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EXPLORING THE POTENTIAL STAT3 GENE IN BROILER WITH ASCITES SYNDROME BY BIOINFORMATICS ANALYSIS

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ABSTRACT

STAT3 plays an important role in vascular remodeling, but there are no studies on its protein function and structure. In this study, the physical and chemical properties, hydrophilicity / hydrophobicity, transmembrane domain, phosphorylation site, glycosylation site, subcellular localization, signal peptide distribution and secondary and tertiary structure of STAT3 protein were predicted online by bioinformatics tools. The results showed that the number of amino acids of STAT3 was 771aa, the theoretical isoelectric point was 5.94, the instability index was 49.21, and the average coefficient of hydrophilicity was-0.389. It was found to be a hydrophilic protein with no transmembrane domain, 45 phosphorylation sites and 4 glycosylation sites. The protein is expressed in the nucleus, there is no signal peptide distribution in the whole sequence, and the protein structure is complex. The secondary structure is mainly composed of α-helix, Extended strand, β-turn and Random coil, accounting for 50.58%, 11.80%, 2.46% and 35.15%, respectively. The tertiary structure is mainly composed of α-helix and Random coil. In summary, this study suggests that the amino acid sequence 75-190aa of STAT3 can be used to express antigens and prepare antibodies, and the sequence 737-754aa of STAT3 can be used to prepare peptide antigens This study provides a basis for further exploring the function of STAT3 protein, and lays a foundation for expression and purification of STAT3 protein, preparation of STAT3 antibody and screening of drug targets. This then provides powerful conditions for pathological detection of pulmonary vascular remodeling and gene drug therapy of ascites syndrome in broilers.

Keywords: STAT3 gene, broiler, ascites syndrome, bioinformatics analysis

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INTRODUCTION

Broiler ascites syndrome (AS, also known as broiler pulmonary hypertension syndrome, PHS), is a nutritional and metabolic disorder of broilers. With the continuous selection and cultivation and the improvement of modern feeding techniques, the rapid growth of broilers also increases oxygen consumption. When the oxygen supply is insufficient, the working load of cardiopulmonary system and pulmonary artery pressure will increase, which will cause vascular wall injury, vascular permeability change, ascites retention and ascites syndrome in broilers (Baghbanzadeh and Decuypere 2008; Kalmar et al. 2013; Khajali and Wideman 2016). Its morbidity and death are high, which has caused huge economic losses to the chicken industry all over the world. Because the cause of the disease is complex and difficult to cure, relative hypoxia is often caused by physiology and pathology, nutrition, environment, heredity and gene and other factors (Wideman et al. 2013; Mohammadalipour et al. 2017). At present, more and more researchers are paying attention to the relationship between related genes and the occurrence of ascites syndrome in broiler, such as hypoxia inducible factor-1α (HIF-lα), Endothelin-1 (ET-1), Vascular endothelial growth factor (VEGF), AT- II, Transforming growth factor- β (TGF- β), signal transducer and activator of transcription 3 (STAT3) (Li et al. 2016; Koyama et al. 2019; Cao et al. 2020; Nakao et al. 2020), etc. Among them, STAT3 participates in a variety of important cellular functions related to cell proliferation, survival and angiogenesis, and plays a prominent role in the protection of the heart (Chai et al. 2016; Nakao et al. 2020). Down-regulating the level of miR-199a-5p by activating STAT3 pathway can protect cardiomyocytes from endoplasmic reticulum stress (ERS)-related apoptosis (Zhou et al. 2019). The protective effect of Soluble receptor for advanced

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glycation end-products (SRAGE) on myocardial ischemia/reperfusion (I/R) injury and the potential cardioprotective mechanism of Heat-shock transcription factor 1 (HSF1) depend on the activation of STAT3 (Yuan et al. 2018). The overexpression or activation of STAT3 in cardiomyocytes can also enhance the expression of VEGF, promote the formation of myocardial capillaries, and alleviate the increase of arterial blood pressure (Hilfiker-Kleiner et al. 2004). In our previous study, in the early AS model experiment, we found that the level of STAT3 gene expression in pulmonary artery tissue of broilers was significantly higher than that of the normal group. It is therefore clear that the expression of STAT3 gene is involved in the pulmonary artery remodeling of AS. However, there are few in-depth studies on the relationship between STAT3 gene and the occurrence and development of ascites syndrome in broilers.

