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Promotor Analysis of Cattle Endometrium throughout Oestrous Cycle and Early Gestation Period

Sayed Ali Askar Musavi [a*], Mohammad Hakim [b] and Noor Ahmad Akbari [c]

[a] Department of Animal Science, Agriculture Faculty, Kabul University Afghanistan, Kabul, Afghanistan.
[b] Department of Animal Science, Agriculture Faculty, Bamyan University Afghanistan, Bamyan, Afghanistan.
[c] Department of Animal Science, Agriculture Faculty, Alberony University Afghanistan, Kapisa, Afghanistan.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Endometrial gene expression is principally controlled by the ovarian steroids and gestation recognition features. An important number of analyses of differential expression genes (DEGs) in bovine endometrium have been reported. Bovine uteri at follicular phase (FS), luteal phase (LS) and implantation phase (IS). A promoter, as associated to genomics, is a section of DNA upstream of a gene where applicable proteins (such as RNA polymerase and transcription factors) bind to inductee transcription of that gene. The subsequent transcription produces an RNA molecule (such as mRNA). RNA polymerase and the basic transcription factors (TFs) bind to the promoter sequence and start transcription. TFs, belong to growing family of regulatory protein, influence

**Corresponding author: E-mail: saamusavi2018@gmail.com;*

transcription by regulating many different cellular function by interacting directly with DNA. 1kb upstream of the promoter region of each DEGs analyzed by NSITE (Recognition of Regulatory motifs) of Softberry (http://www.softberry.com) and predicated several TFs binding site. GO (gene ontology) used for identification of those DEGs have TFs functions. Promoter analyses predicted 150-160 TFs for each phase. DLX4 and IRF4 at FS, and IRF5, IRF9, STAT1 and STAT2 at IS were in common to DEGs and estimated TFs, respectively. The current research identified possibility molecular mechanisms governing inner epithelial role and coming events studies.

Keywords: Endometrium; bovine; transcription factor and promotor.

1. INTRODUCTION

Promoter, a region of DNA sequences, defines where transcription of a gene begins by RNA polymerase. promoter sequences are naturally located directly upstream of the transcription start site. RNA polymerase and the basic transcription factors (TFs) bind to the promoter sequence and start transcription [1]. Transcription factors (TFs) abele to activate or silence transcription of genes by binding to specific DNA noncoding regions, thus playing at vital role in gene [2]. TFs, belong to growing family of regulatory protein, influence transcription by regulating many different cellular function by interacting directly with DNA [3]. TFs can control when, where and how RNA polymerases start. TFs reason accumulative or reducing of gene transcription, protein synthesis, and afterward changing cellular role. A lot of TFs have been documented and a large amount of the human genome performs to code for these proteins. Numerous relatives of TFs occur and associates of each family may share structural features [4]. Some TFs are common in numerous cell types (ubiquitous), they show a broad function in the instruction of inflammatory genes, whereas others are cell-specific and may regulate the phenotypic characteristics of a cell. Several report have been done to examine mammalian TFs at high determination and profundity. Several researchs have conclude TF expression over mRNA expression profiling using RNA sequencing (RNA-seq) joint with genome promoter analysis in human (Lambert *et al.* 2009).

But in bovine endometrium promoter analysis during estrous cycle and implantation, it has not been reported yet and in the present study, we were analysed 1kb promoter region of upstream of each DEG genes in bovine endometrium to compare FS vs. LS and LS vs. IS. The specific aims of this study are to analysis the promoter area of DEGs achieve when contrast each phase.

2. MATERIALS AND METHODS

2.1 Predication of TFs Binding Site

1kb upstream of the promoter region of each DEGs analyzed by NSITE (Recognition of Regulatory motifs) of Softberry (http://www.softberry.com) and predicated several TFs binding site [5].

2.2 Identification the Particular and General TFs

The TFs predicated at each comparing groups in bovine endometrium were include specific and common TFs. The specific transcription factors related to individual one stage and general transcription factors include in both comparing phase. Consequently the general and particular TFs were detached.

