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BIOINFORMATICAL SEARCH FOR TRANSCRIPTION FACTORS BINDING SITES IN *MBL1* PROMOTER OF *RATTUS NORVEGICUS*

In the current work we have analyzed the Mbl1 (mannose-binding lectin) promoter for the presence and functional specifity of transcription factors binding sites (TFBS). We have utilized the weight-position matrices from MatrixFamily Library Version 9.0 and JASPAR CORE Vertebrata databases and two programs – MatInspector and Jaspar. Phylogenetical analysis of rat Mbl1 promoter in comparison with Mus musculus gene-ortholog and the search for functional modules of cooperating transcription factors were conducted with DiAlignTF program. Thus we defined 3 regions in Mbl1 promoter, enriched with conservative transcription factors binding sites, and 6 modules of potentially cooperating TFs.

Key words: mannose binding lectin, weight-position matrices, transcription factor binding sites.

Introduction. Mbl1 refers to the complement system, sometimes called the "complement cascade". It is a complex network of plasma (blood) proteins that cooperate to provide antimicrobial defense and maintain healthy tissue. It's part of the immune system, and *complements* the antibody- and cell-driven responses to infection by pathogens. There are three ways that the complement system becomes activated: the classic complement pathway triggered by antigen-antibody complexes; the lectin pathway triggered by molecular patterns, which are present on many pathogens or exposed neoepitopes on apoptotic, senescent and some tumor cells and/or injured/ inflamed tissues [1 – 4]. These molecular patterns contain sugars, such as D-mannose, fucose and N-acetyl-D-glucosamine; the third way is the unique alternative complement pathway that is always activated at a low level, and doesn't require a microbial surface to trigger it. All these pathways converge on convertase 3 (C3), the central molecule of complement system, that continues the cascade of proteolytic reactions with eventual opsonisation of particles, release of inflammatory peptides and enhanced engulfment by phagocytes of above-mentioned cells as well as cell debris. Whenever MBL is bound to specific molecular patterns it associates with MBL-associated serine proteases (MASPs) and via MASPs initiates complement pathway activation [5] and thrombin-like activity [6]. A number of membrane receptors for MBL, including C1q phagocytic receptor (C1qRp), calreticulin (also known as C1qR), and CR1(CD35), have been described. Interactions with these receptors may also be important in stimulating phagocytosis by MBL [7; 8].

Thereby MBL1 is in the first line of defense in preimmune host. It is produced primarily in the liver and also in kidney, lung and testis [9, 10]. It also refers to acute phase proteins (APP).

There are some evidences that the genes of complement system are regulated by transcription factors including C/EBP (CAAT – binding protein), GR (glucocorticoid receptor), ISGF (interferon – stimulated growth factor) and AP1 (the activator protein 1) [11]. However, the regulation of *Mbl1* expression still remains unknown. The *in silico* search for transcription factors binding sites in promoter of *Mbl1* has revealed the potential regulators of its transcription partly coinciding with its known functions.

Methods. The sequence of 2007 bp (from -1934 to + 73 bp), containing adjacent 5'UTR, was chosen for the search of potential transcription factor binding sites (TFBSs). Two software tools were utilized – MatInspector (http://www.genomatix.de/online_help/help_matinspector/matinspector_help.html) [12] and Jaspar (http://jaspar.gener-eg.net/) [13]. Their open-access databases contain 907 and 217 weight matrices (PWMs) of TFBSs for vertebrates respectively in Matrix Family Library Version 9.0 (August 2012) and JASPAR CORE Vertebrata. PWM represents the complete nucleotide occurrence probabilities and information content evaluation of each matrix position. It allows the quantification of the matrix similarity between the weight matrix and a potential TFBS detected in the target sequence. Similar and/or functionally related transcription factor binding sites are grouped in MatInspector into so-called matrix families (186 for Vertebrates).

The selection of TFBSs was started at recommended thresholds – 0.8/individual families and 0.8/individual matrices for MatInspector and 80 % threshold and minimal 8.000 similarity score for Jaspar. The identified individual matrix matches were sorted on the basis of their corresponding TFs association or not association with liver or hepatocytes. The phrases "transcription factor and liver", "transcription factor and hepatocytes" were used for literature mining with the help of IHOP service (http://www.ihop-net.org/UniPub/IHOP/). Hereafter the selected TFBSs were subjected to phylogenetic fingerprinting – the search of evolutionary conserved TFBSs with regard of their positions by alignment of *Rattus norvegicus* and *Mus musculus Mbl1* promoters with the help of DiAlign TF program (http://www.genomatix.de/online_help/help_dialign/dialign_TF. html). The following settings of similarity scores were used – >0.85 for core similarity and optimized threshold for the matrix similarity. The "core sequence" of a matrix is defined as the usually 4 highest conserved positions of the matrix. The optimized threshold for the matrix similarity allows a maximum of three matches in 10 000 bp of non-regulatory test sequences (1.5 million bp of coding sequences, excluding first exons and genomic repeats).