Therefore, in this study, the physical and chemical parameters, hydrophilicity/hydrophobicity, transmembrane domain, phosphorylation site, glycosylation site, subcellular localization, signal peptide and secondary and tertiary structure of STAT3 protein were analyzed by bioinformatics method, which provided a basis for the study of STAT3 protein expression and antibody preparation. It further laid a foundation for the screening of STAT3 gene drug targets and the prevention and treatment of ascites syndrome in broilers.

MATERIALS AND METHODS

***Amino Acid Sequences*:** The complete amino acid sequences of STAT3 protein (Species, *Gallus gallus* , accession: NP_001026102.2, Gene id: 420027) was obtained from the National Center for Biotechnology Information (NCBI) database (NCBI: https://www.ncbi.nlm.nih.gov/). At the same time, a specific comparison was carried out.

***Prediction of Physicochemical Parameters of STAT3 Protein*:** Online tools from ExPASy ProtParam (https://web.expasy.org/protparam/) were used to analyze STAT3 proteins, including the amino acid composition, molecular weight, total atomic number, theoretical isoelectric point, instability index, extinction coefficient, parent level mean and other physicochemical parameters.

***Prediction of Hydrophilicity, Hydrophobicity and Transmembrane Domains of STAT3 Protein*:** The hydrophilicity and hydrophobicity of the STAT3 proteins was analyzed by the Kyte & Doolittle algorithm of the ExPASy server ProtScale module (https://web.expasy.org/protscale/). The transmembrane domains of the STAT3 proteins was further analyzed by the TMHMM Server (http://www.cbs.dtu.dk/services/TMHMM-2.0/).

***Analysis of Phosphorylation Sites and Glycosylation Sites of STAT3 Protein*:** The potential N-linked phosphorylation and glycosylation sites of STAT3 were predicted using NetPhos 3.1 (http://www.cbs.dtu.dk/services/NetPhos/) and NetNGlyc 1.0 Server (http://www.cbs.dtu.dk/services/NetNGlyc/), respectively.

***Subcellular Localization and Signal Peptide Identification of STAT3 Protein*:** The subcellular localization of STAT3 protein was predicted from the amino acid sequence by online software Predictprotein (https://www.predictprotein.org/). The presence and location of signal peptide cleavage sites in the amino acid sequences were predicted by the SignalP 4.0 (http://www.cbs.dtu.dk/services/SignalP-4.0/) with a D-cutoff score of 0.5.

***Secondary and Tertiary Structure Prediction of STAT3 Protein*:** The secondary and tertiary structures of the STAT3 protein were predicted by the SOPMA (https://npsa-prabi.ibcp.fr/NPSA/npsa_sopma.html)and SWISS-MODEL (https://swissmodel.expasy.org/) software, respectively. In addition, the conserved domain of STAT3 protein was analyzed in the Conserved Domain Database (CDD) of NCBI. (https://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi).