2.3 Identification of TFs from DEGs

The TFs estimated at bovine endometrium have need confirmation, for confirmation the estimated TFs compared with DEGs TFs. GO (gene ontology) used for identification of those DEGs have TFs functions.

3. RESULTS

3.1 Estimated TFs Binding Site

In the present study, one Kb of the upstream area of the promoter of each DEGs were analyzed to predict transcription factor-binding site. While comparing at FS and LS, a total of 153 and 156 TFs were judgement for extremely expressed DEGs at FS and LS, respectively. Correspondingly, when comparing LS and IS, 157 and 153 TFs were estimated for higher and weak expressed DEGs at IS, respectively.

3.2 Identification the Specific and Common TFs

When the total number of TFs estimated then separated the common and specific TFs, 26 were specific for DEGs expressed greater at FS and 29 were specific for higher at LS, respectively. There were 127 estimated TFs in common at FS and LS. Specific TFs were 33 and 29 for higher and lower expressed DEGs at IS, respectively, there were 124 TFs estimated in common at IS and LS (Fig. 1).

Stage assess from the amount of DEGs with binding areas, highest five TFs were assessed while comparing at diverse phases in cattle endometrium are be visible in Table 1. In situation of FS vs. LS, the number of DEGs with binding regions, have the large number of DEGs was estimated. For FS: RFX, RARA, GRDBD, RZR/ROR and MYF. For LS the five top TFs estimated they bind with large number of DEGs they are: SP1, PRKCA, SP3, SP2 and IRF1. In case of IS vs. LS for IS: SP1, IRF9, IRF5, PRKCA and ZIC1 transcription factors predicated they have the large numbers of DEGs. SP1, SP3, PRKCA, AP2 and HR transcription factors expected they have the large numbers of DEGs with the binding site in LS (low IS).

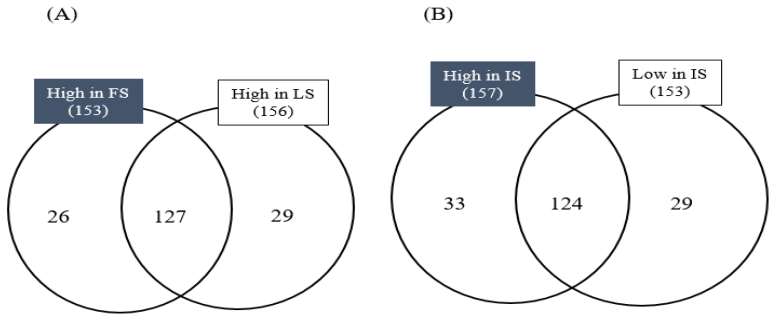

Fig. 1. Set illustrating show the number of TFs evaluate from the promoter area of DEGs at FS vs. LS (A), and LS vs. IS (B). Characters in the parenthesis show the whole amount of approximate TFs for to each phase

Table 1. Approximate highest 5 TFs from the promoter area of DEGs expressed at various phase (FS vs. LS and LS vs. IS) in cattle uterus

Comparing Stages	Descriptions	Estimated TFs	No. of DEGs with binding site
FS vs.LS			
Higher at FS	Regulatory Factor X	RFX	214
	Retinoic acid receptor alpha	RARA	162
	Glucocorticoid DNA binding domain	GRDBD	111
	Related orphan receptor	RZR/ROR	106
	Myogenic factor	MYF	83
Higher at LS	Specificity protein 1	SP1	210
	Protein kinase C alpha	PRKCA	108
	Specificity protein 3	SP3	77
	Specificity protein 2	SP2	76
	Interferon regulatory factor 1	IRF1	66
LS vs. IS			
Higher at IS	Specificity protein 1	SP1	86
	Interferon regulatory factor 9	IRF9	66
	Interferon regulatory factor 5	IRF5	43
	Protein kinase C alpha	PRKCA	36
	Zinc finger	ZIC1	28
Lower at IS	Specificity protein 1	SP1	175
	Specificity protein	SP3	95
	Protein kinase C alpha	PRKCA	91
	Activating protein 2	AP2	85
	Lysine-specific demethylase hairless	HR	79