Further we have analyzed the identified matches of TFBSs for the presence of the cis-regulatory modules using the library Vertebrate_Modules Version 5.6 and the DiAlignTF option. Modules represent the association of at least two TFBSs which are shown to act synergistically or antagonistically. The visualization of results was made with Dia 0.97.2 (25/10/12) program (http://dia.en.softonic.com/).

Results and discussion. In the current work we searched for the potential transcription factors binding sites within *Mbl1* gene promoter of *Rattus norvegicus.* At the first stage of our study we obtained 494 and 270 matrix matches of TFBSs with the help of MatInspector and Jaspar programs respectively. The application of the further filter – the tissue-specificity notably the association of transcription factors with the liver and hepatocytes has cut off their number to 108 and 112 obtained with MatInspector and Jaspar correspondingly.

As transcriptional regulation is mostly evolutionary conserved we have applied phylogenetic footprinting and compared *Mbl1*promoter of *Rattus norvegicus* with its ortholog in *Mus musculus* with the help of DiAlign TF software. We

defined 3 conservative regions enriched with transcription factors (Fig. 1). The first one (-15 – 500 bp) contains binding sites of ISGF (Interferon stimulated growth factor), PEA3 (Polyomavirus enhancer activator 3 or ETS translocation variant 4), Spi-B (Spi-1/PU.1 related transcription factor), 2 TFBSs of HNF-3/Fkh Homolog 2 (FOXD3), HNF6 – Hepatocyte nuclear factor 6 (Onecut- 2), c-Maf (V-maf musculoaponeurotic fibrosarcoma oncogene homolog), C/EBP (Ccaat-enhancer-binding protein), SOX6 (sex-determining region Y (Sry) box-containing protein 6); the second region (- 730 – 955 bp) contains TFBSs of GR (Glucocorticoid receptor), 3 NFAT (Nuclear factor of activated T-cells), Hoxb1 (Homeobox protein Hox-B1), 2 C/EBP, Oct-1(Octamer-binding protein 1) and 2 SRF (Serum response factor) and the third one (- 1670 – 1900 bp) consists of 2 GR, GABP (GA binding protein transcription factor), GATA, 2 Oct-1, HNF6, AP2 (Activator protein 2), STAT3 and STAT5 (Signal transducer and transcription activator), CREB (Cyclic AMP-responsive element-binding protein) and Foxa2 (Forkhead box protein A2) (Fig 2).

For each family of transcription factors within conservative regions of Mbl1 promoter, we searched for Modules of TFs from library Vertebrate_Modules Version 5.6, using DiAlignTF option (Table 1).

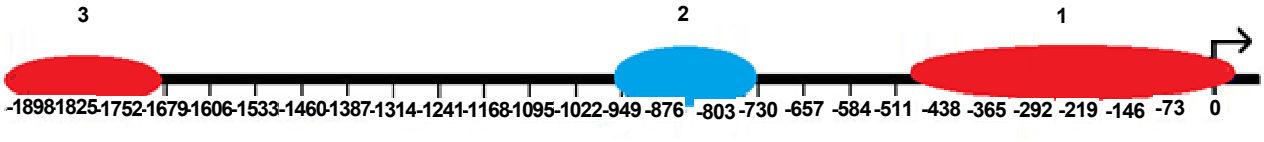

Fig. 1. **Localization of enriched regions containing evolutionary conserved transcription factor binding sites in *Mbl1* promoter of *Rattus norvegicus***

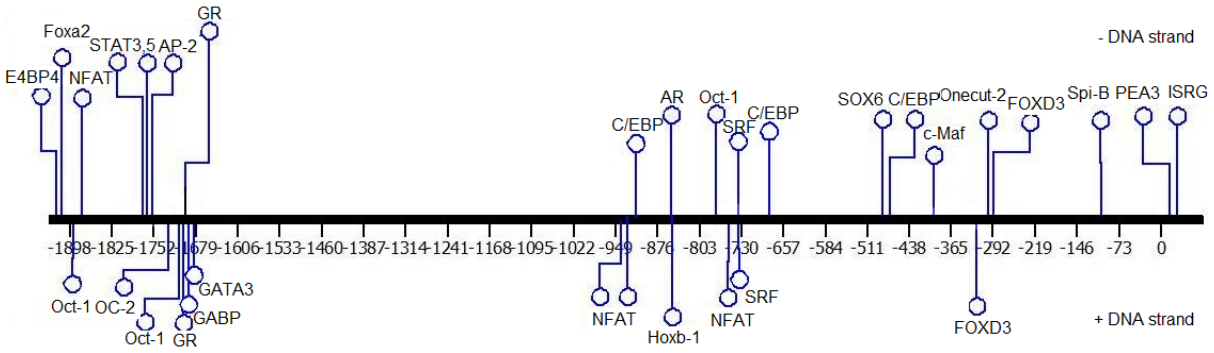

Fig. 2. **Transcription factors and their cognate binding sites within evolutionary conserved regions in *Mbl1* promoter (individual TFs are shown).**