RESULTS

***Gene Information for STAT3 Protein*:** The amino acid sequence of the STAT3 protein was obtained from GenBank as follows:

MAQWNQLQQLDTRYLEQLHQLYSDSFPMELRQFLAPWIESQDWAYAANKESHATLVFHNLLGEIDQQYSR
FLQESNVLYQHNLRRIKQFLQSRYLEKPMEIARIVARCLWEESRLLQTAATAAQQGGQATHPTAAVVTEKQ
QMLEQHLQDVRKRVQDLEQKMKVVENLQDDFDFNYKTLKSQGDMQDLNGNNQSVTRQKMQQLEQMLT
ALDQMRRGIVSELAGLLSAMEYVQKMLADEELADWKRRQQIACIGGPPNICLDRLENWITSLAESQLQTR

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QQIKKLEELQQKVSYKGDPIVQHRPMLEERIVELFRNLMKSAFVVERQPCMPMHPDRPLVIKTGVQFTTKV RLLVKFPELNYQLKIKVCIDKDSGDVAALRGSRKFNILGTNTKVMNMEESNNGSLSAEFKHLTLREQRCGN GGRANCDASLIVTEELHLITFETEVYHQGLKIDLETHSLPVVVISNICQMPNAWASILWYNMLTNNPKNVNF FTKPPIGTWDQVAEVLSWQFSSTTKRGLSIEQLTTLAEKLLGPGVNYSGCQITWAKFCKENMAGKGFSFWV WLDNIIDLVKKYILALWNEGYIMGFISKERERAILSTKPPGTFLLRFSESSKEGGITFTWVEKDISGKTQIQSV EPYTKQQLNSMSFAEIIMGYKIMDATNILVSPLVYLYPDIPKEEAFGKYCRSESQEHSEATDSGSAAPYLKTK FICVTPTSFSNTIDLPMSPRTLDSLMQFGNSSEGAEANAGGQFESLTFDMELTQECASSPM. The specificity of this gene is average, of which the amino acid sequence is 75-190aa and 737-754aa is better (Figure 1).

***The Physicochemical Parameters of STAT3 Protein*:** Through ProtParam online prediction and analysis of the physical and chemical properties of STAT3 protein, it was found that STAT3 is composed of 20 kinds of amino acids, the total number of amino acids is 771 aa, and the Leucine (leu) content is the highest at 10.6% (Figure 2). The molecular weight of STAT3 protein is 88170.87 Da, the molecular formula is $C_{3913}H_{6166}N_{1062}O_{1173}S_{41}$, the total number of atoms is12355 (Ref. https://web.expasy.org/cgi-bin/protparam/protparam), and the theoretical isoelectric point is 5.94. The protein instability index is 49.21 (A value greater than 40 indicates unstable protein), the extinction coefficient is 114540 (it is used for having an estimation of coefficient for absorption of light using spectrophotometer). The aliphatic index of a protein is defined as the relative volume occupied by aliphatic side chains (alanine, valine, isoleucine, and leucine). It may be regarded as a positive factor for the increase of thermostability of globular proteins. And the Grand average of hydropathicity is -0.389 (A negative value indicates that the protein is a hydrophilic protein).

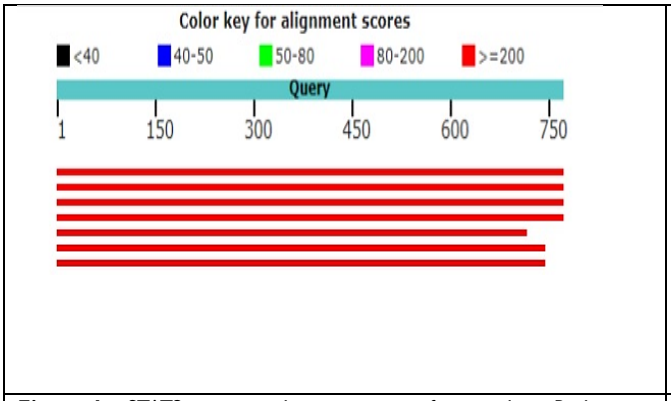

Figure 1: STAT3 amino acid sequence specificity analysis. Red means that the score is greater than or equal to 200.