Table 2. Contrast of assessed TFs and TFs associated with in DEGs at diverse periods (FS vs. LS and LS vs. IS) in cattle uterus

Comparing Stages	No. of TFs in DEGs	No. of estimated TFs	No. of Common TFs	Common TFs	No. of DEGs with binding site
FS vs. LS					
Higher at FS	25	153	7	CREG1	6
				DLX4	40
				ELF5	4
				GFI1	2
				IRF4	11
				MYB	28
				PPARG	11
Higher at LS	28	156	5	EGR1	16
				HNF1B	15
				MTF1	1
				POU5F1	4
				PPARA	5
LS vs.IS					
Higher at IS	21	157	7	CREM	2
				FOXS1	7
				IRF1	31
				IRF5	43
				IRF9	66
				STAT1	15
				STAT2	2
Lower at IS	21	153	3*	CREM	2
				FOXS1	7
				IRF1	32

**Common TFs of highly expressed DEGs at IS and estimated TFs from the promoter region of DEGs in lower expression at IS*

3.3 Identification of TFs from DEGs

Table 2 characterizes the contrast of assessed TFs and the TFs involved in each DEG. In the set of FS vs. LS, 25 and 28 DEGs were show as TFs for extremely be visible at FS and LS, individually. DLX4 and IRF4 were involved in mutually vastly indicate DEGs and estimated TFs of particular at FS. CREG1, ELF5, GFI1, MYB and PPARG were involved in mutually extremely expressed DEGs at FS and estimated TFs of public with FS and LS. Whereas, there were no shared TFs between DEGs of greater expression and particular TFs judged from extremely expressed DEGs at LS. EGR1, HNF1B, MTF1, POU5F1 and PPARA were involved in both vastly expressed DEGs at LS and judged TFs of shared with FS and LS. On the other hand, 21 DEGs were expressed as TFs for highly expressed at IS. While contrasted it with assessed TFs of exact in extremely expressed DEGs at IS, IRF5, IRF9, STAT1 and STAT2 were involved in together clusters. Contrast of greatly expressed TFs with assessed TFs of common with LS and IS, CREM, FOXS1 and IRF1 were connected with both sets. There was no common TFs between DEGs of higher expression and assessed TFs of exact in lesser expressed DEGs at IS. In TFs involved both in extremely expressed and assessed TFs, DLX4 (40 DEGs), MYB (28), IRF5 (43), IRF9 (66) and IRF1 (32) had a huge number of DEGs with binding site in the promoter area.

4. DISCUSSION

Each stage of gene expression in bovine endometrium under control of transcription factors at promotor region. Transcription factors are proteins involved in the process of changing, or transcribing, DNA into RNA. Transcription factors include a large number of proteins, without RNA polymerase, that initiate and control the transcription of genes [6]. Estimate TFs compared with TFs in DEGs which expressed at the cattle uterus. The result of present investigation identified some matchless TFs in cattle endometrium. CREG1, DLX4, ELF5, Gfi1, IRF4, Myb and PPARG identified as a characteristic at FS. Cellular repressor of E1A-

