

## Comparison of Genes of JAK-STAT and PI3K-AKT Cycles between Cattle and Pig in Mammary Gland

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### ABSTRACT

JAK-STAT and PI3K-AKT cycles are one of the most important transcription factors in regulating gene expression in the mammary gland. In this study aimed to achieve the important and effective genes related to JAK-STAT and PI3K-AKT cycles of mammary gland of cattle and pig, the genes of these cycles extracted from KEGG site and compared with each other by using BLAST Bioinformatics Tools. The results of this study showed that most genes in these cycles are common among cattle and pig and VTN and ATF4 genes which compared to the other genes, had the largest interception in term of sequence and also TF, HP and SPP1 genes are expressed in both groups (cattle and pig) in mammary gland.

**Key Words:** JAK-STAT, PI3K-AKT, Gene, Mammary gland

### INTRODUCTION

Mammary gland of ruminants (for example cattle) like all mammals (for example pig) in terms of anatomical structure of milk secretion is similar. Mammary glands are modified sweat glands that are responsible for task of milk production (Frandsen *et al.* 2009). Milk production is done by cell proliferation, so that there are the messages which order to a cell that when enter to the cycle and how long stay in the cell and continue to division. Also there are other messages which order to the cell to exit from the cell cycle. If any of these controlling messages have problem, cell division gets out of normal control. Estrogens, Cyclin and growth factors like insulin are some of the most important cell division cycle controller in breast. The Cycles that are involved in cell proliferation could be named the Janus kinase-signal transducers and activators of transcription (JAK-STAT) and Phosphoinositide-3-kinase-protein kinase B that known as PI3K-AKT (Clarke *et al.* 2004, Gross and Yee 2003, Wang and Rekey 2009). Therefore, given the importance of the genes built in this cycle in most mammalian, in this study, we tried to investigation the genes of JAK-STAT and PI3K-AKT cycles in mammary gland of cows and pig.

### THEORY AND LITERATURE

The breast is a skin gland, therefore relative to body mass is located outside the body that seven tissues are involved in its connection. Breast built of a system series comprises: a support system, excretory system consists of epithelial cells, a conduit system for the storage and transport of milk, blood system, lymphatic and nervous glands. In cattle, breast built of four separate mammary glands which called quarter. Each gland has a node and each node (teat) has a hole. Although sheep and goat has two teats and glands, in some mammals like pigs it appears about 10 to 12. The internal structure of mammary gland consists of connective tissue and secretions and a conduit system that secretory tissue contains lobes and each lobe contains several lobules and each Lobule, containing clusters of alveoli, which is a sac like structure in which milk is synthesized and secreted into the ductal system (Knobi and Neill 2006). In order to synchronize the breast development with reproductive stages and enough milk production, Endocrine system should have an active role that through the intervention of three types of hormones that their surfaces vary from phase to phase: Reproductive (estrogen, progesterone, placental Lactogene, prolactin and oxytocin), metabolism (growth hormone, corticosteroids, thyroid hormones and insulin) and mammary hormones (growth hormone, prolactin, parathyroid hormone-related peptide, and leptin) and in

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addition to the foregoing, the cycles which are associated with cell proliferation like JAK-STAT and PI3K-AKT cycles that are involved in producing cell lines and milk production (Neville *et al.* 2002).

Activation of JAK stimulates cell proliferation, differentiation, cell migration and cell death; this means that it is involved in different processes such as hematopoiesis, mammary gland development and lactation, growth, synthesis and development of adipose tissue safety. Mammalian of JAK family consist of 4 members JAK1, JAK2, JAK3, TYK2 and STAT family members are including STAT1, STAT2, STAT3, STAT4, STAT5, STAT6 which are involved in cell proliferation and form JAK-STAT pathway (Zang *et al.* 2010). Also these cycles and biochemical cycles make it possible to identifying similar genes in addition to various tissues among organisms (Kunej *et al.* 2013). Other cycle that we examined in this study is PI3K-AKT cycle which is a tool to regulate cellular metabolism, growth, reproduction, moving and reset of cell structure by deviation in different cell signaling pathways that has a key role in increasing cell proliferation and finally mammary gland development and breast feeding (Nourizadeh *et al.* 2014). AKT also is known as protein kinase B or PKB, which consists of three closely related isoforms AKT1, AKT2 and AKT3 or (BKB $\alpha$  /  $\beta$  /  $\gamma$ ). We have a good understanding about the mechanisms that are activated by AKT isoforms and growth and other extracellular stimuli factors (Hers *et al.* 2011). AKT1 has a broad tissue distribution and it is implicated in cell growth and survival (Chen *et al.* 2001, Cho *et al.* 2001a). Whereas AKT2 is highly expressed in muscle and fat cells and helps regulate insulin-mediated glucose homeostasis (Cho *et al.* 2001b, Garofalo *et al.* 2003). Distribution of AKT3 is more limited and expressing mainly occurs in testes and brain (Willey 2009). Analysis of the biological cycles due to integration of mathematical models with the experimental data is considered as the most important part of biological systems and as well as this cycles provide activation of different parts of metabolic systems and how to adjust them (Nielson 2009). To interpret biological cycles we can use KEGG. This resource consists of a series of databases of biological cycles. KEGG can communicates between biological database that contains information about genes, proteins, chemical structure, molecular interactions and biological relationships, ligands and cycles and investigate biological performance and cycle control (Kirwan *et al.* 2011, Kunej *et al.* 2013). In addition to investigating the biology of different tissues we can use expressed gene analysis in KEGG.