Table 1. **Modules of associated transcription factors within conservative regions of *Mbl1* promoter**

Modules of associated TFs	DNA strand (+,-)	Distance between TFBSs (bp)	Position in promoter (anchor positions, bp)
ETS – ISGF	- , -	0	-44; -40
FKHD – FKHD	-, +	34 – 42	-290; -320
SRF – NFAT	+, +	3 – 11	-743;-753
C/EBP – NFAT	+, -	4 – 12	-901; -923
AP2- GR	-, -	47 – 55	-1686; -1747
STAT3 – STAT5	-, -	1 – 7	-1774; -1783

The transcription factor ISGF-3 that binds within the first region is an interferon-dependent transcription factor that is activated in cytoplasm in result of interferon α/β binding to its cognate receptors [14]. ISGF-3 activates the target genes and realizes antiviral, antiproliferative and immunomodulatory effects of IFNs. All ETS family members are identified through a highly conserved DNA binding domain, the ETS domain, which is a winged helox-turn-helix structure that binds to DNA sites with a central GGA(A/T) DNA sequence. As well as DNA-binding functions, evidence suggests that the ETS domain is also involved in protein-protein interactions. ETS factors act as transcriptional repressors, transcriptional activators, or both [15, 16].

The ETS transcription factors belong to the family of highly conserved sequence-specific DNA binding proteins, which in association with other transcription factors regulate a number of diverse cellular processes including proliferation and differentiation. The Fox proteins containing the Forkhead boxes are important regulators of liver metabolism, homeostasis and proliferative response [17]. The members of this family have crucial roles in various aspects of immune regulation [18]. The binding sites for HNFs (hepatocyte nuclear factors), are identified in each region within *Mbl1* promoter. These transcription factors regulate liver development, regeneration, hepatocyte proliferation and metabolism [19]. The binding sites for AP-1 are widely represented in promoters of liver-specific genes and mediate the regulatory role of AP-1 in the processes of liver development, homeostasis metabolism and proliferation [20,21]. C/EBP δ is associated with proliferation of liver cells [22] and the acute-phase response (APR) in which the liver plays a prominent role [23].

The C/EBP-δ transcription factor is known to be rarely expressed in the liver but significantly up-regulated at the early stage of the acute phase response [24]. The studies with C/EBP- knockout mice demonstrated that neonatal mice treated with purified bacterial lipopolysaccharide or recombinant IL-1 lack an acute phase response typical for wild-type

mice [25]. Sox [sex-determining region Y (Sry) box-containing] proteins are a family of transcription factors that is characterized by a homologous sequence called the HMG-box (for high mobility group). This HMG box is a DNA binding dimain. Accumulating evidence documents that Sox proteins play additional roles in adult tissue homeostasis and regeneration. Remarkably, their forced expression, in combination with other synergistic factors, reprograms differentiated cells into somatic or pluripotent stem cells [26]. However, despite their wide abundance among the tissues, their functions in liver still remain poorly investigated.

The proteins belonging to the NFAT (nuclear factor of activated T cells) family of transcription factors play a central role in inducible gene transcription during the immune response [27]. They rather frequently cooperate with AP-1 [27]. Serum response factor (SRF) is a transcription factor that binds to a CarG box motif within the serum response element (SRE) of genes that are expressed in response to mitogens. The SRF is essential for hepatocyte proliferation and survival. It controls the postnatal body growth and regulates expression of multiple genes in hepatocytes [28]. The POU-domain transcription factor Oct-1 is widely expressed in adult tissues and it modulates the activity of genes important for the cellular response to metabolic and stress signals [29, 30]. It is proposed that rather than acting as a primary trigger of gene activation or repression, Oct1 is a switchable stabilizer of repressed and inducible states [31]. Oct- 1 was shown to interact with HNF-1 in mutual regulation of liver-specific genes [32]. Glucocorticoid receptors (GR) together with C/EBP are the main activators of the synthesis of acute-phase proteins**.** The regulation of gene expression in hepatocytes by glucocorticoids is essential for normal liver homeostasis, metabolism and hepatocyte proliferation [33].

Transcription factor GATA is expressed in early fetal liver and is essential for organogenesis. It is also implicated in carcinogenesis in several endoderm-derived organs [34]. STAT-mediated intracellular signal cascade plays a critical role in antiviral defense, acute phase response, hepatic injury, repair, inflammation and transformation [35].

