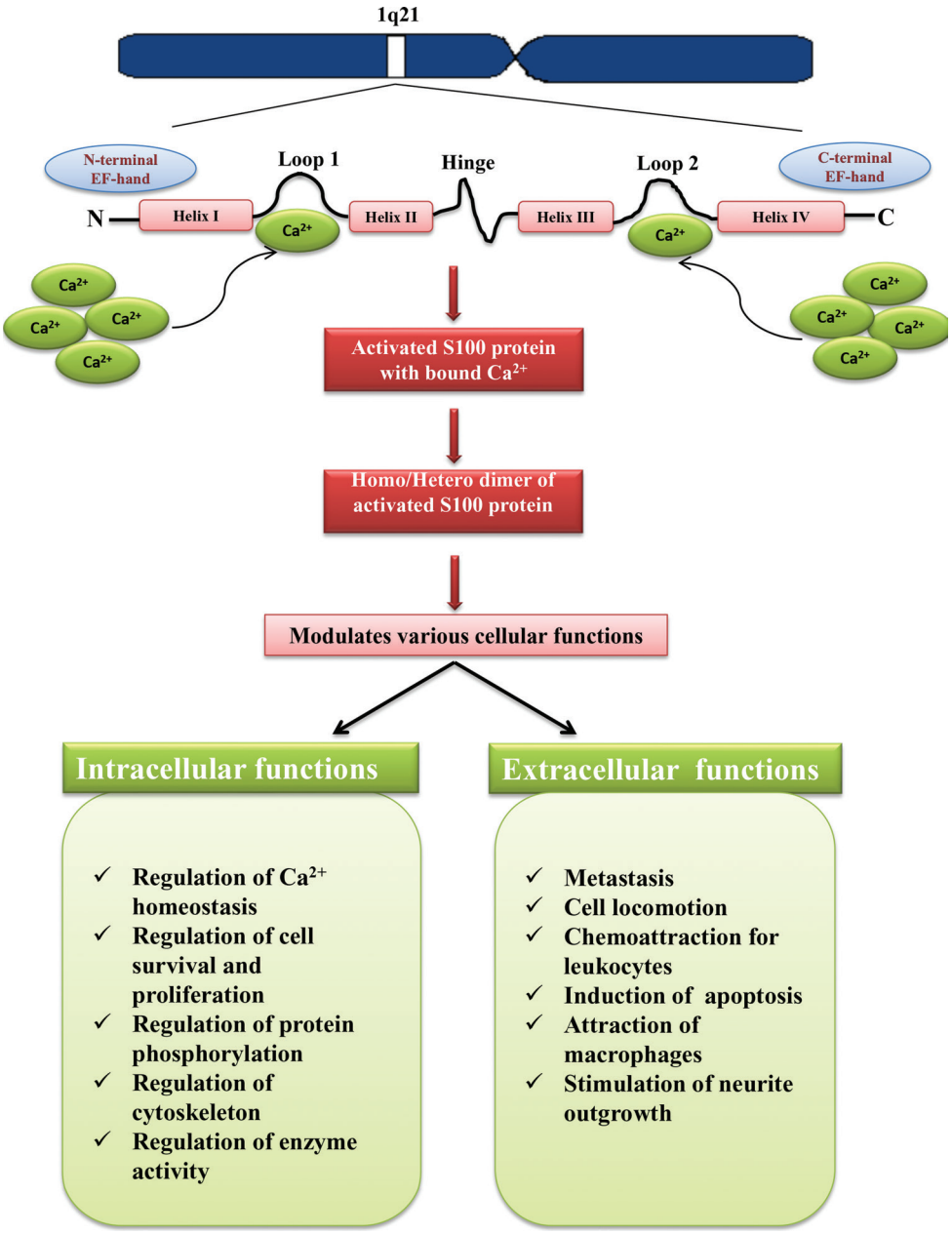

Fig. 1. Schematic diagram represents the chromosomal location, structure and various functions of S100 proteins. *Source*: Refs 14, 18.

cells such as mice placenta and ovaries of cow and pig have been reported to secrete some S100 group proteins such as S100A1, S100A6, S100A9 and S100A8[5,48].