stimulated genes (CREG1) is a novel and vital glycoprotein that controls tissue homeostasis. But, small glycoprotein was primarily defined by Veal et al. [7] as a transcription repressor that counteract E1A-induced transcription stimulation. Result of current study illustrated that it is a small glycoprotein discharge outside the cell or rest in at intracellular membrane compartments [8]. The result of present investigation shows GREG1performed in both estimated at FS and DEG it would also have promoted by E2 and play vital role in gene expression in cattle endometrium at the follicular stage. Earlier research proposed that DLX4 is regulated by E2. The result of present research show DLX4 appeared in both GED and Estimated at FS and likewise encouraged by E2 and play vital role in gene expression in cattle uterus at this phase. E74-like factor 5 (ELF5) is an epithelial-specific member of the ETS transcription factor family [9]. An important role of ELF5 is the rule of cell fate, establishment with specification of the trophectoderm in the blastocyst [10]. ELF5 is in classic human tissues and informed to be expressed in the kidney, prostate, lung, mammary gland, salivary gland, placenta, and stomach [9,11]. Our results show ELF5 emerged in together DEG and assessed at FS and it might be regulated by E2 and show an important function of gene expression in cattle endometrium at this period. Growth factor independence 1 (Gfi1) is a transcriptional repressor which is necessary for the role and development of many different hematopoietic lineages. Gfi1 plays an essential role during granulocytic differentiation and characterized as a T cell oncogene (Zweidler *et al.* 1996). This gene is expressed in the common lymphoid progenitor and developing to T and B lymphocytes. However, during normal development, levels decrease when these cells are matured. In mature hematopoietic cells, its expression is limited to granulocytes. Our finding shows that it is looked in mutually DEG and assessed that it may play immune role against viruses and bacteria in bovine endometrium during FS. IRF4 fit to the IRF family of TFs has been regulated by E_2 [12]. It was too proposed that deregulation of IRF4 activities could additional more infected by pathogens in female [12]. IRF4 is expressed in definitely in macrophage/dendritic cells and also in lymphocytes [13]. Result of present research show, IRF4 assessed as a particular TFs in FS which possibly will protected role versus pathogens in cattle endometrium at FS. Myb is related to a large family of proteins, functionally various described in all eukaryotes. Largest Myb protein have ability to work as TFs with varyiung numbers of Myb domain and also they have ability to bind DNA directly [14]. In mouse and human have been suggested to play vital function in cell cycle regulator and in the explosion and variation of hemopoietic cells. Myb is a portion of DNA binding protein which able to stimulate or block transcription of altered supporters [15]. Thus, the function of Myb activate or repress TFs in different organisms. The present study, Myb emerged in both DEG and estimated at FS possibility has role at gene regulation during FS in bovine endometrium. Peroxisome proliferator-activated receptor gamma (PPARG) is mainly involved in the regulation of genes which are related to lipid metabolism and play a role in adipocyte differentiation and important TFs for adipogenesis [16]. PPARG belongs to the superfamily of nuclear receptors and those genes are activated by PPARG stimulate lipid uptake and adipogenesis by fat cells [17]. Therefore, the main role of PPARG is to control those genes which are responsible for lipid metabolism. In our finding, estimated PPARG TFs specific for FS in bovine endometrium. Furthermore, the PPARG should has role at gene regulation in bovine endometrium during FS.

In comparison of LS vs. FS, some TFs recognized as specific for LS in both new estimated and also in DEG and they are EGR1, HNF1B, MTF1, POU5F1 and PPARA. Early growth response protein 1(EGR1) is a protein which is encoded by *Egr1* and belongs to the EGR family of C2H2-type zinc-finger proteins. It is a nuclear protein and functions as a transcriptional regulator. The target products of activated genes are required for differentiations and mitogenesis. EGR1 is rapidly prompted in several cell types by growth, differentiation and apoptotic stimuli such as growth factors, cytokines, hormones and environmental stresses [18] reported that EGR1 is involved in follicular development, ovulation, luteinization and placental angiogenesis. EGR1deficient female mice were infertile due to lack of mature follicles, ovulation and luteinisation [19]. EGR1 TF regulated by progesterone hormone. Similar in present study, EGR1 appeared in new estimated and DEG TF in bovine endometrium during LS and it will be playing an important role at gene expression in bovine endometrium during LS. “The HNF1B gene offers guidelines for making a protein that binds to particular regions of DNA