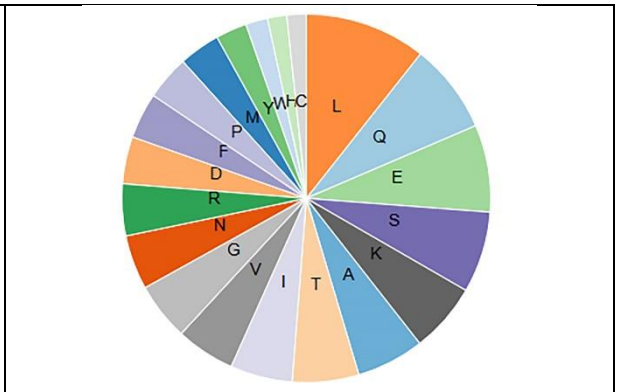

Figure 2: Amino acid composition of STAT3 protein. Among the 20 amino acids that make up STAT3 protein, leucine accounts for the largest proportion.

***Hydrophilicity and Hydrophobicity and Transmembrane Domains of STAT3 Protein*:** The software analysis showed that the highest hydrophobicity score of STAT3 protein was 2.289 and the highest hydrophilicity value was -2.678. The evenly distributed low-score hydrophilic amino acids formed most of the STAT3 polypeptide chain, and the whole polypeptide chain showed hydrophilic amino acids (Figure 3). This is also consistent with the total average hydrophobicity index predicted by ExPASy ProtParam online analysis system. In addition, there was no obvious hydrophobic region in STAT3, so it can be speculated that there is no transmembrane region in it. TMHMM analysis showed that there was no obvious transmembrane region in the amino acid sequence of STAT3 (Figure 4).

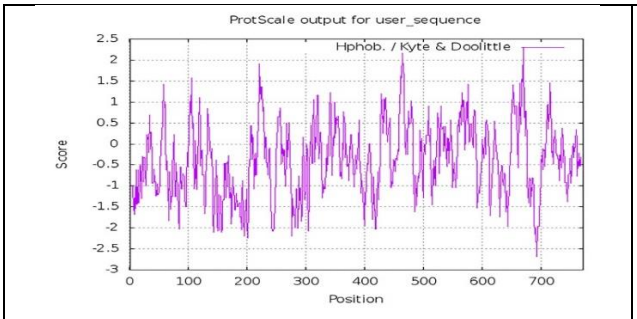

Figure 3: Hydrophobicity/hydrophilicity of STAT3 protein. Positive scores present hydrophobicity and negative scores indicate

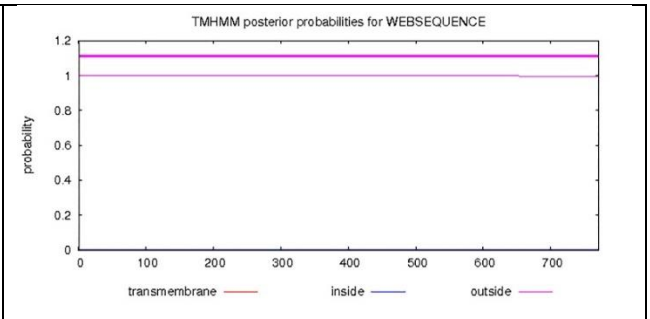

Figure 4: Transmembrane domain of STAT3 protein. The dark purple line represents the STAT3 protein, the purple line below represents

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hydrophilicity. The higher the absolute value, the higher the degree of hydrophobicity/hydrophilicity.	the outer cell membrane, and the blue line represents the inner cell membrane.