S100 proteins regulate embryo implantation, intrauterine growth and normal foetal brain development during pregnancy. S100 family proteins have been found to be dysregulated in various endometrial diseases (Table II). S100A8 proteins are found to be down regulated in receptive phase of endometrium[57]. S100A8 protein recruits mouse and human neutrophils and macrophages at the site of inflammation[58]. Endometrial epithelium and stromal cells also showed expression of S100A10 protein during the implantation window and found to play an important role in endometrial receptivity[54]. The expression of these proteins have been found to be down regulated in the endometrium of infertile patients[54,55]. This is the reason behind the failure of 30 per cent of embryo implantation in assisted reproduction.

Table I. Functions of S100 proteins

S100 protein	Localization	Functions	References
S100A1	Skeletal system, neurons and cardiomyocytes	Functioning of cardiomyocytes and skeletal muscle, regulation of energy metabolism	19
S100A2	Cancerous cells	Down regulated in many cancers	20
S100A3	Localized in root of hair and some cancerous astrocytes	Differentiation of epithelial cell and hair cuticular barrier formation	21
S100A4	Tumorous tissue	Stimulating cell proliferation, mobility and migration	22
S100A5	Tumorous tissue	Elevated in bladder cancer cases	23
S100A6	Tumorous tissue	Cell cycle progression, cytoskeletal movement and tumour formation	24
S100A7	Tumorous tissue	Cytoskeletal functions, adhesion and migration, upregulated in breast cancer	25
S100A8	Macrophages, dendritic cells, microvascular endothelial cells	Necessary for embryo implantation, promotes myeloid cells differentiation	5
S100A9	Neutrophils, dendritic cells	Inhibits myeloid cells differentiation, induces inflammation	26
S100A10	Neutrophils, dendritic cells	Interacts with serotonin receptors and control depression like status	27
S100A11	Neutrophils, dendritic cells	Controls cell proliferation and survival	28
S100A12	In neutrophils and inducible in macrophages	Regulates VSCM functions	29
S100A13	Fibroblasts, osteoblasts and melanoma cells	Regulates secretion factor (FGF)-1 and IL-1α from various cell types	30
S100A14	Tumorous tissue	Inhibits cancer progression *via* suppression of p53 mediated pathway	31
S100A15	-	Acts as an extracellular factor	32
S100A16	Tumorous tissue	Disrupts insulin sensitivity and promotes obesity	33
S100B	Astrocytes, certain neuronal populations, Schwann cells, melanocytes, chondrocytes, adipocytes, skeletal myofibers	Stimulator of cell cycle and migration and an inhibits apoptosis	34
S100G	Neutrophils, dendritic cells	Maintains cytosolic Ca^{2+} concentration	35
S100P	Tumorous tissue	Cell migration and potentially metastasis	36
S100Z	Tumorous tissue	Down regulated in several tumours	37, 38

VSCM, vascular smooth muscle cell; FGF, fibroblast growth factor; IL, interleukin

A study conducted by Passey *et al*[5] showed that S100A8 knockout gene in mice caused a late embryonic lethality and suggested its role in fetomaternal tolerance. A study on transcriptome-based analysis in equine pregnancy revealed that S100A6 protein was expressed in conceptus side, and S100A2, S100A4, S100A6 and S100A8 were present in maternal endometrium on day 16 in mare[59]. A key role of these proteins has been suggested in epidermal growth factor-stimulated embryo adhesion, acquisition of endometrial receptivity, immunotolerance, apoptosis of dead endometrial epithelial cells and prolactin secretion, a marker for onset of decidualization[60,61]. S100 β protein is also found to be up regulated in trisomy cases, and their upregulation is an indicator of a brain lesion in developing foetus[58]. Thus, monitoring of S100 protein could be helpful in the detection of brain distress in intrauterine growth-retarded (IUGR) foetuses[50]. In preeclampsia and IUGR cases, amniotic fluid S100B protein concentration was found to be elevated[23].