## MATERIALS AND METHODS

First, the genes which are highly expressed in mammary gland of cows and pigs, were identified by using the Display Differential Digital (DDD) that is a powerful web-based bioinformatics tool to determining gene expression in different tissues. Then in order to finding the genes that are related to JAK-STAT and PI3K-AKT cycles, we used KEGG internet source and its related genes in cattle and pigs were obtained (Fig. 1 and 2). After the identification of genes associated with the JAK-STAT and PI3K-AKT cycles, the information such as sequencing DNA, the sequence of the reference RNA (RNA seq Ref) and the number of chromosomal genes in organisms were obtained from NCBI. Finally, the RNA seq Ref of individual genes related to JAK-STAT and PI3K-AKT cycles in the organisms were compared by means of Bioinformatics BLAST. In this case, the RNA seq Ref related to the genes in each organism compared to RNA seq Ref of similar genes in other organisms (Nourizadeh *et al.* 2014).

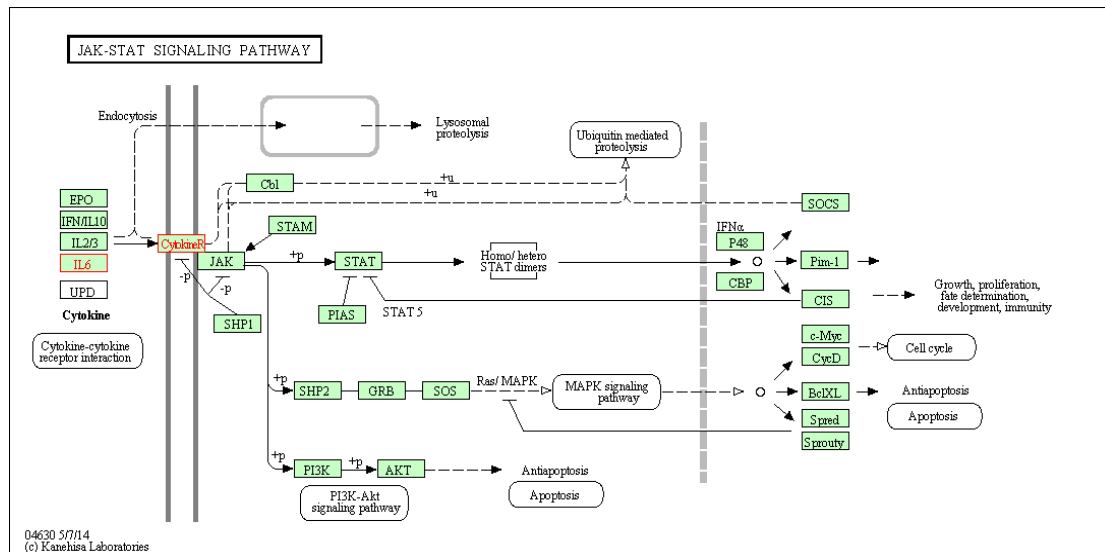


Figure 1. JAK-STAT cycle.