and controls activity of other genes. On the basis of this function, the protein created from the HNF1B gene is named a TF. The HNF1B protein is part of a large group of TFs which is called homeodomain proteins. The homeodomain is an area of the protein that allows it to bind to DNA. The HNF1B protein is found in many organs and tissues including the lungs, liver, intestines, pancreas, kidneys, reproductive system, and urinary tract" [20]. HNF1B-associated are likely to be involved in regulating metabolic functions associated with renal cyst formation [21]. HNF1B in human expressed in several organs such as kidney, uterus, prostate, stomach and etc. This is the first time that author estimated the HNF1B and its specific TFs in bovine endometrium. Present study predicated the HNF1B is unique TFs I bovine endometrium during LS. It may have key role at gene expression during LS in bovine endometrium.

Metal regulatory transcription factor 1 (MTF1) is a pluripotent transcriptional regulator involved in cellular adaptation to various stress conditions and primarily exposure to heavy metals but also to hypoxia or oxidative stress. MTF1 is evolutionarily preserved from mammals to insects and has been described for many species including human, mouse, capybara, pufferfish, zebrafish, trout and Drosophila melanogaster [22]. MTF-1 is also involved in the transcriptional regulation of other metal-responsive genes such as zinc transporter 1 [23] recognized that the deficiency of MTF-1 in mouse embryo is lethal at day 14. They concluded MTF-1 also serves a developmental role. Therefore, MTF-1 is a main TFs for regulate metals and it is playing a vital function in several species. Our results also show the MTF-1 in both new estimated and DEG in bovine identified during LS and it will be essential for gene expression in bovine endometrium at the period of LS. POU5F1 is a TF containing a POU homeodomain. It plays a role in embryonic development (especially early embryogenesis) and is essential for embryonic stem cell pluripotency regulatory network [24]. It shows that it is a vital regulators of tissue-specific gene expression in lymphoid and pituitary differentiation and in early mammalian growth. To recognize members of the POU family of TFs, it may be involved in the tissue-specific regulation of genes expression in insulin-secreting cells of pancreas [25]. According to reference [26], POU5F1 highly expressed in embryonic stem cells in some mammals. Our result indicates that POUF1 is specific TF during LS in bovine endometrium. Kim et al. [27] reported that POUF1 TF is controlled by reproductive hormone in human. During LS in bovine also level of progesterone is high and it may be controlled by progesterone and gene expression regulated in the endometrium. Peroxisome proliferator-activated receptor alpha (PPARα) is a member of the steroid hormone receptor super family which is involved in the control of cellular lipid utilization. This makes PPARα as a candidate gene for type 2 diabetes and dyslipidemia [28]. PPARs are members of a large family of ligand-inducible TFs that consist of receptors for retinoid, thyroid, and steroid hormones it controls the expression of target genes by binding to DNA sequence elements [29]. Analysis of PPAR mRNA distribution showed that the mammalian PPARa is predominantly expressed in tissues with high catabolic rates for fatty acids and peroxisomal metabolism such as liver, heart, kidney, intestinal mucosa, and brown adipose tissue, [29]. The PPARs regulated by progesterone in human, monkey and rabbit. Our finding also shows PPARA appeared as specific TFs during LS in bovine endometrium and it may regulate through progesterone and play vital role at gene expression. Progesterone is a steroid hormone predominantly produced by the corpus luteum after ovulation and exerts its primary action by activating progesterone receptor [30]. Also Rekawiecki R et al. [31] reported "the cause of these processes is progesterone, which, on the genomic pathway, performances over nuclear receptors that, by attributing to the promoter of a target gene, activate its transcription".