***Analysis of Phosphorylation and Glycosylation sites of STAT3 Protein*:** The results of predictive analysis of the phosphorylation site of STAT3 protein using the bioinformatics software NetPhos 3.1 showed that in the STAT3 peptide chain, when the threshold of potential phosphorylation sites is 0.5, there are multiple phosphorylation sites of STAT3 protein (Figure 5), of which serine (Ser) has 43 sites (23, 25, 40, 51, 69, 92, 181, 194, 269, 273, 292, 372, 381, 399, 403, 405, 429, 458, 465, 513, 514, 521, 590, 599, 611, 613, 614, 629, 636, 647, 649, 668, 689, 691, 695, 700, 718, 728, 734, 741, 742, 755, 769), and Threonine (Thr) has 24 positions (121, 133, 138, 178, 196, 277, 346, 347, 389, 412, 433, 500, 515, 516, 526, 527, 600, 622, 632, 698, 709, 715, 717, 763), and Tyrosine (Tyr) has 7 sites (45, 79, 176, 230, 446, 584, 640). There are four glycosylation sites in STAT3 protein, namely, 192-NQSV, 401-NGSL, 538-NYSG and 740murNSSE (Figure 6).

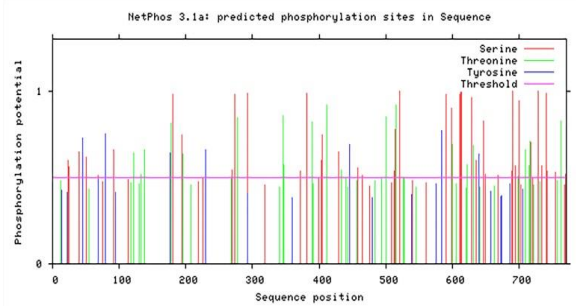

Figure 5: Phosphorylation site of STAT3 protein. The red lines represent the serine phosphorylation site, the green lines denote the threonine phosphorylation site, the blue lines denote the tyrosine phosphorylation site, and the purple line represent the threshold.

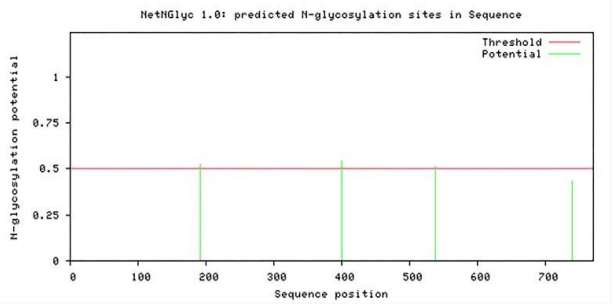

Figure 6: Glycosylation sites of STAT3 protein. The green line represents the potential glycosylation site and the red line represents the threshold.

***Subcellular Localization and Signal Peptide Identification of STAT3 Protein*:** The predicted subcellular localization compartment of STAT3protein is the nucleus (Figure 7). The protein has no signal peptide sequence, and the entire coding sequence can be completely used for prokaryotic expression (Figure 8).

Figure 7: Subcellular localization compartment of STAT3 protein. This viewer shows a cell schematic with the predicted subcellular localization compartment highlighted in green. The predicted compartment is also referenced by a GO ID for better clarity.

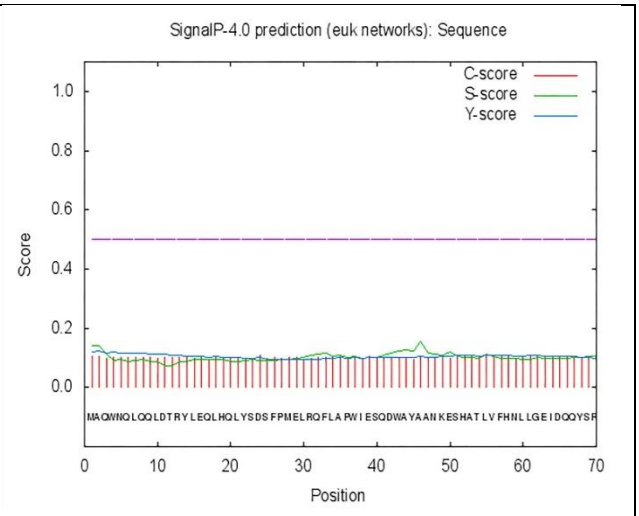

Figure 8: Signal peptide of STAT3 protein. The red line represents the C score, the green line represents the S score, and the blue line represents the Y score.