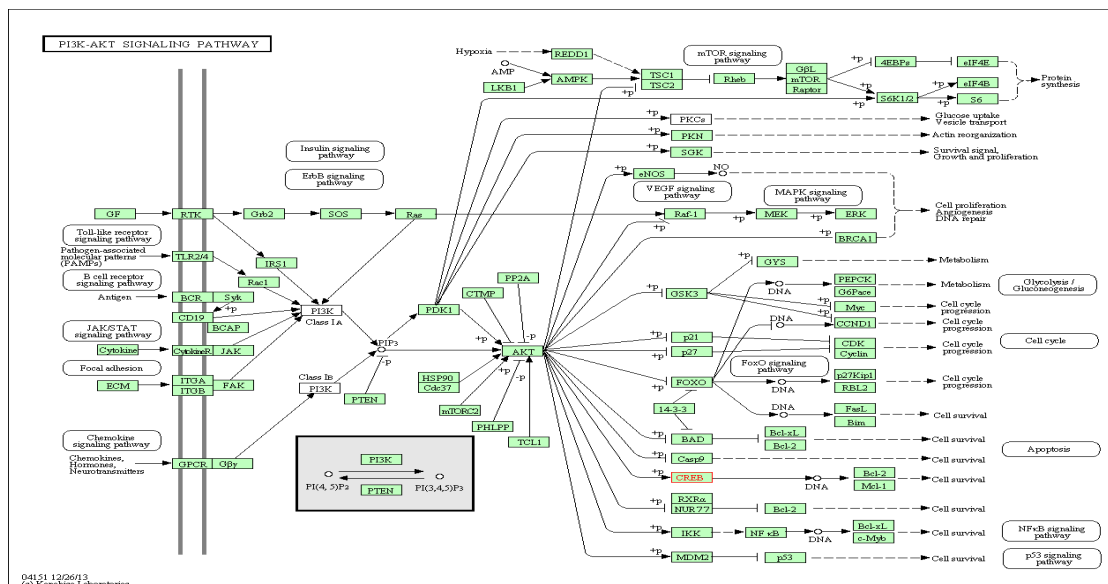


Figure 2. PI3K-AKT cycle.

## RESULTS AND DISCUSSION

Results of DDD showed that secreted phosphoprotein 1 (SPP1) and activating transcription factor 4 (ATF4) genes in PI3K-AKT cycle and Haptoglobin (HP) and Transferrin (TF) genes in JAK-STAT cycle have the highest expression in mammary gland of cows and pigs. Results of JAK-STAT genes cycle analysis showed that this cycle is associated with 8 genes in cattle and 3 genes pig and 2 of these genes in these organisms is common. Evaluation of PI3K-AKT-cycle genes identified that this cycle is associated whit 15 genes in cattle and 9 genes pigs and 4 genes are common among these animals (the common genes have been reported in table 1). Following the Table 1 ATF4, HP, and Vitronectin (VTN) genes have the highest degree of compliance in cattle and pig. Comparative genomics based on the theory that means the most important biological processes are p53 signaling pathway

between different species. The results of this theory confirm non-random conserved expression of ortholog genes. According to this theory, biological processes and important genes are conserved between different species (Polivka and Janku 2014).

**Table 1.** Common genes between cattle and pig in JAK-STAT and PI3K-AKT cycles.

Gene	MAX SCORE	Total Score	Query Cover %	E-Value	Max Ident %
TF	769	5935	23	0.0	76
HP	778	778	14	0.0	83
VTN	614	2018	83	1e-178	82
SPP1	1123	2012	4	0.0	78
ATF4	1618	1618	96	0.0	82

Finally, after evaluation of these cycles we faced TF gene which was in both JAK-STAT and PI3K-AKT cycles. This gene is located on chromosome number 1 of cow and chromosome number 13 of pig which is reported in Table 2. TF is a glycoprotein found in many species for the transport of iron and is located in different areas of QTL. However several studies have shown that this gene is caused higher productivity and milk fat (Gross and Yee 2003, Yang *et al.* 2003).

**Table 2.** Chromosomal location of common genes of cattle and pig in JAK-STAT and PI3K-AKT cycles.

Gene	Number of chromosome in cattle	Number of chromosome in pig	JAK-STAT	PI3K-AKT
TF	1	13	+	+
HP	18	6	+	-
VTN	19	18	-	+
SPP1	6	8	-	+
ATF4	5	5	-	+

## CONCLUSIONS

The results of this study showed that 66% of pigs and cattle genes are similar in JAK-STAT cycle and 44% of the genes in these two animals in PI3K-AKT cycle are common too. These cycles provide identification of common and similar genes in different tissues and between different species. The comparison of genes showed that VTN and ATF4 have the most similarity in term of sequence information among cattle and pig in PI3K-AKT cycle and HP showed the same performance in JAK-STAT cycle. In term of chromosomal location, only ATF4 was located on chromosome number 5 in both animals (table 2). Genes that are shown Table 1 play an important role in cell proliferation in mammary gland. This information on the selection of important and effective genes in order to increase milk production in cattle and pigs and other animals can be great assistance to reformers and evaluation of genes of these cycles in other tissues of organisms is recommended in order to complete information about of JAK-STAT and PI3K-AKT cycles.

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