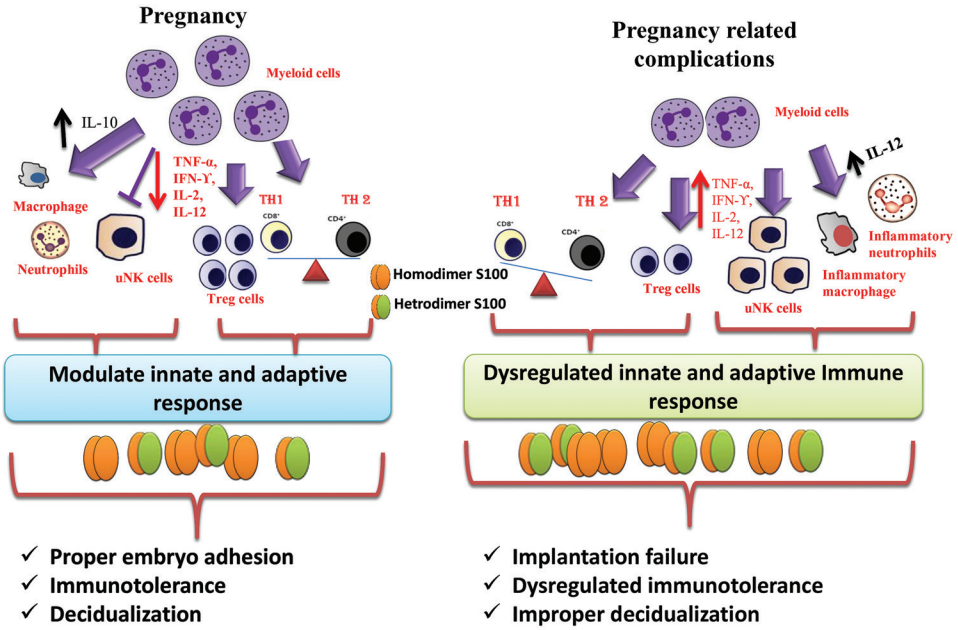

Fig. 2. Schematic diagram represents interaction of S100 proteins with immune cells for the regulation of various hallmark processes of pregnancy. IFN-γ, interferon gamma; IL, interleukin; TH, T helper; TNF-α, tumor necrosis factor alpha; uNK, uterine natural killer. *Source*: Refs 4, 47.

Table II. Altered expression profile of S100 proteins in various human pregnancy-related diseases

Pregnancy-related diseases	S100 family	References
Pregnancy-associated with Down syndrome	Upregulated S100ß	49
IUGR	Upregulated S100ß	50
SGA babies SGA foetus	No change in S100ß	51
Pre eclampsia+IUGR	Upregulated S100ß	52
Miscarriage	Down regulated S100A11 Up regulated S100A8, S100A9	53 4,47
Pre eclampsia	Up regulated S100ß	52
Pre-term labour	Up regulated S100ß	51
IVF failure	Down regulated S100A11, S100A10	54
PCOS	Up regulated S100A12	55
Endometriosis	Up regulated S100A4	56
Endometriosis associated with infertility	Up regulated S100P	56
Gestational diabetes	Up regulated S100A9	57

IUGR, intrauterine growth restriction; SGA, small for gestational age; IVF, *in vitro* fertilization; PCOS, polycystic ovary syndrome

Conclusion

The present review summarizes the role of S100 proteins in high-risk pregnancy cases along with its structure and mechanism of action. This also covers the importance of S100 proteins as a main player of successful implantation, embryonic growth and birth of physically and mentally healthy child. The optimal expression and signalling of S100 proteins, at particular stages of pregnancy is a pre-requisite for avoiding high-risk pregnancy cases and can serve as therapeutic target and prognostic biomarker in pregnancy-related complications.

***Financial support & sponsorship*:** The first author (RV) and the second author (PV) acknowledge the Department of Biotechnology, New Delhi, India, for providing financial assistance in the form of Research Associateship and Senior Research Fellowship, respectively. The third author (SB) thanks the University Grant Commission, New Delhi, India, for providing financial assistance in the form of Senior Research Fellowship.

***Conflicts of Interest*:** None.

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