***Secondary and Tertiary Structure of STAT3 Protein*:** The prediction of the secondary structure of STAT3 protein by SOPMA software showed that there were 390 α-helixes, 91 Extended strands, 19 β-turns and 271 Random coils in the STAT3 amino acid sequence, accounting for 50.58%, 11.80%, 2.46% and 35.15% of the secondary structure, respectively (Figure 9). According to the prediction of SWISS-MODEL, there are many α-helixes in the tertiary structure of STAT3 protein, which are mainly alpha helix and Random coil (Figure 10), which is basically

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consistent with the prediction of secondary structure. STAT3 protein has a large number of conserved domains, among which STAT3 amino acid sequence 100aa-475aa is the most abundant (Figure 11).

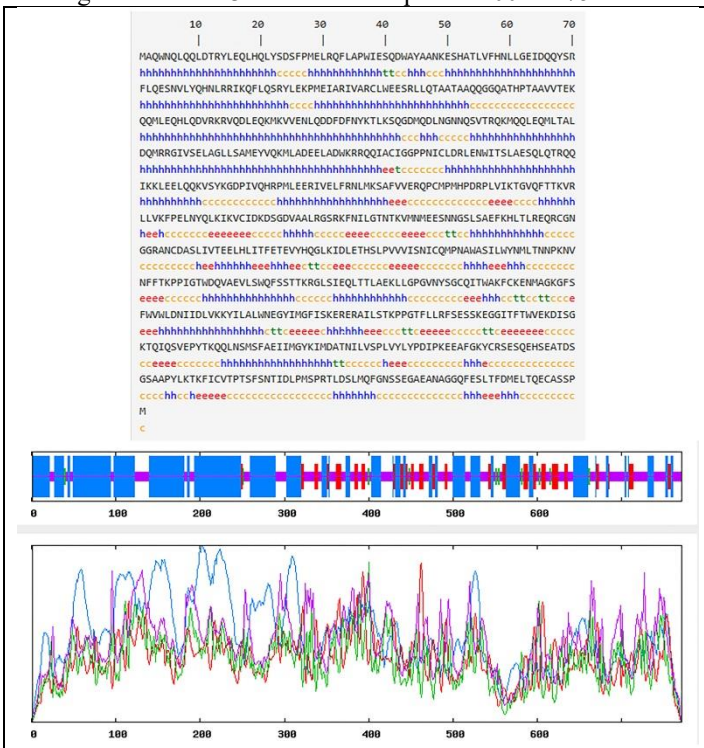

Figure 9: The secondary structure of STAT3 protein. H stands for α-helix and c for disordered crimped state. Blue represents α-helix; purple represents irregular crimping; red represents extension chain; green represents β-rotation.

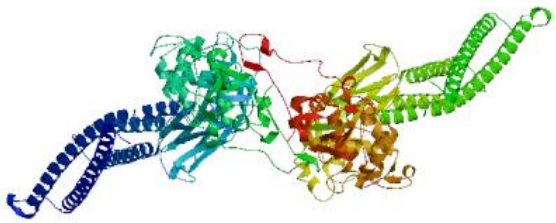

Figure 10: Tertiary structure of STAT3 protein. Red indicates α-helix, yellow indicates β-turning angle, green indicates Random coil, and blue indicates transmembrane region.

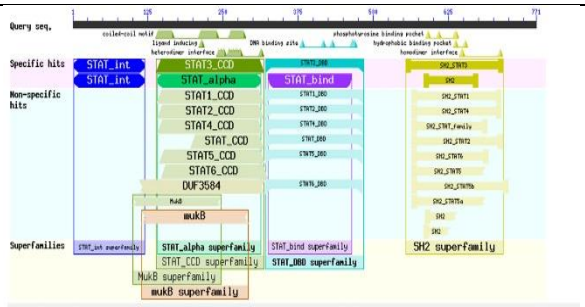

Figure 11: CD-Search results for the protein sequence of STAT3. Functional sites are mapped to the query sequence and depicted as triangles.