The search for the modules in *Mbl1* promoter has revealed six pairs of transcription factors acting in coordination and sometimes physically interacting with one another. There are two modules localized in the first region of *Mbl1* promoter. The ISGF and representatives of ETS family of TFs may interact with one another. For example, *PU.1,* a member of ETS family, interacts with ISGF/IRF in enhancers of *Igκ*, *Igλ, IL-1β 5* genes and in promoters of *CD20, gp91, Toll-like receptor 4* genes. This interaction is mediated by the proline-glutamate-serine-threonine-rich (PEST) domain of *PU.1* [36]. This interaction is significantly enhanced by phosphorylation of serine 148, a residue located within the PEST domain of *PU.1* [37].

The module between two representatives of FKHD TF family was found in -290; -328 position. Its functional role was investigated in promoter of transthyretin (TTR) gene [38]. It was revealed, that the presence of both HNF3-S binding site, located in TTR promoter (−106 to −94) and HNF3-W BS in TTR enhancer (−140 to −131) is essential for TTR transcription activation.

Next, we found SRF – NFAT module in -734; -762 position. The association of both transcription factors has been established in smooth muscle cells (SMCs) for intronic serum response factor (SRF)-binding CArG element in alpha-actin gene promoter [39].

C/EBP – NFAT module was defined in -894; -932 position. Interactions between C/EBP – NFAT was revealed in peroxisome proliferator-activated receptor – 2 gene (*Ppar2*). They form a composite enhancer complex to potentiate expression of the *Ppar2* gene [40].

AP2-GR module is located in -1686; -1747 positions. AP2 and GR binding sites are closely located in phenyl – ethanolamine N-methyltransferase (PNMT) gene promoter and cooperatively regulate its expression [41].

The majority of STAT transcription factors associate with each other to regulate gene expression. Two adjacent STAT binding sites were defined in -1774; -1783 positions. STAT3 forms heterodimer with STAT5 and both coregulate gene expression in response to Colony-stimulating factor (CSF-1) and other cytokines [42].

Thus, in the current work we predicted *in silico* the TFBSs in *Mbl1* promoter of *Rattus norvegicus*. The involvement of multiple transcription factors reveals the potential complex regulation of the processes at the first line of organism defence via *Mbl1* gene. The obtained results comprise the justiiified basis for taskoriented experimental validation.

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БІОІНФОРМАЦІЙНИЙ ПОШУК ДЛЯ САЙТІВ З'ЄДНАННЯ ТРАНСКРИПЦІЙНИХ ФАКТОРІВ В *Mbl1 ПРОМОТОРУ RATTUS NORVEGICUS*

Проведено біоінформатичний аналіз промотору щурячого гена Mbl1, який кодує манозозв'зуючий лектин, на наявність та функціональну специфічність сайтів зв'язування транскрипційних факторів. В роботі було використано позиційно-вагові матриці з баз данних Matrix Family Library Version 9.0 та JASPAR CORE Vertebrata, а також дві програми пошуку сайтів зв'язування – MatInspector та Jaspar. Було проведено філогенетичний аналіз з промотором гена-ортолога Mus musculus та здійснено пошук функціональних модулів знайдених транскрипційних факторів в програмі DiAlign TF. В результаті в промоторі гена Mbl1 щура нами було визначено 3 ділянки, збагачені консервативними сайтами зв'язування транскрипційних факторів, та знайдено 6 модулів потенційної кооперативної взаємодії між транскрипційними факторами.

Ключові слова: манозо-зв'язуючий лектин, позиційно-вагові матриці, сайти зв'язування транскрипційних факторів.

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БИОИНФОРМАЦИОННЫЙ ПОИСК ДЛЯ САЙТОВ СОЕДИНЕНИЯ ТРАНСКРИПЦИОННЫХ ФАКТОРОВ В *Mbl1* ПРОМОТОРА *RATTUS NORVEGICUS*

Проведен биоинформатический анализ промотора крысиного гена Mbl1, который кодирует маннозосвязывающий лектин, на наличие и функциональную специфичность сайтов связывания транскрипционных факторов. В работе были использованы позиционно-весовые матрицы из баз данных Matrix Family Library Version 9.0 и JASPAR CORE Vertebrata, а также две программы поиска сайтов связывания – MatInspector и Jaspar. Филогенетический анализ с промотром гена-ортолога Mus musculus и поиск функциональных модулей найденных транскрипционных факторов осуществлены в программе DiAlign TF. В результате в промоторе гена Mbl1 крысы нами было определено 3 участка, обогащенных консервативными сайтами связывания транскрипционных факторов, и найдено 6 модулей потенциального кооперативного взаимодействия между траснкрипционными факторами.

Ключевые слова: маннозо-связывающий лектин, позиционно-весовые матрицы, сайты связывания транскрипционных факторов.