While LS and IS in bovine even of p_4 is high and it may have essential function at gene expression in bovine endometrium at LS and IS periods. The transcriptional activity of interferon regulatory transcription factor-1 (IRF1) is dramatically upregulated by viral infection and stimulated by proinflammatory cytokines, chemokines and prostaglandins which mediated by infection and inflammation [32]. Rulan Bai et al. [33] informed regulated the expression of pregnancy linked transcription factors in bovine endometrial stroma cells. IRF1 is a positive regulatory transcription factor that binds to a common motif in the promoter region of interferons and several IFN-inducible genes which include double-stranded RNA-dependent protein kinase [34]. Likewise, IRF1 can control expression of ISGs in response to IFN-I and IFN-II by straight binding the ISRE or IRFE [34]. IRF1 is necessary for the

development of natural killer cells and the differentiation of CD8+T cells. IRF1 controls gene expression in developing thymocytes and it is required for lineage commitment and selection of CD8+thymocytes. Mice lacking IRF1 displayed reduced numbers of mature CD8+T cells within the thymus and peripheral lymphatic organs [35]. IRF1 is responsible for the important factors expression of innate responses and the development and function of adaptive immunity. The IRF groups are cytokine and inhibit the activity of virus and bacteria and they are mostly initiated during pregnancy. In contrast, our study recognized that IRF1 appeared as TF and bind with the large number of DEG. Perhaps the IRF1 has role at gene expression in bovine endometrium during LS and there is possibility that IFN type I-II present during LS.

Hepatocyte nuclear factor 3 (HNF3) is a protein and it may have a limited tissue distribution than the other two factors reported previously and showing the limited distribution appearance based on transcriptional control of the HNF-3A gene. The HNF3 DNA binding activities were purified from rat liver extracts and the rat cDNA subsequently cloned and sequenced. The rat HNF3 genes have been expressed not only in liver but also in stomach, intestine and lung which are all tissue derived at least partly from embryonic endometrium. HNF3 gene is important in early endoderm and liver development and in addition to their role in adult liver transcription [36]. The HNF3 mostly expressed in liver and also in rat reported expressed other organs. For first time, present study estimated that HNF3 is a TF in bovine endometrium during LS. According to reference Azmi et al. [37], HNF3 and progesterone have positive correlation in human. There is possibility in bovine endometrium that HNF3 regulates through progesterone during LS with high level of progesterone in bovine. In another hand, serum response factor (SRF) is a member of superfamily of TFs.

Furthermore, comparing IS DEG TFs with IS estimated TFs displayed STAT1, STAT2, IRF5, and IRF9 in both groups. Relationship of IRF9 with STAT1–STAT2 heterodimers ISGF3 or with STAT2 homodimers (STAT2/IRF9) in response to IFN-I, redirects these complexes to a distinct group of target genes harboring the ISRE [35]. Moreover, STAT1 and STAT2 remained persistently phosphorylated and also they were in the nucleus upon long-term encouragement of cells with IFNt [38]. STAT1 and STAT2 proteins are important intercessor of type I and III IFN signalling, those which are reported as a necessary factor of the cellular antiviral functions and they are also the principal component of the TFs composite in the IFN signalling pathways (Au-Yeung *et al*. 2013) IRF5 is crisis TFs in the type I IFN pathway and control` the expression of IFN reliant on genes [39]. Gene transcription encourage by them and binding to DNA fragment like ISRE in the cis-regulatory portion of target genes [40]. The function of IRF9 on STAT1, STAT2 and ISRE is like intermediator [41]. “NTFT producing the tyrosine phosphorylation of STAT1most of the forming of STAT1, STAT2 and IRF9 heterodimers and likewise recognized as IFN-stimulated gene factor 3 complex (ISGF3), which is translocated to the nucleus and attach to the interferon-stimulated response element which exist within the promoter of ISGs and controls their expression” [42]. In present study, STAT1, STAT2, IRF5 and IRF9 estimated as specific TFs at IS and according to previous reports, they have key function to gene expression in bovine endometrium during IS [43].

5. CONCLUSION

In conclusion, the current study create that specific TFs were tinted over and done with enquiry of the promoter area for each DEG. While, it is essential to illuminate their roles widely, still the TFs exposed in this research signify fundamental knowledge for upcoming researches.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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