DISCUSSION

Broiler ascites syndrome has brought more and more economic losses to the global broiler industry, and the prevention and treatment of broiler ascites syndrome has become the focus of research. According to previous studies, STAT3 plays an important role in vascular remodeling and can alleviate pulmonary hypertension. In this

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study, the bioinformatics analysis of STAT3 gene and its encoded protein was carried out, and the prediction of the property and structure of STAT3 protein provided the basis for the study of STAT3 protein expression.

Bioinformatics technology has been maturely used in the prediction of protein structure and function, and the predicted results are efficient and accurate. In this study, the physical and chemical properties of STAT3 protein were predicted by online software ExPASy ProtParam. The results showed that the protein was complex and hydrophilic. The hydrophilic and hydrophobic results predicted by ExPASy ProtScale not only proved that STAT3 was a hydrophilic protein, but also showed that STAT3 had no transmembrane domain. This indicates that STAT3 protein is not a membrane protein and can be expressed in prokaryotic expression system. This result was verified by the prediction of TMHMM. Most of the hydrophilic structures are located on the surface of the protein. These hydrophilic regions not only improve the efficient solubility of the protein, but also become sites for STAT3 antigen recognition, which is beneficial to the occurrence of immune reaction in the preparation of STAT3 antibodies (Durell and Ben-Naim 2017). In the prediction of subcellular localization, our results indicated that STAT3 protein is expressed in the nucleus. Combined with the prediction that STAT3 has no transmembrane domain and signal peptide distribution, it indicates that STAT3 does not need to enter other organelles with membrane structure, and the sequences encoded by STAT3 can be used for prokaryotic expression and can be diffused freely in cells after STAT3 protein expression (Tardif et al. 2012). Phosphorylation and glycosylation play key roles in cellular immunity, protein signal transduction, regulation of gene expression, protein translation, protein degradation and cell cycle regulation (Blom et al. 2004; Lu et al. 2020). Glycosylation has important role in secondary protein processing, stability and function inside the cell. It affects 3-dimensional structure configuration of protein (Sun at al. 2019). In this study, it was predicted that STAT3 protein has more phosphorylation sites and glycosylation sites by software, which reflects the complexity of STAT3 protein function. The complexity of STAT3 protein structure is reflected in its secondary and tertiary structure. Through the online software prediction, it was found that STAT3 protein is composed of many kinds of structures, among which α-helixes and Random coil accounts for a large proportion, and also that STAT3 protein is a heterozygous protein (Zhang et al. 2011). Different secondary structures and super secondary structures combine to form independent stable structural regions (Yang et al. 2020). The conserved domain of STAT3 protein is the same or invariable domain in the STAT3 protein family. These domains have important functions, cannot be changed, and have strong stability. When selecting STAT3 amino acid sequence to express protein, we should select the sequence with rich domain and good stability to express STAT3 protein, which is beneficial to the successful expression and purification of Amino acid protein (Marchler-Bauer et al. 2010; Bugge et al. 2016).

Conclusion: In conclusion, the structure and function of STAT3 protein are complex. It is a hydrophilic non-membrane protein, which is mainly expressed in the nucleus, and the distribution of non-signal peptide is more favorable for its expression. The region specificity of 75-190aa of STAT3 and the stability of secondary structure are both good. It can be used to express antigens and prepare antibodies, and the amino acid sequence 737-754aa of STAT3 has better specificity and hydrophilicity to prepare polypeptide antigens. The above analysis is helpful for us to further explore the function of STAT3, provide a basis for the expression and purification of STAT3 protein, antibody preparation and drug target screening, and lay a foundation for the prevention and treatment of ascites syndrome in broilers.

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Conflict of Interest Statement: The authors declare that there are no conflicts of interest.

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